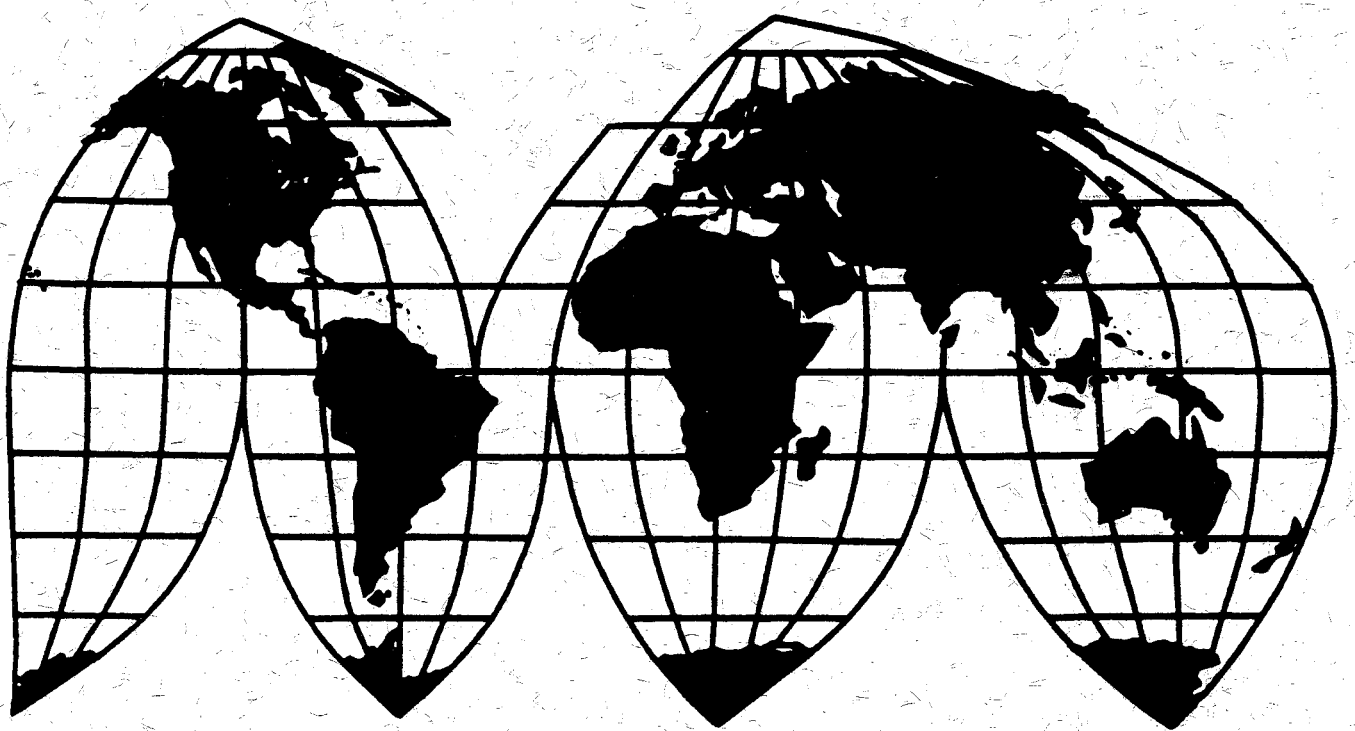
In the Matter of

Certain Diltiazem Hydrochloride and Diltiazem Preparations

Investigation No. 337-TA-349

Publication 2902 **June 1995**

U.S. International Trade Commission



Washington, DC 20436

U.S. International Trade Commission

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U.S. International Trade Commission

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In the Matter of

Certain Diltiazem Hydrochloride and Diltiazem Preparations

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UNITED STATES INTERNATIONAL TRADE COMMISSION
Washington, DC 20436

In the Matter of	
CERTAIN DILTIAZEM HYDROCHLORIDE AND DILTIAZEM PREPARATIONS	Investigation No. 337-TA-349

NOTICE OF COMMISSION DECISIONS AFFIRMING IN PART, TAKING NO POSITION IN PART, AND VACATING IN PART AN INITIAL DETERMINATION; GRANTING OF A JOINT MOTION TO TERMINATE CERTAIN RESPONDENTS ON THE BASIS OF A SETTLEMENT AGREEMENT; DENIAL OF A MOTION TO INTERVENE

AGENCY: U.S. International Trade Commission.

ACTION: Notice.

SUMMARY: Notice is hereby given that the U.S. International Trade Commission has determined to affirm the claim interpretation and infringement findings and to take no position on the issues of validity and unenforceability in the initial determination (ID) issued by the presiding administrative law judge (ALJ) on February 1, 1995, in the above-captioned investigation in accordance with Beloit Corporation v. Valmet Oy, TVW Paper Machines, Inc. and the United States International Trade Commission, 742 F.2d 1421 (Fed. Cir. 1984). The Commission has also vacated as moot ALJ Order No. 52. Finally, the Commission has determined to grant a joint motion to terminate certain respondents on the basis of a settlement agreement, and to deny a motion to intervene in the investigation.

FOR FURTHER INFORMATION CONTACT: Cynthia P. Johnson, Esq., Office of the General Counsel, U.S. International Trade Commission, telephone 202-205-3098.

SUPPLEMENTAL INFORMATION:

On February 1, 1993, Tanabe Seiyaku Co., Ltd. (Tanabe) and Marion Merrell Dow, Inc. (MMD) (collectively "complainants") filed a complaint under section 337 alleging unfair acts in the importation and sale of diltiazem hydrochloride and diltiazem preparations ("diltiazem") by nine proposed respondents: (1) Abic Ltd. of Netanya, Israel ("Abic"); (2) Gyma Laboratories of America, Inc. of Garden City, New York ("Gyma"); (3) Profarmaco Nobel SRL of Milan, Italy; (4) Mylan Pharmaceuticals, Inc. of Morgantown, West Virginia; (5) Mylan Laboratories, Inc. of Pittsburgh, Pennsylvania (collectively referred to as the "Profarmaco respondents"); (6) Orion Corporation Fermion of Espoo, Finland; (7) Interchem Corporation of Paramus, New Jersey; (8) Copley Pharmaceuticals, Inc. of Canton, Massachusetts; and (9) Rhone-Poulenc Rorer, Inc. of Collegeville, Pennsylvania

(collectively referred to as the "Permion respondents"). Complainants alleged infringement of claim 1 of U.S. Letters Patent 4,438,035 ("the '035 patent"). On March 25, 1993, the Commission voted to institute an investigation of the complaint of Tanabe and MMD. 58 Fed. Reg. 16846 (March 31, 1993).

On May 6, 1993, complainants moved to amend the complaint and notice of investigation to add Plantex U.S.A., Inc. as a respondent. On May 20, 1993, the ALJ issued an ID amending the complaint and notice of investigation to add Plantex as a respondent. Plantex participated in the investigation with respondent Abic, Inc.

On February 1, 1995, the presiding ALJ issued his final ID finding that there was no violation of section 337. He found that claim 1 of the '035 patent was not infringed by any of respondents' processes, that claim 1 was invalid as obvious under 35 U.S.C. § 103, and that the '035 patent was unenforceable because of complainants' inequitable conduct during reexamination proceedings before the U.S. Patent and Trademark Office. In a separate order (Order No. 52), issued on the same date, the ALJ granted respondents' motion for evidentiary sanctions against complainants.

On March 30, 1995, the Commission determined to review the following issues in the ID: (1) claim interpretation; (2) whether claim 1 of the '035 patent is infringed by respondents' processes; (3) whether claim 1 of the '035 patent is invalid as obvious under 35 U.S.C. § 103; (4) whether the '035 patent is unenforceable; and (5) Order No. 52. Order No. 52 was considered to be part of the ID. The Commission posed several specific questions for the parties. The Commission also requested information on the status of the Abic respondents.

On April 13, 1995, complainants and Abic Ltd. and Plantex U.S.A. ("the Abic respondents") filed a joint motion to terminate the investigation as to the Abic respondents on the basis of a settlement agreement. Additionally, on April 13, 1995, Mr. James Gambrell filed a motion to intervene in the investigation.

This action is taken under the authority of section 337 of the Tariff Act of 1930 (19 U.S.C. § 1337) and Commission interim rule 210.56 (19 C.F.R. § 210.56).

Copies of the Commission's Order, the Commission Opinion in support thereof, the nonconfidential version of the ID, and all other nonconfidential documents filed in connection with this investigation are or will be available for inspection during official business hours (8:45 a.m. to 5:15 p.m.) in the Office of the Secretary, U.S. International Trade Commission, 500 E Street S.W., Washington, D.C. 20436, telephone 202-205-2000. Hearing-impaired persons are advised that information on this matter can be obtained by contacting the Commission's TDD terminal on 202-205-1810.

By order of the Commission.

Donna R. Koehnke

Donna R. Koehnke
Secretary

Issued: June 1, 1995

UNITED STATES INTERNATIONAL TRADE COMMISSION
Washington, D.C. 20436

In the Matter of	)	
	)	Investigation No. 337-TA-349
CERTAIN DILTIAZEM HYDROCHLORIDE AND DILTIAZEM PREPARATIONS	)	

ORDER

On February 1, 1993, Tanabe Seiyaku Co., Ltd. and Marion Merrell Dow, Inc. filed a complaint under section 337 of the Tariff Act of 1930 (19 U.S.C. § 1337) alleging infringement of claim 1 of U.S. Letters Patent 4,438,035 ('035 patent) in the importation and sale of certain diltiazem hydrochloride and diltiazem preparations. On March 25, 1993, the Commission voted to institute an investigation of the complaint. Notice of the investigation was published in the Federal Register on March 31, 1993. 58 Fed. Reg. 16846.

On February 1, 1995, the presiding ALJ issued his final ID finding that there was no violation of section 337. He found that claim 1 of the '035 patent was not infringed by any of the respondents' accused processes, that claim 1 was invalid as obvious under 35 U.S.C. § 103, and that the '035 patent was unenforceable because of complainants' inequitable conduct during reexamination proceedings before the U.S. Patent and Trademark Office. In a separate order (Order No. 52), issued on the same date, the ALJ granted respondents' motion for evidentiary sanctions against complainants.

On March 30, 1995, the Commission determined to review the following issues in the ID: (1) claim interpretation; (2) whether claim 1 of the '035 patent is infringed by respondents' processes; (3) whether claim 1 of the '035 patent is invalid as obvious under 35 U.S.C. § 103; (4) whether the '035 patent is unenforceable; and (5) Order No. 52. Order No. 52 was considered to

be part of the ID. The Commission posed several specific questions for the parties to address. The Commission also requested information on the status of the Abic respondents.

On April 13, 1995, complainants and respondents Abic Ltd. and Plantex U.S.A. (the Abic respondents) filed a joint motion to terminate the investigation as to the Abic respondents on the basis of a settlement agreement. Additionally, on April 13, 1995, Mr. James Gambrell, one of complainants' patent law experts, filed a motion to intervene in the investigation.

Having considered the subject ID, including Order No. 52, the briefs on review, and the responses to the briefs on review, it is hereby

ORDERED THAT --

1. The investigation is terminated with a finding of no violation of section 337 of the Tariff Act of 1930.

2. The ALJ's claim interpretation and findings that claim 1 of the '035 patent is not infringed by the processes in issue of the Profarmaco respondents and the Fermion respondents are affirmed.

3. The Commission takes no position on the ALJ's findings of invalidity and unenforceability in accordance with Beloit Corporation v. Valmet Oy, TVW Paper Machines, Inc. and the United States International Trade Commission, 742 F.2d 1421 (Fed. Cir. 1984).

4. Order No. 52 is vacated as moot.

5. The joint motion to terminate the investigation as to the Abic respondents is granted.

6. The motion to intervene filed by Mr. James Gambrell is denied.

7. The Secretary shall serve copies of this Order, and the forthcoming Commission opinion in support thereof, on the parties of record and on the Department of Health and Human Services, the Department of Justice, and the Federal Trade Commission, and publish notice thereof in the Federal Register.

By order of the Commission.

Donna R. Koehnke

Donna R. Koehnke
Secretary

Issued: June 1, 1995

UNITED STATES INTERNATIONAL TRADE COMMISSION
Washington, DC 20436

In the Matter of	) RECEIVED OFC OF THE SECRETARY U.S. INT'L TRADE	Investigation No. 337-TA-349
CERTAIN DILTIAZEM HYDROCHLORIDE AND DILTIAZEM PREPARATIONS	) '95 JUN -8 P4:57	

COMMISSION OPINION

Introduction

This investigation is before us for final disposition on review of an initial determination (ID) filed by the presiding administrative law judge (ALJ) on February 1, 1995. The ALJ found no violation of section 337 based on his findings that the patent claim at issue, claim 1 of U.S. Letters Patent 4,438,035 ('035 patent), was not infringed by any of the respondents, was not valid because it was obvious in view of the prior art, and was unenforceable due to inequitable conduct in its procurement. On review, we have determined to affirm the ALJ's claim interpretation and findings that claim 1 of the '035 patent is not infringed. We do not find it necessary to reach the issues of validity and enforceability, and therefore take no position on these issues. See Beloit Corporation v. Valmet Oy, TVW Paper Machines, Inc. and the United States International Trade Commission, 742 F.2d 1421 (Fed. Cir. 1984).

By virtue of the Commission's previous determination not to review the ALJ's findings on importation and the existence of a domestic industry, the ID's findings and conclusions on those issues became the Commission's final determination. See 60 Fed. Reg. 17366 (April 5, 1995).

Procedural History

On February 1, 1993, Tanabe Seiyaku Co., Ltd. (Tanabe) and Marion Merrell Dow, Inc. (MMD) (collectively "complainants") filed a complaint under section 337 alleging unfair acts in the importation and sale of diltiazem hydrochloride and diltiazem preparations (diltiazem). The complaint identified nine proposed respondents: (1) Abic Ltd. of Netanya, Israel ("Abic"); (2) Gyma Laboratories of America, Inc. of Garden City, New York ("Gyma"); (3) Profarmaco Nobel SRL of Milan, Italy; (4) Mylan Pharmaceuticals, Inc. of Morgantown, West Virginia; (5) Mylan Laboratories, Inc. of Pittsburgh, Pennsylvania (collectively referred to as the "Profarmaco respondents"); (6) Orion Corporation Fermion of Espoo, Finland; (7) Interchem Corporation of Paramus, New Jersey; (8) Copley Pharmaceuticals, Inc. of Canton, Massachusetts; and (9) Rhone-Poulenc Rorer, Inc. of Collegeville, Pennsylvania (collectively referred to as the "Fermion respondents"). Complainants alleged infringement of claim 1 of the '035 patent. On March 25, 1993, the Commission voted to institute an investigation of the complaint of Tanabe and MMD.

On May 6, 1993, complainants moved to amend the complaint and notice of investigation to add Plantex U.S.A., Inc. as a respondent. On May 20, 1993, the ALJ issued an ID amending the complaint and notice of investigation to add Plantex as a respondent.[1] The Commission determined not to review that ID. On June 17, 1993, the Abic respondents moved to designate the investigation "more complicated". This motion was granted on June 28, 1993.

On November 23, 1993, complainants filed a motion to suspend the investigation pending the outcome of reexamination proceedings before the U.S.

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[1] Plantex participated in this investigation with Abic. Plantex and Abic are collectively referred to as the "Abic respondents."

Patent and Trademark Office ("PTO") concerning the '035 patent. On November 23, 1993, the ALJ issued an ID suspending the investigation, which was not reviewed by the Commission. On August 29, 1994, the suspension of the investigation (which lasted about 8 months) was lifted following completion of the reexamination proceedings before the PTO. The PTO confirmed the patentability of all claims of the '035 patent, including claim 1, the claim at issue in this investigation.

The evidentiary hearing before the ALJ commenced on October 17, 1994, and concluded on November 3, 1994. The ALJ issued his final ID on February 1, 1995. Additionally, the ALJ issued an order (Order No. 52) granting respondents' motion for sanctions against complainants. Sanctions were imposed only as alternative relief, i.e., only if the Commission determined based on all the evidence of record that respondents infringed claim 1 of the '035 patent.

On February 21, 1995, complainants filed a petition for review of the ALJ's final ID. They also filed a separate petition for review of Order No. 52. On the same day, the Commission investigative attorney (IAs) filed a petition for review of the ALJ's domestic industry finding. On March 6, 1995, the IAs, the Fermion respondents, and the Profarmaco respondents filed oppositions to complainants' petition for review. Respondent Gyma Laboratories also filed an opposition to the petition for review, indicating that it principally relies on and concurs in the response filed by the Profarmaco respondents. The Abic respondents did not file an opposition to complainants' petition for review. Complainants indicated in their petition for review that they had settled their differences with the Abic respondents. Complainants further indicated that they were not therefore petitioning for

review of the portion of the ID that finds that the Abic process does not infringe claim 1 of the '035 patent. On March 2, 1995, complainants filed a motion for leave to file an affidavit by James Gambrell.

On March 30, 1995, we issued notice of our decision to review certain portions of the ID. 60 Fed. Reg. 17366. (April 5, 1995). In that notice, we set forth the issues for review as follows: (1) claim interpretation (2) whether claim 1 of the '035 patent is infringed by respondents' processes; (3) whether claim 1 of the '035 patent is invalid as obvious under 35 U.S.C. § 103; (4) whether the '035 patent is unenforceable; and (5) Order No. 52.[2] We also requested information on the status of the Abic respondents, in view of the fact that complainants had indicated in their petition for review that they had amicably settled their differences with the Abic respondents. With regard to the Gambrell affidavit, we stated that reopening the record to accept the affidavit at this late stage of the investigation would not be appropriate. We received briefs from the parties on those issues, and on the issues of remedy, the public interest, and bonding. We also received a joint motion from complainants and the Abic respondents to terminate the investigation as to the Abic respondents. Additionally, Mr. Gambrell filed a motion to intervene in this investigation with respect to the ALJ's findings on enforceability.

After consideration of the arguments and evidence on the issues under review, we affirm and adopt the ALJ's claim interpretation and findings that the claim 1 of the '035 patent is not infringed by either the Fermion or Profarmaco respondents. We also grant the joint motion to terminate the

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[2] Although issued as a separate order, Order No. 52 was considered by the Commission to be part of the ID.

investigation as to the Abic respondents. Accordingly, the issue of whether the Abic process infringes claim 1 of the '035 patent under the doctrine of equivalents is moot. Because we find no violation of section 337 based on the findings of noninfringement in the ID, we take no position on the issues of validity and unenforceability. Order No. 52, which was issued as alternative relief, is vacated as moot. Finally, Mr. Gambrell's motion to intervene is denied in view of the late stage of the proceedings. Further briefing on the issue of enforceability is not necessary. Moreover, as indicated above, we do not reach the issue of enforceability.

Claim Interpretation and Infringement

Complainants have alleged only that the accused processes of the Fermion and Profarmaco respondents infringe claim 1 of the '035 patent under the doctrine of equivalents. The ALJ found that none of respondents' accused processes infringe under the doctrine of equivalents. A party alleging infringement has the burden of proving infringement by a preponderance of the evidence. Assuming properly construed claims, infringement is a factual determination. Envirotech Corp. v. Al George, Inc., 730 F.2d 753, 758 (Fed. Cir. 1984). Any determination of patent infringement must result from a two-step process. First, a claim must be interpreted to determine its proper scope and meaning. Second, it must be determined whether an accused device or process is within the scope of the properly interpreted claim. Genentech v. Wellcome Foundation, 29 F.3d 1555, 1561 n.6 (Fed. Cir. 1994). Claim interpretation is accomplished through an examination of particular claim language, the patent specification, the prosecution history of the patent, and other claims. SRI Int'l v. Matsushita Electric Corp., 775 F.2d 1107, 1118 (Fed. Cir. 1985). Extrinsic evidence, including testimony of witnesses

concerning the meaning of disputed terms in a claim, is also relevant. Tandon Corp. v. ITC, 831 F.2d 1017, 1021 (Fed. Cir. 1987); Markman v. Westview Instruments, Inc., No. 92-1049 (Fed. Cir. April 5, 1995).

The ALJ interpreted claim 1 and found that none of the allegedly infringing processes infringed the claim under the doctrine of equivalents. We agree with the ALJ's interpretation of claim 1 and his findings that the processes at issue do not infringe that claim under the doctrine of equivalents. Accordingly, we adopt the portion of the ID pertaining to claim interpretation and infringement and the corresponding factual findings.[3] We have added additional comments to address Federal Circuit precedent decided after the issuance of the ID.

The invention claimed in claim 1 of the '035 patent is a method for forming a benzothiazepine derivative by condensing a substrate with 2-(dimethylamino)ethyl halide either in the presence of potassium hydroxide in acetone or in the presence of potassium carbonate in a solvent selected from acetone, lower alkyl acetate, a mixture of acetone and water, and a mixture of lower alkyl acetate and water, and if required, further converting the product into a pharmaceutically acceptable acid addition salt thereof. Thus, the claim at issue, and the specification, are drafted very specifically. ID at 10-16. Nonetheless, as stated by the ALJ, complainants propose an interpretation of claim 1 which on its face would cover an indeterminate number of bases and solvents. As the ALJ found, such an interpretation is divorced from the prior art, from any connection to the objectives stated in the patent, and from statements made by complainant Tanabe to the PTO, the

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[3] As noted above, we granted the joint motion to terminate the Abic respondents. Consequently, the findings in the ID regarding allegedly infringing Abic process are moot.

European Patent Office, and other foreign patent offices. ID at 11. Moreover, as recently stated by the Federal Circuit:

> An applicant should not be able deliberately to narrow the scope of examination to avoid during prosecution scrutiny by the PTO of subject matter with the objective of more quickly obtaining a patent (or avoiding the risk of estoppel), and then obtain in court, either literally or under the doctrine of equivalents, a scope of protection which encompasses that subject matter.

Genentech Inc. v. The Wellcome Foundation Limited, 29 F.3d 1555, 1564 (Fed. Cir. 1994).

Complainants' arguments focus in part on their assertions that the ALJ improperly interpreted the claims by using the representations made to the European Patent Office and the inventors' own internal laboratory notebooks to interpret claim 1, and hence to apply narrowly the doctrine of equivalents. Complainants also argue that one of respondents' experts admitted that claim 1 covers a "wide range of bases and solvents", and that the base/solvent combinations of respondents' processes are encompassed by claim 1. See, e.g., Complainants Response to The Commission Notice at 10-17.

A recent en banc decision by the Federal Circuit, Markman v. Westview Instruments, Inc., No. 92-1049 (Fed. Cir. April 5, 1995), is instructive on the use of extrinsic evidence in the interpretation of claims. Markman states that "the interpretation and construction of patent claims, which define the scope of the patentee's rights under the patent, is a matter of law exclusively for the court." Id. at 2. To ascertain the meaning of claims, three sources are considered: the claims, the specification, and the prosecution history. Markman at 18. Expert testimony, including evidence of how those skilled in the art would interpret the claims, may also be used. Id. at 20. The court noted that extrinsic evidence could be considered by the trier of fact to enable it to interpret the claims. Extrinsic evidence is

defined as consisting of all evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises. Id. Markman states that such evidence may be helpful to explain scientific principles, the meaning of technical terms, and terms of art that appear in the patent and prosecution history. Id. The court made clear, however, that extrinsic evidence is to be used to aid in understanding the patent, not for the purpose of varying or contradicting the terms of the claims. Id. at 21. This decision makes clear that through the process of construing claims by, among other things, utilizing extrinsic evidence that the court finds helpful and rejecting other evidence that is unhelpful, and resolving disputes en route to pronouncing the meaning of claim language as a matter of law based on the patent documents themselves, the court is not crediting certain evidence over other evidence or making factual findings. Id. at 22. Rather, the court is looking to the extrinsic evidence to assist in its construction of the written document, a task it is required to perform. Id. Claim construction, enlightened by such extrinsic evidence as may be helpful, is still based on the patent and prosecution history. Id. at 20.

Thus, it is clear from the Markman opinion that the use of extrinsic evidence, including inventor testimony, can be used by the trier of fact to aid in the understanding of the claims of a patent. Similarly, in Southwall Technologies, Inc. v. Cardinal IG Company, Slip Op. 94-1243 (Fed. Cir. May 10, 1995), the Federal Circuit stated that a patentee may not proffer an interpretation for the purposes of litigation that would alter the indisputable public record consisting of the claims, the specification, and the prosecution history, and treat the claims as a "nose of wax". Southwall Technologies, Inc., Slip Op. at 13, citing Senmed, Inc., 888 F.2d at 819 n.8,

12 USPQ2d at 1512 n.8. In other words, evidence extrinsic to the patent and prosecution history, such as expert testimony, cannot be relied on to change the meaning of the claims when that meaning is made clear by those documents. Southwall, Slip. Op. at 13.

The ALJ properly construed claim 1 of the '035 patent as a matter of law. He considered the claims, the specification, and the prosecution history. He also admitted evidence by experts on both sides of the issue, evidence of other relatively contemporaneous Tanabe patents, evidence of prior art that used broad language relating to bases and solvents, and the inventors' contemporaneous laboratory notebooks. The ALJ used the evidence to assist in understanding the patent, but did not use it for the purposes of varying or contradicting the terms of the patent. Based on his interpretation of the claim at issue, and considering all of the evidence, he concluded that claim 1 of the '035 patent should be construed to include its express language and a "very narrow range" of equivalents, which did not extend far enough to encompass the accused processes of the Profarmaco and Fermion respondents. We agree with that conclusion.

Conclusion

In view of our affirmance and adoption of the portion of the ID relating to claim interpretation and infringement, we find that there is no violation of section 337.

PUBLIC VERSION

UNITED STATES INTERNATIONAL TRADE COMMISSION
Washington, D.C.

In the Matter of	
CERTAIN DILTIAZEM HYDROCHLORIDE AND DILTIAZEM PREPARATIONS	Investigation No. 337-TA-349

INITIAL DETERMINATION
Administrative Law Judge Sidney Harris

Pursuant to the Notice of Investigation, 58 Fed. Reg. 16846 (Wednesday, March 31, 1993), this is the Administrative Law Judge's Initial Determination in the Matter of Certain Diltiazem Hydrochloride and Diltiazem Preparations, U.S. International Trade Commission Investigation No. 337-TA-349. Commission Interim Rule 210.53(a).[1]

The Administrative Law Judge hereby determines that no violation of § 337 of the Tariff Act of 1930, as amended, has occurred in the importation or sale of certain diltiazem hydrochloride and diltiazem preparations by reason of infringement of claim 1 of U.S. Letters Patent 4,438,035.

[1] The Commission's final rules became effective on August 31, 1994. However, the new rules do not apply to proceedings, such as this investigation, that were instituted before the effective date. See 59 Fed. Reg. 39020 (1994). Therefore, all Commission rules applied in this Initial Determination are interim rules.

PUBLIC VERSION

UNITED STATES INTERNATIONAL TRADE COMMISSION
Washington, D.C.

In the Matter of	)	
	)	
CERTAIN DILTIAZEM HYDROCHLORIDE AND DILTIAZEM PREPARATIONS	)	Investigation No. 337-TA-349
	)	

INITIAL DETERMINATION
Administrative Law Judge Sidney Harris

APPEARANCES:

For Complainant Tanabe Seiyaku Co., Ltd. and Marion Merrell Dow, Inc.:

S. Leslie Misrock, Esq.
Brian D. Coggio, Esq.
William J. Sipio, Esq.
Joseph Diamante, Esq.
Sandra Bresnick, Esq.
Marcia H. Sundeen, Esq.
PENNIE & EDMONDS

For Respondent Gyma Laboratories of America, Inc.:

Marvin R. Stern, Esq.
Michael R. Slobasky, Esq.
John E. McKie, Esq.
JACOBSON, PRICE, HOLMAN & STERN

For Respondents Abic Ltd. and Plantex U.S.A., Inc.:

Alan T. Bowes, Esq.
Charles R. Brainard, Esq.
Steven J. Lee, Esq.
Frederick H. Rein, Esq.
Suzanne Parker, Esq.
William T. Enos, Esq.
KENYON & KENYON

TABLE OF CONTENTS

FINDINGS OF FACT

I. PROCEDURAL HISTORY

By publication in the Federal Register on March 31, 1993, the Commission gave notice of the institution of an investigation under section 337 of the Tariff Act of 1930, as amended (19 U.S.C. § 1337), pursuant to an amended complaint filed by Tanabe Seiyaku Co., Ltd. Osaka, Japan and Marion Merrell Dow, Inc., Kansas City, Missouri ("Complainants") on March 23, 1993. The complaint, as amended, alleges violation of subsection (a)(1)(B)(ii) of section 337 in the importation into the United States, the sale for importation, and the sale within the United States after importation of certain diltiazem hydrochloride and diltiazem preparations alleged to be manufactured abroad by a method covered by claim 1 of U.S. Letters Patent 4,438,035, and that there exists an industry in the United States as required by subsection (a)(2) of section 337. The complaint requests that the Commission institute an investigation and, after a full investigation, issue a permanent exclusion order and permanent cease and desist orders.

On March 25, 1993, the Commission ordered that an investigation be instituted to determine whether there is a violation of subsection (a)(1)(B)(ii) of section 337 in the importation into the United States, the sale for importation, or the sale within the United States after importation of certain diltiazem hydrochloride and diltiazem preparations made abroad by a process allegedly covered by claim 1 of U.S. Letters Patent 4,038,035, and whether there exists an industry in the United States as required by subsection (a)(2) of section 337.

The Commission named Tanabe Seiyaku Co., Ltd. and Marion Merrell Dow, Inc. as the complainants, and the following companies as respondents:

Abic Ltd.
Netanya, Israel

Copley Pharmaceuticals, Inc.
Canton, Massachussets

Gyma Laboratories of America, Inc.
Garden City, New York

Profarmaco Nobel SRL
Milan, Italy

Mylan Pharmaceuticals, Inc.
Morgantown, West Virginia 26505

Mylan Laboratories, Inc.
Pittsburgh, Pennsylvania

Orion Corporation Fermion
Espoo, Finland

Interchem Corporation
Paramus, New Jersey

Rhone-Poulenc Rorer, Inc.
Collegeville, Pennsylvania

Juan Cockburn, Esq. and John M. Whealan, Esq., Office of Unfair Import Investigations, were designated as the Commission Investigative Attorneys. Notice of Designation of Additional Commission Investigative Attorney (September 9, 1993).

Chief Administrative Law Judge Janet D. Saxon designated Administrative Law Judge Sidney Harris to preside over this investigation.

A preliminary conference in this investigation was conducted on April 29, 1993. Appearances were made on behalf of complainants, all respondents and the Office of Unfair Import Investigations ("OUII").

On May 6, 1993, complainants moved to amend the complaint and notice of investigation to add a respondent. Motion Docket No. 349-10. On May 20, 1993, the administrative law judge issued Order No. 6, an initial determination amending the complaint and notice of investigation to add the

following company as a respondent in this investigation:

Plantex U.S.A., Inc.
Englewood Cliffs, NJ.

The Commission determined not to review Order No. 6. Notice of Commission Determination Not to Review an Initial Determination Amending the Complaint and Notice of Investigation to Add a Respondent. June 16, 1993.

On June 17, 1993, Abic respondents moved to designate the investigation "more complicated." Motion No. 349-24. The motion was granted in Order No. 14 on June 28, 1993.

On September 30, 1993, Fermion respondents moved for summary determination that claims 1-2 of U.S. Patent No. 4,438,035 are invalid under 35 U.S.C 102(b). Motion No. 349-64.

On November 16, 1993, Abic and Plantex respondents moved for Sanctions. Motion No. 349-91. This motion was granted in part. Order No. 52.

On November 23, 1993, complainants filed a motion to suspend this investigation in connection with reexamination proceedings at the Patent and Trademark Office ("PTO") concerning the '035 patent. Motion Docket No. 349-105. On November 24, 1994, the administrative law judge issued Order No. 33, an initial determination suspending this investigation. The initial determination was not reviewed. Notice of Commission Decision Not to Review an Initial Determination Suspending the Investigation (December 28, 1993).

On August 29, 1994, the suspension of this investigation was lifted, following completion of the reexamination proceedings during which the patentability bf all claims of the '035 patent was confirmed. Order No. 34.

All motions not previously ruled upon are hereby denied.

A. Tutorial

On October 4, 1994, a tutorial session in the nature of a prehearing

conference was held for the purpose of informing the administrative law judge of the basic chemistry involved in this investigation. No party objected to this tutorial session in which each of the parties was represented.[2]

The tutorial session was conducted by expert witnesses for the parties. No cross-examination of the experts was permitted. However, each of the non-governmental parties had one of their expert witnesses present information that they believed would be useful to establish as a matter of background, and each could object to inaccurate presentations by another party. OUII did not have an expert present information at the tutorial session. Dr. Baldwin presented on behalf of complainants.[3] Dr. Taylor presented on behalf of the Abic respondents. Dr. Taber presented on behalf of the Profarmaco respondents. Dr. Lindholm presented on behalf of the Fermion respondents.

The administrative law judge found the information covered during the tutorial session to be valuable, and the tutorial session to be an efficient way to inform the administrative law judge of the background chemistry of this

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[2] The tutorial session (including the subject matter to be covered therein) was discussed with the parties in advance. See Notice of September 29, 1994; Notice of September 30, 1994; Order No. 34; Order No. 40.

[3] It may be noted that no hearing testimony from Dr. Baldwin appears in the record. Dr. Baldwin was involved in the pre-hearing phase of this investigation on complainants' behalf. Dr. Baldwin was also expected to testify for complainants as a key expert witness at the hearing. However, counsel informed the administrative law judge and the other parties in the hearing room on the day his testimony was to commence that Dr. Baldwin could not be located at his hotel, and it was believed that he had taken ill. No details concerning Dr. Baldwin's whereabouts or condition were available to the administrative law judge for a period of days. A copy of a facsimile letter from Dr. Baldwin to complainants' counsel was belatedly submitted to the administrative law judge in which Dr. Baldwin stated that he had become ill prior to his scheduled hearing testimony, and expressed concern for any problems caused by his absence. See Tr. 473-488, 1146-1148, 1775-1776.

investigation.[4] The tutorial session may also prove useful to the Commission. A section of findings based on the tutorial session is included in the numbered findings of fact in this Initial Determination. The tutorial session was transcribed, and the transcript of the tutorial session is certified to the Commission as part of the record. In effect, it constitutes a specialized textbook of the chemistry involved in this investigation.

The hearing in the matter of Certain Diltiazem Hydrochloride and Diltiazem Preparations commenced on October 17, 1994 and concluded on November 3, 1994. All parties were represented at the hearing. In connection with the hearing, no party objected to the Commission's exercise of personal jurisdiction over the respondents, or to subject matter jurisdiction in this investigation.

This Initial Determination is based on the entire record of this proceeding. Proposed findings not herein adopted, either in form or in substance, are rejected as not being supported by the evidence or as involving immaterial matters.

The findings of fact include references to supporting evidentiary items in the record. Such references are intended to serve as guides to the depositions, exhibits, and testimony supporting the findings of fact; they do not necessarily represent complete summaries of the evidence supporting each finding. Some of the findings of fact are contained only in the opinion.

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[4] Tutorial sessions have been used by other judges as a way of gaining necessary background, particularly in cases involving complicated or specialized fields of science. See, e.g., Apple Computer, Inc. v. Microsoft Corp., 799 F. Supp. 1006, 24 U.S.P.Q.2d 1081 (N.D. Cal. 1992), order clarified on other grounds by 27 U.S.P.Q.2d 1081 (N.D. Cal. 1993), aff'd, 35 F.3d 1434, 32 U.S.P.Q.2d 1086 (9th Cir. 1994), petition for cert. filed, 63 U.S.L.W. 3518 (U.S. Dec. 19, 1994); Honeywell Inc. v. Sperry Rand Corp., 180 U.S.P.Q. 673 (D. Minn. 1973).

The following abbreviations are used in this Initial Determination:

CX - Complainant's Exhibit (followed by its number and the reference page(s)).

CPX - Complainant's Physical Exhibit

RX - Respondent's Exhibit (followed by its number and the reference page(s)).

RPX - Respondent's Physical Exhibit

FF - Finding of Fact

Dep.- Deposition

Tr.- Transcript

B. The Private Parties

1. Complainants

Tanabe Seiyaku Co., Ltd. ("Tanabe") is a Japanese corporation with its corporate headquarters at 2-10 Dosho-machi 3 Chrome, Chuo-ku, Osaka, 541 Japan. Tanabe is the owner of the '035 patent.

Marion Merrell Dow, Inc. ("MMD") is a Delaware corporation with a principal place of business at 9300 Ward Parkway, Kansas City, Missouri 64114.

2. Respondents[5]

Abic Ltd. ("Abic") is an Israeli corporation with a place of business at Industrial Zone 5, Hayozma Street. P O Box 2077, Kiryat Nordau, Netanya, Israel 52120.

Plantex U.S.A. ("Plantex") is a New Jersey corporation.

Orion Corporation Fermion ("Fermion") is a Finnish corporation with a place of business at Orioninitic 1, SF 02200 Espoo, Finland.

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[5] Respondents have generally grouped themselves into three categories, with each category including the foreign diltiazem HCl manufacturer and its associated importers and domestic manufacturers of dosage forms. Reference will sometimes be made herein to those groups by reference to the foreign manufacturer of bulk diltiazem, i.e., "Abic", "Fermion", and "Profarmaco".

Copley Pharmaceuticals, Inc. ("Copley") is a corporation organized under the laws of Delaware with a principal place of business at 25 John Road, Canton, Massachusetts 02021.

Interchem Corporation ("Interchem") is a corporation organized under the laws of New Jersey with a principal place of business at Route 120 North, Paramus, New Jersey 07652.

Rhone-Poulenc Rorer, Inc. ("Rhone-Poulenc") is a corporation organized under the laws of Pennsylvania with a place of business at 500 Arcola Road, Collegeville, Pennsylvania 19426.

Profarmaco Nobel SRL ("Profarmaco") is an Italian corporation with a principal place of business at Via Cucchiari, 20155 Milan, Italy.

Mylan Pharmaceuticals, Inc. ("Mylan Pharmaceuticals") is a corporation organized under the laws of West Virginia with a principal place of business at 781 Chestnut Ridge Road, Morgantown, West Virginia.

Mylan Laboratories, Inc. ("Mylan Labs") is a corporation organized under the laws of Pennsylvania with a principal place of business at 1030 Century Building, Pittsburgh Pennsylvania 15222.

Gyma Laboratories of America, Inc. ("Gyma") is a corporation organized under the laws of New York with a place of business at 65 Commercial Avenue, Garden City, New York 11530

II. INTERPRETATION OF CLAIM 1 OF THE '035 PATENT

A. General Law Applicable to Claim Interpretation

An analysis of validity and infringement allegations requires a proper construction of the patent claim at issue to determine its scope. Palumbo v. Don-Joy Co., 762 F.2d 969, 974 (Fed. Cir. 1985). Claims must be given the same meaning for validity and infringement analyses. White v. Dunbar, 119

U.S. 49, 51 (1886).

Furthermore, any determination of patent infringement must result from a two-step process. First, a claim must be interpreted to determine its proper scope and meaning. Second, it must be determined whether an accused device or process is within the scope of the properly interpreted claim. Genetech, Inc. v. Wellcome Found. Ltd., 29 F.3d 1555, 1561 n.6 (Fed. Cir. 1994)(citing Lemelson v. General Mills Inc., 968 F.2d 1202, 1206 (Fed. Cir. 1992), cert. denied, 113 S.Ct. 976 (1993)).

Claim interpretation is accomplished through an examination of particular claim language, the patent specification, the prosecution history, and other claims. SRI Int'l Matsushita Elec. Corp., 775 F.2d 1107, 1118 (Fed. Cir. 1985). Claims are normally construed as they would be by one of ordinary skill in the art, Fromson v. Advance Offset Plate, Inc., 720 F.2d 1565, 1571 (Fed. Cir. 1983), unless it is apparent that the patentee used claim language differently. Envirotech Corp. v. Al George, Inc., 730 F.2d 753, 759 (Fed. Cir. 1984). Courts may rely on expert testimony to determine how one of ordinary skill in the art would interpret claim language. Advanced Cardiovascular Sys. v. Scimed Life Sys., 887 F.2d 1070, 1073 (Fed. Cir. 1989); Medtronic, Inc. v. Intermedics, Inc., 799 F.2d 734, 742 (Fed. Cir. 1989). Extrinsic evidence including testimony of witnesses concerning the meaning of disputed terms in a claim is also relevant. Tanabe Corp. v. Int'l Trade Comm'n, 831 F.2d 1017, 1021 (Fed. Cir. 1987).

It is not necessary that a claim be amended in order for the prosecution history to limit the claim. As the Federal Circuit held in Hughes Aircraft Co. v. United States, 717 F.2d 1351 (Fed. Cir. 1983):

> The doctrine of prosecution history estoppel precludes a patent owner from obtaining a claim construction that would resurrect

> subject matter surrendered during prosecution of his patent application. The estoppel applies to claim amendments to overcome rejections based on prior art . . . and to arguments submitted to obtain the patent, Coleco Industries, Inc. v. ITC, 573 F.2d 1247, 1257, 197 U.S.P.Q. 472, 480 (Cust. & Pat. App. 1978).

717 F.2d at 1562 (emphasis added).[6]

With respect to an infringement analysis under the doctrine of equivalents, the Federal Circuit further stated in Hughes:

> The doctrine of equivalents is subservient to file wrapper estoppel. It may not include within its range anything that would vitiate limitations expressed before the Patent Office. Thus a patent that has been severely limited to avoid the prior art will only have a small range between it and the point beyond which it violates file wrapper estoppel.

717 F.2d at 1563 (quoting Autogiro Co. of America v. United States, 384 F.2d 391, 400-01 (C.C.P.A. 1967)).

Indeed, the Federal Circuit held more recently in North American Vaccine, Inc. v. American Cyanamid Co., 7 F.3d 1571 (Fed. Cir. 1993), as follows:

> A patent applicant cannot disclose and claim an invention narrowly and then, in the course of an infringement suit, argue effectively that the claims should be construed to cover that which is neither described nor enabled in the patent.

7 F.3d at 1577.

Also in Genetech the Federal Circuit said:

> An applicant should not be able deliberately to narrow the scope of examination to avoid during prosecution scrutiny by the PTO of subject matter with the objective of more quickly obtaining a patent (or avoiding the risk of an estoppel), and then obtain in court,

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[6] In Coleco, the court held that:

> We are in a position of enunciating a rule broader than the traditional "file wrapper" estoppel doctrine. A patentee having argued a narrow construction for his claims before the United States Patent and Trademark Office (PTO) should be precluded from arguing a broader construction for the purposes of infringement.

573 F.2d at 1257 (emphasis in original).

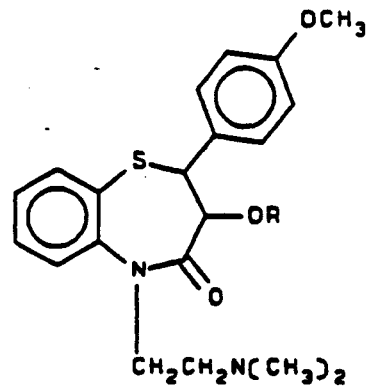
whether literally or under the doctrine of equivalents, a scope of protection which encompasses that subject matter.

29 F.3d at 1564 (citing North American Vaccine, 7 F.3d at 1577).

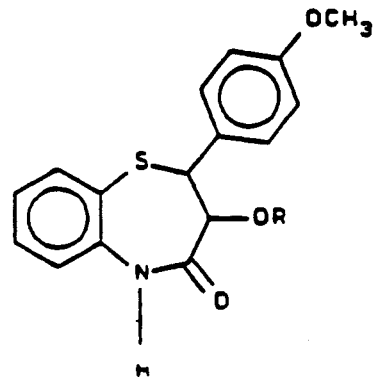
B. The Base/Solvent Combinations of Claim 1 of the '035 Patent

Claim 1 of the '035 patent is as follows:

A method of preparing a benzothiazepine derivative of the formula:



wherein R is hydrogen or acetyl, or a pharmaceutically acceptable acid addition salt thereof, which comprises condensing a compound of the formula:



wherein R is the same as defined above, with 2-(dimethylamino)ethyl halide either in the presence of potassium hydroxide in acetone or in the presence of potassium carbonate in a solvent selected from acetone, lower alkyl acetate, a mixture of acetone and water and a mixture of lower alkyl acetate and water, and if required, further converting the product into a pharmaceutically acceptable acid addition said thereof.

FF B 1.

Complainants allege that respondents infringe claim 1 of the '035 patent under the doctrine of equivalents, rather than by literal infringement. See, e.g., Complainants' Post-Trial Brief at 2. Consequently, complainants take the position that claim 1 of the '035 patent covers the base/solvent combinations specified therein, as well as others under the doctrine of equivalents. Complainants state the following:

> One skilled in the art would understand from reading the '035 patent that:
>
> (1) hydroxide and carbonate bases, other than the specific bases recited in the patent, can be interchanged for the bases set forth in the '035 patent;
>
> (2) solvents other than ones specifically mentioned in the '035 patent, which do not interfere with any of the reactions, are stable in water, and can dissolve the substrate, can be interchanged for the solvents set forth in the '035 patent; and
>
> (3) therefore, the '035 patent is not limited to the specific base/solvent combinations recited therein.

Complainants' Post-Trial Brief at 6-7. Complainants further contend inter alia that from reading the '035 patent, one of ordinary skill in the art would understand that there are no restrictions either on yield of the N-alkylated product, or on the rate or speed of the N-alkylation reaction. See Id. at 7-8.

Complainants propose an interpretation of the '035 patent which on its face would cover an indeterminate number of bases and solvents. This interpretation is divorced from the prior art, from any connection to the objectives stated in the patent and from other statements made by Tanabe to the PTO, the European Patent Office and other foreign patent offices. These sources all tend to show that Tanabe believed it had discovered certain specific base/solvent combination which would permit diltiazem or diltiazem

precursor to be made in high yield and in a safe and economical manner. The evidence in this investigation demonstrates that in the case of the '035 patent, the applicant submitted narrow claims, and arguments designed to limit the scope of the claims, thereby attempting to avoid the prior art. The law, as discussed above, in light of the undisputed facts will not allow the claim to be interpreted in the way proposed by complainants.

On January 17, 1983, the PTO received a Statement of Art from Tanabe's counsel, dated January 6, 1983. FF B 3. The statement called the examiner's attention to U.S. Patent No. 3,562,257 and Chem. Eng. News, 44 (15), 48 (1966). FF B 4. In order to differentiate the claimed invention of the '035 patent from the '257 patent (in which the N-alkylation of diltiazem was disclosed), Tanabe made a clear and succinct statement of what the claimed invention is, as follows:

> In contrast, Applicants' invention is the condensation of the acylated form of reference compound II (our II) without prior conversion to the alkali metal salt thereof but rather in the presence of potassium hydroxide in acetone or potassium carbonate in acetone, lower alkyl acetate, water-acetone, or water-lower alkyl acetate.

FF B 5. As seen in claim 1 and in the above statement, the inventors' chose to state their claim in the form of exact base/solvent combinations rather than in terms of categories of bases and solvents, which they had done in the '257 patent and other patents secured by Tanabe. See FF B 33-34, 40-42.

Tanabe distinguished the alleged invention of the '035 patent over the prior art '257 patent on the grounds that the precise base/solvent combinations claimed by Tanabe provide high yields under safe and economical

conditions.[7] In order to contrast the claimed invention of the '035 patent with the '257 patent, Tanabe represented to the PTO, as follows:

> In view of the fact that the instant invention eliminates entirely the dangerous prior art step of conversion into the alkali metal salt and reduces the two step process to a single step, Applicants' invention is not anticipated by the prior art. Furthermore, it is clear that the reference process yields are in the range of 65 to 70% when converting compound II to compound I. Applicants' invention, on the other hand, gives yields which are no less than 87%. It is therefore clear that applicants' invention is patentable over the prior art.

FF B 6 (emphasis added).

The yields reported in the examples in the '035 patent specification range from 87.3% to 92.7%. FF B 14-20. Indeed, in the experimentation conducted by Tanabe scientists in advance of the filing of the '035 patent, N-alkylations were considered failures if they did not result in high yields of diltiazem. Other base/solvent combinations which did not result in high yields in Tanabe's prior testing were not recited in the claim language, or mentioned to the PTO in connection with the claimed invention. FF B 88. Thus, the yield resulting from the N-alkylation is an integral part of the claimed invention.

One must view Tanabe's representations to the PTO as statements of one skilled in the art. In fact, the Federal Circuit has stated that one may go further and look at the patent as one skilled in the art who is also a prospective competitor seeking to rely on the patent and its prosecution history to avoid infringement. Hayes Int'l, Inc. v. Jessop Steel Co., 8 F.3d 1573, 1578 (Fed. Cir. 1993); Hoganas AB v. Dresser Indus., Inc., 9 F.3d 948, 954 (Fed. Cir. 1993).

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[7] In the '257 patent prosecution applicants sought process as well as product claims. The process claims were rejected by the examiner and abandoned by the applicant. RX 1130.

Tanabe limited the scope of its '035 patent application from the outset, rather than in response to a rejection from the patent examiner. Consequently, the claimed invention of the '035 patent cannot be construed to cover any method of producing diltiazem in any yield whatsoever. Rather, the '035 patent teaches only an improved method of N-alkylation that results in high yields. Furthermore, the '035 patent teaches only a specific set of base/solvent combinations in order to achieve those yields.

Claim 1 of the '035 patent identifies only two specific bases for use in the claimed N-alkylation reaction: potassium hydroxide and potassium carbonate. FF B 21. Every example of the '035 patent refers only to potassium bases. FF B 25.

The use of sodium bases is at issue in this investigation because of the processes used by some of the respondents. Yet, neither sodium hydroxide nor sodium carbonate is mentioned or referred to anywhere in the '035 patent for use as a base in the claimed N-alkylation reaction.[8]

The exclusive use of potassium bases is significant to one of skill in the art because sodium hydroxide and sodium carbonate are well-known bases. They are readily available and widely used in the chemical processing industry. Normally one might think of sodium bases in conjunction with potassium bases. FF B 29. Inasmuch as the cost of producing potassium carbonate is four to five times greater than the cost of producing sodium carbonate, sodium carbonate is almost always used for applications in which the two carbonates are equivalent chemically. FF B 30. Nonetheless, Tanabe restricted the '035 claim language to two potassium bases-- potassium

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[8] The only place in the '035 patent where sodium bases are discussed at all is in connection with the prior art '257 process. FF B 26.

hydroxide and potassium carbonate -- and excluded the sodium bases. FF B 31.

The terms "alkali metal hydroxides" and "alkali metal carbonates" are, and were, well-known terms which would have included potassium bases, sodium bases, and certain other bases. One of ordinary skill in the art would find it unlikely that the Tanabe scientists had inadvertently forgotten to mention sodium hydroxide or sodium carbonate when describing their invention in the '035 patent. FF B 32. Yet, nowhere in the specification of the '035 patent is there any mention of, or reference to, any specific alkali metal salts other than potassium salts in connection with the claimed N-alkylation. FF B 24. Nowhere in the specification of the '035 patent is there any mention of or reference to "alkali metal hydroxides" or "alkali metal carbonates." FF B 23. Other chemical process patents obtained by Tanabe during the relevant time frame used the phrase "alkali metal" and "alkali metal hydroxide."[9] In the case of the '035 patent, it is not surprising that Tanabe chose language that excluded sodium bases inasmuch as it had experienced failure in attempting to use sodium carbonate as a base, even in combination with acetone, which is one of the solvents of the '035 patent. FF B 86.

The evidence shows that a chemist of ordinary skill in the art would read claim 1 of the '035 patent to cover only potassium bases, and not sodium bases. FF B 22.

The '035 patent does not mention the use of any organic solvent other than acetone and lower alkyl acetates for use in the N-alkylation process. FF

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[9] E.g. U.S. Patent No. 4,416,819; U.S. Patent No. 4,443,615; U.S. Patent No. 4,438,044 and U.S. Patent No. 5,260,438. FF B 33. Additionally, in defining bases for use in the N-alkylation of TZP with DMC, the '257 patent includes the phrase "alkali metal" which it defines as: "alkali metal (e.g., sodium, potassium, etc.)." FF B 43.

B 35. It is particularly noteworthy that although the '035 patent disclosed a subclass of "lower alkyl acetates," it did not disclose a class or subclass of lower alkyl ketones. FF B 36. Rather, the disclosure of ketones was limited to a single ketone, i.e., acetone. FF B 37. The '035 patent disclosed in its examples the use of such solvents as ethanol, toluene, methanol, and chloroform in the work-up of the product of the alkylation, but does not teach that those solvents are useful as solvents for the N-alkylation reaction. FF B 39.

Tanabe knew how to disclose solvents generally when it wished to do so, and in a manner that is meaningful to one of ordinary skill in the art. In the '257 patent, Tanabe disclosed that the N-alkylation of that patent is carried out in "a solvent (e.g. dioxane, toluene, xylene, dimethylsulfoxide)." FF B 40. Thus, the disclosure of the '257 embraces a range of solvents from toluene to DMSO. FF B 41. Tanabe also disclosed broad ranges of solvents in its other patents. FF B 42.[10]

Therefore, one of ordinary skill in the art reading the '035 patent, especially in conjunction with the Statement of Art in which the specificity of the base/solvent combinations was emphasized, would conclude that the only solvents taught by the '035 patent as suitable for the claimed N-alkylation reaction were acetone and lower alkyl acetates, which in some cases may be mixed with water.

The limited nature of the base/solvent combinations that were known to

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[10] Tanabe's decision not to disclose the use of other ketones might have been based on experimental failures, such as Tanabe's failed TZP N-alkylation experiment with potassium hydroxide as the base and toluene as the solvent. FF 83-85. Testimony at the hearing by the inventors might have elucidated this subject further.

have worked to meet the objectives of the '035 patent, and its foreign counterparts, is further reflected in admissions made by Tanabe overseas. In that regard it is important to note that instructions given to foreign counsel and representations to foreign patent offices must be considered when they comprise relevant evidence. Caterpillar Tractor Co. v. Berco, S.P.A., 714 F.2d 1110, 1116 (Fed. Cir. 1983).

With respect to the '035 counterpart applications in Finland, Israel and the European Patent Office ("EPO"), Tanabe did not take the preventive measures that it did at the PTO, i.e., to prevent a rejection of the application over the prior art by limiting the claims from the outset. The '035 counterpart applications were initially rejected by all three of those patent offices (all citing U.S. Patent No. 3,075,967 to Krapcho).

The European examiner reasoned as follows:

> The problem is solved by replacing the bases of the prior art (A) [the '257 patent] (alkali metal, alkali metal hydride or an alkali metal amide) by potassium hydroxide or potassium carbonate and the solvents of the prior art (A) (dioxane, toluene, xylene and dimethylsulfoxide) by acetone, alkyl acetate, a mixture of acetone and water and a mixture [of] alkyl acetate and water. Firstly, it cannot be seen, at present, what kind of improvement is obtained by such a modification. Secondly, the solution to the problem which avoids the use of sodium hydride and dimethylsulfoxide is obvious to the man skilled in the art, since the replacement of certain unsatisfactory bases and solvents by very common bases (for instance the base alkali metal hydroxide is used in document (B) [the Krapcho '967 patent] for a similar reaction) belongs to the routine work of a man skilled in the art. Thus in the absence of any evidence of a surprising effect, the process lacks an inventive step (Articles 52(1) and 56). Therefore, at present, the Claims 1 to 7 are not considered to be patentable.

FF B 89.

In response to these rejections by the three foreign patent offices, Tanabe argued that the invention was patentable over the alkali metal hydroxide base of the '967 patent because Tanabe's five specific base/solvent

combinations gave unexpectedly better results than other combinations of bases and solvents, including combinations which contained either the base, or the solvent, of the '035 combinations, but not both. FF B 91. In support of that argument, Tanabe submitted a Comparative Test Report to show the European and other examiners that the five specific base/solvent combinations were better than other base/solvent combinations, even combinations which included one of the '035 bases or one of the '035 solvents. FF B 92. Tanabe presented data in the Comparative Test Report showing that the potassium hydroxide-acetone combination was superior to combinations of potassium hydroxide with other solvents such as dioxane or toluene. FF B 93. Tanabe also presented data showing that the potassium hydroxide/acetone combination was superior to combinations of acetone with another alkali metal base, sodium hydroxide. FF B 95.

Based on the experimental data reflected in the Comparative Test Report, Tanabe argued that its invention, as limited to the five specific base/solvent combinations, was not obvious:

> Judging from the facts (i) that [Krapcho] teaches neither the use of potassium carbonate as the base nor the use of specific base-solvent combinations to be employed in the method of the present invention; (ii) that, when the condensation reaction was carried out by the use of sodium hydroxide or sodium carbonate as the base, the yield of the product was less than 10%; and (iii) that, even if potassium hydroxide or potassium carbonate was used as the base, the yield of the product was less than 30% in the case where dioxane, toluene or methanol was used. It is believed that the above mentioned advantages of the present invention have never been taught or suggested by [Krapcho]. Thus the specific base-solvent combinations of the present invention is not obvious.

FF B 96.

Tanabe made the identical arguments and submitted the same Comparative Test Report in response to rejections by the Israeli and the Finnish patent offices. FF B 97. Patents were granted to Tanabe from the EPO, Israeli

Patent Office and the Finnish Patent Office only after Tanabe provided experimental evidence showing the surprising results obtained from the five specific base/solvent combinations actually disclosed and claimed. FF B 98.

In addition to complainants' contentions concerning bases and solvents, complainants take the position that:

> One skilled in the art would readily know that the '035 patent teaches the use of water through a reading of claim 1 which mentions water; through the disclosure of wet solvents in the patent; and through a chemical understanding that water is generated when hydroxide ions react with the DMC·HCl and the TZP substrate.

Complainants' Post-Trial Brief at 7.

As stated above, the plain language of the claims shows that when potassium carbonate is used as the base, claim 1 of the '035 patent covers an N-alkylation reaction "in a solvent selected from acetone, lower alkyl acetate, a mixture of acetone and water and a mixture of lower alkyl acetate and water." FF B 1. Thus, the claim permits the choice of water with acetone or lower alkyl acetate, when potassium carbonate is the base. The claim does not require the use of water.

The optional nature of the use of water is supported by the patent specification. The only specific mention of the use of water in the '035 patent relates to added water, i.e., water that is physically added by the operator of the process. FF B 72. The reference in claim 1 of the '035 patent to a "mixture of acetone and water and a mixture of lower alkyl acetate in water," relates solely to physically added water, as taught for example in the specification as follows:

> Concomitantly, when the mixed solvent (i.e., a mixture of acetone and water or a mixture of lower alkyl acetate in water) is used as the solvent, it is preferred to carry out the reaction by refluxing a mixture of the compound (II), the compound (III), potassium carbonate and acetone or lower alkyl acetate, <u>adding water</u> to the mixture and then further refluxing the aqueous mixture. In this

case, a suitable amount of water to be added is 0.01 to 0.1 ml per ml of acetone or lower alkyl acetate.

FF B 73.

The relative unimportance given to the use of water in the '035 patent is underscored by Examples 4 and 5, which use potassium carbonate, and do not mention any added water.[11]

The combinations of potassium carbonate and acetone (without added water) or potassium carbonate and lower alkyl acetate (without added water) will not generate water during the claimed N-alkylation process because the reaction temperatures at which the claimed process is carried out in the preferred embodiments are too low to cause the decomposition of potassium bicarbonate to form water, which would be evidenced by the evolution of carbon dioxide. FF B 79.

An October 1991, "Process Development Study for the Manufacture of Diltiazem Hydrochloride" by the Chemistry Technology Division of Tanabe reported that when the N-alkylation of TZP was carried out using C

C as the base and C as the solvent:

C
C
C
C
C
C

C

FF B 80 (emphasis added). The reaction did not proceed at C mL with C

C because the C was too low. The reaction also did not

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[11] Contrary to the '035 specification, experiments performed by Tanabe scientists in 1981 demonstrated that using C as the base in the '035 process without C . FF B 76. When Examples 4 and 5 of the '035 patent, which specify no added water, were run with powdered potassium carbonate and no added water, the N-alkylation reaction did not proceed. FF B 77.

proceed at C with C water because the amount of water was more than would dissolve in the ethyl acetate. At C with C water, enough water was in solution so that the reaction proceeded. FF B 81.

It has not been explained why Tanabe reported yields in Examples 4 and 5 of the '035 patent when their experimentation showed the reaction did not proceed under these condition. The possible explanation offered by Tanabe is that the acetone and ethyl acetate contained water. However, nowhere is the purity (e.g., water content) of either the acetone or ethyl acetate used in Examples 4 and 5 in the '035 patent mentioned. FF B 78. Another explanation is that Examples 4 and 5 are incorrect, since they are not repeatable using the directions of the '035 patent. FF B 78. They do not teach the use of water in the reaction and could not be duplicated in the testing done for this investigation.

Further, according to the claim language, when potassium hydroxide is used as the base in the N-alkylation process of claim 1 of the '035 patent, it is only used in combination with acetone. In contrast to the teachings about potassium carbonate, the '035 patent teaches that potassium hydroxide can be used only with acetone, and that it cannot be used with mixtures of acetone and added water. FF B 49. Indeed, in Example 1, the only example in the patent using potassium hydroxide, sodium sulfate, a well-known drying agent, is used in large amounts by stirring it with the potassium hydroxide/acetone combination. FF B 50. Thus, the '035 patent teaches that when potassium hydroxide is the base, if any water is initially present in the acetone solvent or is formed in the reaction, it should be removed. FF B 51.[12]

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[12] Instead of calling the inventors to testify about why the drying agent is added - whether to remove water from the process as respondents' claim or for (continued...)

Therefore, water is disclosed to be an optional component in the potassium carbonate embodiments of the claimed invention. The '035 patent

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[12](...continued)
another reason, the complainants attempted to put their own gloss on the patent specification through the testimony of an expert witness:

> BY MR. COGGIO:
>
> Q Do you recall some testimony about the sodium sulfate being added to Example 1 in the patent?
>
> A Yes.
>
> Q Does that to you indicate water is not present in Example 1?
>
> A No.
>
> Q Is water present before the reaction begins?
>
> A Water is probably present in the solvent because there's no statement saying they're using dry acetone, nor is there any attempt to specifically carry out the reaction in protected conditions. In many cases, if a chemist wants to do an anhydrous system, carry out a reaction under anhydrous conditions the experiment will specify this is done under an inert atmosphere such as dry nitrogen or a closed system so atmospheric water will not get in. We all know and we take a lot of efforts to avoid this, we all know solvents which are exposed to the air contain water.
>
> JUDGE HARRIS: But in Example 1, Dr. Kende, don't you think it was the intent of the inventors to have -- to remove water from the system.
>
> THE WITNESS: Yes, that's what they say. They say they added sodium sulfate and they indicate they act -- it acts as a dehydrating agents. But, Your Honor, if you take no extraordinary steps to dry acetone my experience is acetone is sopping wet. It is very difficult to tell, but my guess is they are trying to minimize the huge amount of water that is normally present in lab acetone. Water is generated during the reaction both from KOH and DMC hydrochloride and as the reaction proceeds.

Kende Tr. 3396-3397.

Dr. Kende's "guess" is not informed by consultation with the inventors or confirmed by any other statement in the patent or prosecution history.

also teaches the removal of water from the embodiment using potassium hydroxide. Water is not therefore taught as an essential component of either embodiment. FF B 48. Furthermore, nothing in the '035 patent explicitly teaches that water is involved in the way in which the claimed N-alkylation process works. FF B 69. Nowhere in the '035 patent is there any explicit teaching that water is critical to the success of the claimed N-alkylation reaction.[13] FF B 70. Therefore, a chemist of ordinary skill in the art reading the claims and examples of the '035 patent would not conclude that water is necessary for the claimed N-alkylation process. FF B 70.

In this case the usual circumstance that an inventor need not put every equivalent in the patent claim in order to receive the benefits of the doctrine of equivalents is reversed. Chemists of ordinary skill in the art would know that there were many potential equivalents to the bases and solvents stated in the claim if the object was merely to yield some percentage of diltiazem. FF B 102. The inventors of the '035 patent through their choice of claim language, their Statement of Art submitted to the PTO, the examples in the patent specification, and the admissions made to the EPO, and other foreign patent offices, show they intended to exclude all bases and solvents other than as particularly claimed, including those that might generally be thought of as equivalent, because the inventors believed that only through the unique base/solvent combinations stated could their requirements to produce diltiazem in high yield be realized. Thus, the '035 patent is an improvement patent based on precisely defined base/solvent combinations.

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[13] As shown above, Tanabe came to their conclusion concerning the criticality of water in 1991 in refining its commercial process.

As the Supreme Court held in White v. Dunbar:

> The claim is a statutory requirement, prescribed for the very purpose of making the patentee define precisely what his invention is; and it is unjust to the public, as well as an evasion of law, to construe it in a manner different from the plain import of its terms.

119 U.S. at 52. Thus, the '035 patent must not be construed to include subject matter that Tanabe did not place before the examiner during prosecution, and which the examiner therefore did not have the opportunity to approve or reject.[14]

Further, the art surrounding the claimed invention of the '035 patent is crowded with references that N-alkylate TZP, the substrate of the '035 patent, and similar chemical compounds, and solve many of the stated problems with the N-alkylation disclosed in the '257 patent.[15]

Therefore, claim 1 of the '035 patent is entitled for the purpose of proving infringement to a very narrow range of equivalents.

C. Acetylation Is Not Included in Claim 1 of the '035 Patent

It is undisputed that Tanabe sends bulk diltiazem to MMD for formulation

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[14] In Unique Concepts, Inc. v. Brown, 939 F.2d 1558, 1562, 19 U.S.P.Q.2d 1500, 1504 (Fed. Cir. 1991), the Federal Circuit held as follows:

> The statute requires that an inventor particularly point out and distinctly claim the subject matter of his invention. 35 U.S.C. § 112 (1988). It would run counter to this statutory provision for an applicant for patent to expressly state throughout his specification and in his claims that his invention includes [a limitation] and then be allowed to avoid that claim limitation in a later infringement suit by pointing to one paragraph in his specification stating an alternative that lacks that limitation, and thus interpret the claim contrary to its plain meaning. Such a result would encourage an applicant to escape examination of a more broadly-claimed invention by filing narrow claims and then, after grant, asserting a broader scope of the claims based on a statement in the specification of an alternative never presented in the claims for examination.

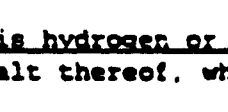
[15] See, infra, section on validity.

into dosage form, and further that diltiazem is not merely N-alkylated TZP, but rather the acetylated form of N-alkylated TZP. See Complainants' Proposed Findings of Fact at 30; Complainants' Post-Trial Brief at Brief at 4. Acetylation occurs in the Tanabe manufacturing process after the N-alkylation step.

Consequently, in opposition to complainants' contention that a domestic industry exists, respondents have made a series of arguments in this investigation pertaining to the issue of whether claim 1 of the '035 patent covers the Tanabe process through acetylation, or whether the product transferred from Tanabe to MMD is at least one step removed from the process of the '035 patent because of the acetylation that occurs after N-alkylation.[16]

Therefore, it is necessary to determine whether claim 1 of the '035 patent covers an acetylation step that is performed after N-alkylation.

The plain language of the claim defines formula II (as shown below) as a starting material in which R (found after the oxygen on the thiazepine ring) may be hydrogen or acetyl:

> A method of preparing a benzothiazepine derivative of the formula:
>
> 
>
> wherein R is hydrogen or acetyl, or a pharmaceutically acceptable acid addition salt thereof, which comprises condensing a compound of the formula:
>
> 

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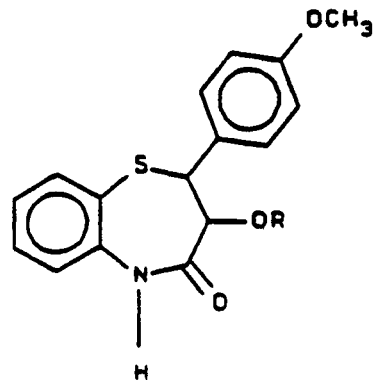
[16] The pharmaceutical compound is in fact diltiazem hydrochloride. However, there is no dispute that claim 1 covers hydrochlorination. Indeed, the plain language covers conversion of the N-alkylation product into "a pharmaceutically acceptable acid addition salt," and hydrochlorination is performed in one of the Examples in the specification. See Kende Tr. 560-564.



wherein R is the same as defined above . . . .

FF B 1 (emphasis added).

When R in the starting material is acetyl (i.e., when the substrate is TZP-OAc), then R in the product of the N-alkylation (formula I) is acetyl. This product would not therefore have to undergo an additional acetylation step. However, when R in the starting material is hydrogen (i.e., when the substrate is plain TZP), then R in the product is hydrogen. This product would have to be acetylated to obtain diltiazem. FF B 103.

In the C process, R is H (hydrogen) in both the starting material and the product of the N-alkylation. FF B 104. Consequently, the product of the N-alkylation in C process must undergo an additional acetylation step.

Complainants contend that to one skilled in the art, the '035 patent teaches the conversion of the diltiazem intermediate (compound I where R is hydrogen) to diltiazem where R is acetyl, especially since acetylation is a standard reaction in organic chemistry. Complainants take the position that the specification clearly indicates that the invention of the '035 patent covers processes for the manufacture of diltiazem. Complainants' Post-Hearing Brief at 3-5.

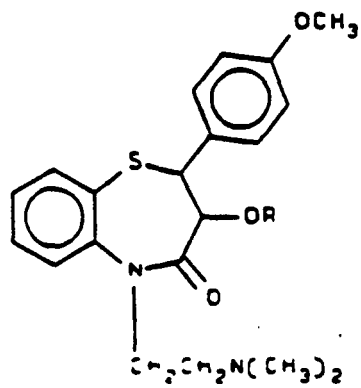
However, the portion of the specification relied on by complainants teaches two compounds: (1) diltiazem which is the result of N-alkylating acetylated TZP and (2) diltiazem intermediate which is the result of N-alkylating plain TZP. The specification provides in pertinent part as follows:

> The benzothiazepine derivative (I) in which R is aetyl [sic], especially cis-(+)-2-(4-methoxyphenyl)-3-acetoxy-5-[2-(dimethylamino)ethyl]-2,3-dihydro-1,5-benzothiazepine-4(5H)-one, is useful as a coronary vasodilator. On the other hand, the benzothazepine derivative (I) in which R is hydrogen, especially cis-(+)-2-(4-methoxyphenyl)-3-hydroxy-5-[2-(dimethylamino)ethyl]-2,3-dihydro-1,5-benzothiazepine-4(5H)-one, is useful as an intermediate of the above-mentioned coronary vasodilator.

FF B 103 (emphasis added).

The fact that the '035 patent teaches how to obtain either of two distinct products is of course reflected in claim 1, as follows:

> A method of preparing a benzothiazepine derivative of the formula:



> wherein R is hydrogen or acetyl, or a pharmaceutically acceptable acid addition salt thereof, which comprises condensing a compound of the formula . . . .

FF B 1 (emphasis added).

There is no explicit language anywhere in the '035 patent disclosing acetylation of the N-alkylated product when R in the starting material is

hydrogen. FF B 108.

No acetylation step is referred to or discussed in any of the seven examples of the '035 patent. FF B 109. In contrast, the only explicit reference to acetylation in the '035 patent is a preparation example to convert the starting material where R is hydrogen (TZP) to the starting material where R is acetyl (TZP-OAc). FF B 110.

One of ordinary skill in the art would know that where R is hydrogen, acetylation must occur in order to obtain diltiazem. However, the fact is that the '035 patent does not proceed to claim the acetylation step, and claims only the means by which the extra acetylation step may be avoided through the use of N-alkylated TZP (TZP-AOc) as the starting material.

Complainants have stressed that the acetylation step one would carry out on the N-alkylated TZP is common knowledge to those skilled in the art. That assertion raises the question whether Tanabe failed to claim the acetylation step because such a step would not be patentable due to lack of novelty, whereas the use of acetylated TZP in the N-alkylation reaction was something that was believed to be innovative. In any event, the '035 patent clearly disclosed two products, and left it to one of skill in the art to acetylate the diltiazem intermediate in the manner that is deemed appropriate.

While taking the position that the '035 patent must claim the acetylation step, complainants, relying on the Hybritech case[17] take the position that Tanabe need not have included acetylation of the diltiazem intermediate in claim 1 because a patent need not teach and preferably omits what is already well known in the art. Complainants' Post-Trial Brief at 4 (citing

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[17] Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987).

Complainants' Proposed Conclusion of Law 16). However, in the portion of Hybritech relied on by complainants, the Federal Circuit held that a patent need not teach, and preferably omits, that which what is well known in the art in connection with the enablement requirement of 35 U.S.C. § 112. There is no indication in the Federal Circuit's opinion that a patent applicant is relieved of the requirement of 35 U.S.C. § 112 (second paragraph) that the subject matter which the applicant regards as his invention be distinctly claimed.

Complainants also take the position that the '257 patent adds significantly to the interpretation of claim 1 of the '035 patent because the '257 patent is fully incorporated by reference in the '035 patent, and further that the '257 patent describes an acetylation step that can be readily used to produce diltiazem as claimed in the '035 patent. Complainants' Post-Trial Brief at 4 (citing Complainants' Proposed Conclusion of Law 17).

However, complainants have not presented legal authority for the proposition that incorporation of another patent in a specification may be used to expand the coverage of a claim. Indeed, a process claim "cannot be expanded to include additional process steps found in the specification but not expressly claimed." Phillips Petroleum Co. v. U.S. Steel Corp., 604 F. Supp. 555, 565 (D. Del. 1985). See also In re Seversky, 474 F.2d 671, 674 (C.C.P.A. 1973)("[A] mere 'reference' to another application, or patent, or publication is not an 'incorporation' of anything therein into the application containing such reference for the purposes of the disclosure required by 35 U.S.C. § 112."). Furthermore, in order to gain any benefit through incorporation, one must "clearly identify the subject matter which is incorporated and where it is to be found." Id. In this instance, the

references to the '257 patent are by way of background and do not specifically refer to acetylation. FF B 114.

Tanabe knew how to specify steps in addition to the alkylation step when it wanted them to be covered in a claim. FF B 112. For example, Tanabe expressly included formation of an acid addition salt as an optional step in claim 1 of the '035 patent. FF B 113. Furthermore, Tanabe's application for the '257 patent contained a claim 89 for the N-alkylation of TZP. FF B 115. The '257 application also had claim 90 which expressly recited an acetylation step to follow the alkylation step of claim 89. FF B 116.[18] In addition, Tanabe's British patent that corresponds to the '257 patent contains process claims, including one that expressly covers acetylation of N-alkylated TZP. FF B 118.

Complainants have not demonstrated that one of ordinary skill in the art would read the '035 patent to cover acetylation after N-alkylation in order to obtain diltiazem. Indeed, the evidence shows that the '035 patent discloses two distinct N-alkylation products, one of which is explicitly not-actylated.

III. CLAIM 1 OF THE '035 PATENT IS NOT INFRINGED

A. General Law Applicable to the Doctrine of Infringement

A party alleging infringement has the burden of proving infringement by a preponderance of the evidence Assuming properly construed claims, infringement is a factual determination. In re Certain Doxorubicin, 20 U.S.P.Q.2d 1602, 1608 (1991)(citing Envirotech Corp. v. Al George, Inc., 730 F.2d 753 (Fed. Cir. 1984)).

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[18] As it was issued, the '257 patent contains a detailed explanation of acetylation in the specification. FF 117.

None of the manufacturing respondents uses the combinations of bases and solvents expressly claimed by claim 1 of the '035 patent. Therefore, complainants do not contend that respondents literally infringe. Complainants take the position that respondents should be found to infringe claim 1 of the '035 patent under the doctrine of equivalents. Complainants' Post-Trial Brief at 2.

The doctrine of equivalents "permits infringement to be found if the accused device or process performs substantially the same function in substantially the same manner to achieve substantially the same result." Doxorubicin, 20 at 1608 (citing Graver Tank & Mfg. Co. v. Linde Air Prods. Co., 339 U.S. 605 (1950)). A finding of equivalency is a factual determination. Doxorubicin, 20 U.S.P.Q.2d at 608 (citing Graver Tank at 609).

Complainants contend that "[a]ccording to Graver Tank, 339 U.S. at 609, the test of equivalency is determined by interchangeability." Complainants' Post-Trial Brief at 8 (emphasis in original). Complainants' statement, however, does not accurately reflect the law of equivalents as stated by the Supreme Court in Graver Tank. Complainants' citation to "interchangeability" is contained in the following paragraph of the Graver Tank opinion:

> What constitutes equivalency must be determined against the context of the patent, the prior art and the particular circumstances of the case. Equivalence, in the patent law, is not the prisoner of a formula and is not an absolute to be considered in a vacuum. It does not require complete identity for every purpose and in every respect. In determining equivalents, things equal to the same thing may not be equal to each other and, by the same token, things for most purposes different may sometimes be equivalents. Consideration must be given to the purpose for which an ingredient is used in a patent, the qualities it has when combined with other ingredients, and the function which it is intended to perform. An important factor is whether persons reasonably skilled in the art would have known of the interchangeability of an ingredient not contained in the patent with one that was.

339 U.S. at 609 (emphasis added).

Interchangeability if known by persons reasonably skilled in the art is as the Supreme Court called it a "factor" that must be considered along with the "particular circumstances of the case." "Equivalence is not the prisoner of a formula." The purpose for which an ingredient is used in a patent must be considered.

A fraud on a patent occurs only when a person appropriates an invention, while making insubstantial changes to avoid the literal language of the claims. Graver Tank, 339 U.S. at 607-08. Indeed, the Federal Circuit emphasized the Graver Tank rationale that it is only to "insubstantial" changes that the doctrine of equivalents may be applied:

> [W]here an infringer, instead of inventing around a patent by making a substantial change, merely makes an insubstantial change, essentially misappropriating or even "stealing" the patented invention, infringement may lie under the doctrine of equivalents.

London v. Carson, Pirie, Scott & Co., 946 F.2d 1534, 1538 (Fed. Cir. 1991).

The use of the doctrine of equivalents is limited by prosecution history estoppel. But, it is not necessary that a claim be amended in order for the prosecution history to limit the claim. As the Federal Circuit held in Hughes Aircraft Co. v. United States, 717 F.2d 1351 (Fed. Cir. 1983):

> The doctrine of prosecution history estoppel precludes a patent owner from obtaining a claim construction that would resurrect subject matter surrendered during prosecution of his patent application. The estoppel applies to claim amendments to overcome rejections based on prior art . . . and to arguments submitted to obtain the patent, Coleco Industries, Inc. v. ITC, 573 F.2d 1247, 1257, 197 U.S.P.Q. 472, 480 (Cust. & Pat.App. 1978).

717 F.2d at 1362 (emphasis added).

The test for equivalence is an element by element comparison. Pennwalt Corp. v Durand-Wayland, Inc., 833 F.2d 931, 4 U.S.P.Q.2d 1737 (Fed. Cir. 1987), cert. denied, 485 U.S. 961, 485 U.S. 1009 (1988). The Federal Circuit

has held that the "doctrine of equivalents cannot be used to erase meaningful structural and functional limitations of the claim on which the public is entitled to rely in avoiding infringement." Conopco, Inc. v May Dep't Stores Co., 32 U.S.P.Q.2d 1225, 1226 (Fed. Cir. 1994)(citing Pennwalt, 833 F.2d at 935, 4 U.S.P.Q.2d at 1739). Similarly, the doctrine of equivalents cannot be used to create new limitations where none exist in the patent. See, e.g., Talk To Me Prods. Inc. v Lanard Toys Inc., 31 U.S.P.Q.2d 1062, 1063 (Fed. Cir. 1994).

B. The Profarmaco Process Does Not Infringe Claim 1 of the '035 Patent

The evolution of the Profarmaco process evidences an intent to design around the '035 patent, and an intent not to copy the '035 patent process.

In approximately late 1982, Profarmaco began work to synthesize diltiazem. FF CP 1. Using the German counterpart to the '257 patent, one of the Profarmaco scientists, Dr. Piselli, ran several experiments involving the N-alkylation step. FF CP 2. In these experiments, he used sodium hydride and anhydrous dimethylformamide ("DMF") to become more familiar with the N-alkylation of TZP. FF CP 3.

Knowing that sodium hydride is unacceptable for commercial scale synthesis, Dr. Piselli almost immediately tried potassium carbonate and DMF. FF CP 4. The potassium carbonate/DMF combination was selected because of a 1978 article by Professor Makosza (an organic chemist known as the "inventor of phase transfer") which specifically disclosed the use of potassium carbonate and DMF in similar reactions. FF CP 5.

The Makosza article described the possibility of replacing the reagents described in the '257 patent with potassium carbonate and DMF. FF CP 6. The article specifically described the advantages of potassium carbonate/DMF over

sodium hydride, including the elimination of potentially dangerous reactions caused by anhydrous organic solvents. FF CP 7. Dr. Piselli had previously used such a system at Profarmaco, and he therefore followed Makosza's suggestions and tried potassium carbonate/DMF in his first experiments. FF CP 8.

The potassium carbonate/DMF process -- the first one that Dr. Piselli tried -- was successful. Within two months, Dr. Piselli had developed an industrial process using potassium carbonate/DMF. FF CP 9-10. Profarmaco used this process for producing bulk diltiazem from approximately mid-1983 to July 15, 1986. FF CP 11.

In order to increase the consistency of the yield, Profarmaco experimented with the addition of water to the reaction and found that C C (by volume) of water caused more consistent yields. During the summer of 1986, Profarmaco therefore modified its process to include the addition of C water to its potassium carbonate/DMF process. FF CP 12.

Shortly after December 30, 1986, Profarmaco first learned from a French pharmaceutical firm, Sanofi, of Tanabe's European patent application corresponding to the '035 patent. FF CP 13. This was the first time anyone at Profarmaco became aware of the existence of the '035 patent or any of its equivalents or counterparts. FF CP 14.

Profarmaco reviewed the European '035 counterpart patent application, and concluded that its potassium carbonate/DMF process did not infringe. FF CP 15. Profarmaco therefore continued using this process for five additional years. FF CP 16.

In April 1989, after expiration of the '257 patent, Gyma, Profarmaco's exclusive agent in the United States, wrote to MMD requesting disclosure of

any process patents which MMD contended might cover processes for the manufacture of diltiazem. FF CP 17. MMD responded shortly thereafter by identifying four patents, including the '035 patent. FF CP 18. Gyma forwarded MMD's process patent disclosure letter to Profarmaco for review. After reviewing the '035 patent, Profarmaco continued to use its potassium carbonate/DMF process. FF CP 19,20.

On June 13, 1991, Profarmaco received from its Italian patent attorneys (in connection with an inquiry from Profarmaco on a different matter) Tanabe's October 1, 1984 submission to the European Patent Office, including the Comparative Test Report. FF CP 21. Dr. Russolo, Profarmaco's Managing Director and General Manager, testified that, Profarmaco immediately decided to ascertain whether it could develop a process using a base not specified in the '035 patent claims and, particularly, bases and solvents that Tanabe had expressly represented to the EPO not to be the subject of its invention. FF CP 22.

On June 27, 1991, two weeks after receipt of the Comparative Test Report, Profarmaco held an R&D meeting attended by, among others, Drs. Russolo and Piselli. FF CP 23. At that meeting, Dr. Piselli was directed to try to develop an N-alkylation process using sodium carbonate as the base.[19] FF CP 24.

Sodium carbonate was chosen as a target base because Tanabe had identified the base in the Comparative Test Report as being outside the scope of its invention. FF CP 26. Profarmaco therefore viewed the use of sodium

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[19] Specifically, the meeting minutes state: "try the attachment of the chlorobase [i.e., 2-dimethylaminoethyl-chloride ("DMC")] with sodium carbonate/DMF with different percentages of water." FF CP 25.

carbonate as a "zero-risk situation" by using what the inventors said was not part of their claimed invention. FF CP 27. DMF was identified because that was the solvent that Profarmaco was then using in its current potassium carbonate/DMF process which was "a very good process." FF CP 28.

Four days after this R&D meeting, Dr. Piselli conducted the first experiment using sodium carbonate in the period following receipt of the Comparative Test Report. FF CP 29. Dr. Piselli used sodium carbonate and DMF with C percent water. FF CP 30. During approximately the next eight months, Profarmaco was able to develop a new process for N-alkylating TZP using sodium carbonate as the base. FF CP 31.

Profarmaco experimented by including and not including a phase transfer catalyst, by conducting the reaction at various temperatures, by varying times, by using various solvents, and by adding or removing water. Experimental evidence provided by complainants in this investigation shows that water removal is not critical in order to get a low yield from the Profarmaco process. However, Profarmaco discovered during the course of these experiments that only by removing water (through azeotropic distillation) could Profarmaco achieve an industrially valid process, with high yield and low levels of impurities [20] FF CP 32-37.

During the next eight months, Profarmaco scientists conducted approximately 100 experiments with different base/solvent combinations, and by February 1992, determined to use sodium carbonate and toluene, a base and a

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[20] Dr. Piselli characterized the removal of water as very important and essential. FF CP 36. If water is not removed from the current Profarmaco process, the reaction is "never complete" and there are by-products and impurities. FF CP 37. Profarmaco also discovered that if the temperature of the reaction is less than C , then the N-alkylation reaction cannot be completed. FF CP 38.

solvent, both of which were expressly identified by Tanabe in the Comparative Test Report as not included within its invention. FF CP 39.

On March 6, 1992, the sodium carbonate and toluene process went to the pilot plant. FF CP 40. By June 4, 1992, that process had been prepared for production and was ready for use. FF CP 41.

Profarmaco conducts its process for manufacturing bulk diltiazem in a C reactor vessel with a volume of C cubic meters. FF CP 42. The reactor vessel contains a distillation column; C

C

C

C and a variety of other equipment. The distillation device which allows for azeotropically distilled vapors to be cooled, condensed, and then either removed from the system or returned to the reactor vessel, is known as a Markusson trap. FF CP 43.

In the step immediately preceding N-alkylation, Profarmaco carries out the C . Profarmaco first charges C C . Profarmaco then C C . Following this step, Profarmaco allows the contents of the reactor vessel C , which results in the formation of two phases. a lower aqueous phase and an upper phase containing C . The Profarmaco operator, following the separation, C

C . Following this procedure, the operator causes C

C , thus removing any last traces or

droplets of water which may have adhered to the sides of the reactor vessel. Any water that is gathered as a result of C is then discharged by the operator C

C FF CP 44.

The next step is the N-alkylation. That process is carried out in the same reactor vessel which already contains DMC free base in a toluene solution. To that solution Profarmaco adds sodium carbonate which, by its specification, may not contain more than C% water by weight. It also adds TZP, which is prepared at Profarmaco, and which is heated by Profarmaco to remove all water. FF CP 45. Once the TZP and sodium carbonate have been added to the toluene solution containing DMC base, the operator heats the reactor vessel as quickly as possible using the maximum amount of steam flowing through the jackets surrounding the reactor vessel. At C °, the operator reduces the steam flow so that the inside temperature will reach about C°C without the reactor's contents overflowing. Through thermal inertia, the reaction mixture increases in temperature to approximately C C° and the reaction mixture is then heated to C °. It takes C for the reaction mixture to reach C°; C for the reaction mixture to reach C °; and the reaction mixture is then heated at C ° for C hours. FF CP 46.

At the C ° range, the water/toluene solution begins to distill azeotropically. Carbon dioxide evolution begins at approximately C° and water collects in the Markusson trap also at approximately C°. Because water is heavier than toluene, the water collects in the Markusson trap while the toluene returns to the reaction vessel. FF CP 47. Profarmaco observed in the R&D laboratory a relationship between carbon dioxide evolution and N-

alkylation. Profarmaco has observed that the N-alkylation reaction takes place while carbon dioxide evolution is occurring. FF CP 48.

Profarmaco takes five separate steps to prevent water from entering the reactor vessel and to remove water created during the N-alkylation step. FF CP 49.

The differences between the Profarmaco process currently employed to manufacture bulk diltiazem in the N-alkylation step and the processes claimed in the '035 patent (and in the Examples contained in the patent) include the following:

a) Profarmaco uses sodium carbonate as a base; the '035 patent specifies potassium carbonate and potassium hydroxide;

b) Profarmaco uses toluene as a solvent; the '035 patent uses acetone and lower alkyl acetates, or mixtures of those solvents and water;

c) according to complainants' theory of the case, the '035 patent either generates water during the process or calls for the addition of water. No water is added to the Profarmaco process. Profarmaco's process requires that water be removed constantly throughout the N-alkylation reaction and that efforts be made to remove water during the previous step;

d) Profarmaco's process is conducted at a temperature of approximately C °; the '035 processes are conducted at a maximum of 77°. CX 1.

e) in the Profarmaco process, Profarmaco arrives at a solution in toluene of the intermediate; Profarmaco is therefore ready to conduct the subsequent acetylation reaction in the same reactor vessel using the same reactants. By contrast, in the '035 process the intermediate is isolated.

See FF CP 50.

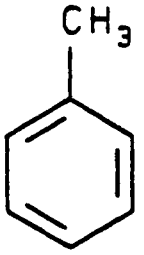
Solvents

According to complainant's expert Dr. Gokel, the key difference between the Profarmaco process and the '035 process is the use of toluene as the solvent. The predominant structural feature of each of the solvents claimed in the '035 patent is the presence of a carbonyl group, which is shown

enclosed by the dotted lines in the following formulas:

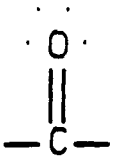
FF CP 55.

Toluene is an aromatic hydrocarbon whose structure is illustrated by the formula:



FF CP 56. Toluene contains neither a carbonyl group nor any structure analogous to a carbonyl. Toluene is not a ketone (like acetone) or an ester (like an alkyl acetate). FF CP 57.

The oxygen atoms in the carbonyls of the solvents claimed in the '035 patent have two unbonded pairs of electrons which can be donated to positively charged species (i.e., "cations"), such as potassium ions (K^+), as depicted below:



FF CP 58. The second oxygen atom in an alkyl acetate also possesses two pairs of unbonded electrons that can be donated. FF CP 59.

A donor solvent is a solvent which can donate electron density to stabilize an electron deficient species such as a cation. A donor solvent provides stabilization to an electron deficient species, such as a sodium or potassium cation, which are both electron deficient. FF CP 60. The '035 carbonyl solvents are good donor solvents. FF CP 61. By contrast, toluene is a very poor donor solvent. FF CP 62.

Acetone and lower alkyl acetates are stronger donors than toluene. Because '035 carbonyl solvents can donate electrons, particularly when they contain water, they are able to solvate (or solubilize) and thus stabilize cations of inorganic bases, such as the potassium bases of the '035 patent. FF CP 64-65. Potassium bases are more soluble in carbonyl solvents than are sodium bases. FF CP 66. Due to its poor donorability, toluene cannot effectively solvate (or solubilize) and thus stabilize cations of inorganic bases, such as potassium ions or sodium ions. FF CP 67. Sodium carbonate is not soluble in toluene. FF CP 68.

The differences between toluene and the solvents of the '035 patent may be appreciated by comparing their donor numbers. The '035 carbonyl solvents, methyl acetate, acetone and ethyl acetate range in donor number from 16.4 to 17.1. FF CP 69. The donor number for toluene is 0.1. FF CP 70. Thus, the '035 carbonyl solvents are more than 160 times better donors than is toluene.

FF CP 71.

The '035 carbonyl solvents, methyl acetate, ethyl acetate and acetone, are of medium polarity, having dipole moments ranging between 5.7 and 9.0 and dielectric constants ranging from 6.0 to 20.56. FF CP 72. Toluene is a non-polar solvent, having a dipole moment of 1.0 and dielectric constant of 2.38. FF CP 73.

The information reported in Dr. Gokel's report entitled "Fermion and Profarmaco Versions of Tanabe Diltiazem Synthesis" reflects what Dr. Gokel "constructed to aid [his] thinking at an early stage" in the present litigation. In determining the equivalence between the Fermion and Profarmaco processes with the '035 process, Dr. Gokel considered many parameters relating to the solvents used for the N-alkylation reaction. One of the parameters that Dr. Gokel considered and thought might influence his opinion was solvent polarity parameters, while another was a comparison of the water miscibilities of the different solvents. FF CP 53-54.

Because water is soluble in the '035 carbonyl solvents, it increases the dielectric constant of the '035 carbonyl solvents. FF CP 74. Ionic species are solvated and stabilized better by polar solvents than by non-polar solvents. FF CP 75. Toluene, being a non-polar solvent, lacks the ability to dissolve inorganic bases. FF CP 76

The '035 carbonyl solvents are substantially soluble in water, and water is substantially soluble in those solvents. FF CP 77. Acetone is infinitely soluble in water, and water is infinitely soluble in acetone. FF CP 78. Methyl acetate is very soluble in water (approximately 23%), and water is very soluble in methyl acetate. FF CP 79. Ethyl acetate is soluble in water at 2.94%, and water is soluble in ethyl acetate at 8.08%. FF CP 80. In contrast,

it is well-known that water is immiscible in toluene. FF CP 83. Toluene is soluble in water at only 0.052% and water is soluble in toluene at only 0.033%. FF CP 81. The solubility of water in the "wet toluene" used in the Profarmaco process is substantially lower at only .03%. FF CP 82.

The least soluble of the '035 carbonyl solvents (ethyl acetate) is more than 50 times more soluble in water than toluene, and water is more than 200 times more soluble in ethyl acetate than in toluene. FF CP 84. It is clear that toluene does not represent an insubstantial change from the solvents specified in the '35 patent.

At least four different sets of experiments have been made of record in the present investigation demonstrating that when the solvent toluene is substituted for the '035 carbonyl solvents in the '035 process the reaction proceeds very differently: (1) the experiments underlying the EPO Comparative Test Report submitted by Tanabe during the prosecution of the European application corresponding to the '035 patent; (2) experiments conducted by Tanabe scientists in the early 1980s. (3) experiments conducted by complainants' expert Dr. Baldwin; and (4) experiments conducted by Profarmaco. See FF CP 126.

Experiment No. 8 in Table 1 of the Comparative Test Report, in which "no reaction" was reported for an N-alkylation reaction using potassium hydroxide and toluene, is consistent with the 24% yield that the complainants' expert Dr. Baldwin obtained in JEB 15, wherein potassium hydroxide and toluene also were used.[21] FF CP 154.

Experiments carried out by complainants' expert Dr. Baldwin demonstrate

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[21] Where "no reaction" is reported in Experiments 8 and 12 of the Comparative Test Report, Tanabe did not necessarily mean zero yield but rather meant a poor yield. FF CP 138.

that toluene does not work as a solvent in the '035 process. Similarly, experiments carried out by Dr. Baldwin demonstrate that sodium carbonate does not work efficiently as a base in the '035 process. FF CP 146.

In Experiment JEB15, which was designed to simulate a process of the '035 patent in which toluene was interchanged for a solvent of the '035 patent, a yield of 24% was obtained when N-alkylating TZP with potassium hydroxide as the base and toluene as the solvent at a reaction temperature of 111°C. FF CP 147.

In Experiment JEB16, which was designed to simulate a process of the '035 patent in which toluene was interchanged for a solvent of the '035 patent, a yield of 56% was obtained when N-alkylating TZP with potassium carbonate as the base and toluene as the solvent at a reaction temperature of 111°C. FF CP 146.

In Experiment No. 8 of Table 1, the yield of product was reported as "no reaction" when potassium hydroxide and toluene were used at a reaction temperature of 50-60°C for a reaction period of 7 hours. FF CP 135. The reaction temperature of 50-60°C was within the range described in the '035 patent. FF CP 135.

In a Tanabe technology department report, dated October 1981 (approximately two months prior to the December 1981 date of the Japanese priority patent application upon which the '035 patent is based), Tanabe scientists reported that the N-alkylation of TZP at a reaction temperature of C °C using C as the base and C as the solvent did not work. Tanabe repeated the reaction several times, varying the reaction temperature and amount of water added, but were unable to obtain an appreciable product. FF CP 140.

Dr. Gaino, one of the co-inventors named in the '035 patent, reported in his notebook that N-alkylating TZP using C as the base and C as the solvent failed to work. FF CP 141.

Thus, the Tanabe research reports reflect the Tanabe scientists' finding that toluene is not a useful solvent for the '035 process. Taber, Tr. 2139.

During the course of this investigation, Dr. Piselli of Profarmaco conducted certain experiments. See FF CP 170-177. In Experiment 15, Dr. Piselli replicated Example 3 of the '035 patent except that he substituted toluene in place of ethyl acetate. Dr. Piselli used the reflux temperature of ethyl acetate, as used in the patent example. The yield was extremely low and the product was not pure. FF CP 176.

Finally, in Experiment 16, Dr. Piselli replicated Example 3 of the '035 patent except that he substituted toluene for acetone. There was no yield at all in the reaction. Dr. Piselli used the boiling temperature of acetone. FF CP 177.

Bases

Evidence received at the hearing demonstrates the non-equivalency of the base of the Profarmaco process with those of the '035 patent. Sodium carbonate is not equivalent to the potassium bases claimed in claim 1 of the '035 patent. See FF CP 93. Potassium salts are generally more soluble in organic solvents than are sodium salts. FF CP 95. The carbonyl containing solvents, such as those of the '035 patent, are known to be able to solvate potassium, at least to some degree. However, the same phenomenon is not known to occur with sodium, at least not to the same degree. FF CP 94.

Furthermore, experimental data demonstrates that sodium carbonate reacts quite differently than potassium carbonate in the '035 process. See FF CP

127.

In the Comparative Test Report, Experiment No. 11 of Table 1, a yield of 10% was reported when using sodium hydroxide and acetone under reflux conditions for a reaction period of 15 to 20 hours. FF CP 136.

In Experiment No. 12 of Table 1, the yield of product was reported as "no reaction" when sodium carbonate and acetone were used under reflux conditions for a reaction period of 15 to 20 hours. FF CP 137.

Tanabe performed experiments about three months prior to the December 1981 date of the Japanese priority patent application upon which the '035 patent is based wherein C and C were substituted for potassium carbonate as the base for N-alkylating TZP in acetone. When using either C or C , Tanabe scientists were unable to make the N-alkylation reaction work. The experiment using sodium carbonate and acetone corresponded with Experiment No. 12 in Table 1 of the European Comparative Test Report using sodium carbonate and acetone wherein "no reaction" is reported. FF CP 137

In Experiments 1-3, Dr. Piselli repeated Example 3 of the '035 process. These experiments were run three times. FF CP 164. The yields obtained by Dr. Piselli in these three repetitions of Example 3 of the '035 patent were virtually identical to the yield indicated in the '035 patent itself. Similarly, the product produced, based on the Thin Layer Chromatography analysis and melting point range, appears to be identical to that indicated in Example 3 of the '035 patent. FF CP 165.

In Experiments 4-6, Dr. Piselli used Example 3 of the '035 patent as a starting point for three experiments, in which he substituted sodium carbonate for potassium carbonate. Dr. Piselli ascertained that after a period of time

that was slightly longer than that specified in Example 3 of the '035 patent, each of the three experiments provided a low yield. FF CP 166. In Experiment 4, Dr. Piselli therefore extended the reaction time to 15 hours, and in Experiment 6 extended the reaction time to 30 hours and changed a number of other factors. In each instance, the yield remained low. FF CP 167.

Also, in Experiments 5 and 6, the purity of the product obtained was poor, as characterized by a "NEG" indication in the "Purity by TLC" column. FF CP 168. Similarly, the melting points of the product obtained in Experiments 5 and 6 were significantly lower than the melting range for the product obtained by a simple replication of the Example 3 of the '035 patent.[22] FF CP 169.

In Experiments 7 and 8, Dr. Piselli replicated Example 4 of the '035 patent. FF CP 171. The yields and quality obtained in Experiments 7 and 8 compare favorably with the yields and quality reflected in Example 4 of the '035 patent. FF CP 172.

In Experiments 10 and 11, Dr. Piselli replicated Example 4 of the '035 patent, except that he substituted sodium carbonate for potassium carbonate. FF CP 174. Those experiments produced a low yield and a poor quality product, as reflected by the "neg" comment in the purity by TLC column. These results were not improved by continuing the reaction for 18 hours. FF CP 174.

Experiments 4-6 and 10-11 demonstrate that sodium carbonate is not a useful base in the '035 process. See 175.

Tanabe Research Reports similarly reflect the finding of Tanabe scientists that sodium carbonate is not useful as a base in the '035 process.

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[22] With respect to Experiments 4-6, Dr. Piselli testified that the yields reflected in those experiments "is not a process. It's something that should be abandoned." FF CP 170.

FF CP 144.

In Dr. Baldwin's Experiment JEB17, the yield of product obtained dropped from 90.7% to 35% when sodium carbonate was substituted for potassium carbonate under some reaction conditions of Example 2 of the '035 patent. FF CP 149.

In Experiment JEB18, the yield of product obtained dropped from 92.7% to 65% when sodium carbonate was substituted for potassium carbonate under some reaction conditions of Example 3 of the '035 patent. FF CP 150.

In Experiment JEB19, the yield of product obtained dropped from 90.7% to 10% when sodium carbonate was substituted for potassium carbonate under some reaction conditions of Example 2 of the '035 patent. FF CP 151.

In Experiment JEB20, a yield of 97% was obtained when sodium carbonate was substituted for potassium carbonate under some reaction conditions of Example 3 of the '035 patent, but only after heating the reaction mixture at reflux temperature for 23 hours (almost 4 times the reaction time in Example 3). FF CP 152.

Experiment No. 12 in Table 1 of the Comparative Test Report, in which "no reaction" was reported for an N-alkylation reaction using sodium carbonate and acetone, is consistent with the 10% yield that the complainants' expert Dr. Baldwin obtained in JEB 19, wherein sodium carbonate and acetone also were used. FF CP 153.

The Profarmaco Process Does Not Work the Same Way As the '035 Process

The solubility of water in the '035 carbonyl solvents, and vice versa, contributes to the ability of the '035 carbonyl solvents to solvate (or solubilize) the potassium bases disclosed in the '035 patent. FF CP 85. One of ordinary skill in the art in 1981 would have known that the solubility of

potassium salts in acetone would be enhanced by the addition of water. FF CP 86. Water stabilizes and thus makes more soluble negatively charged hydroxide and carbonate ions (i.e., "anions") in a reaction solution. FF CP 87.

The '035 carbonyl solvents possess both hydrophilic (water-loving) and lipophilic (oil-loving) properties. FF CP 88. Because the '035 carbonyl solvents have both hydrophilic and lipophilic properties, they are able to bring together in solution TZP, the inorganic base, and DMC (in the form of aziridinium). FF CP 89. Because the '035 carbonyl solvents have both hydrophilic and lipophilic properties, the TZP, inorganic base, and DMC all dissolve in the organic-aqueous phase surrounding the inorganic base particles. FF CP 90.

In contrast, toluene has strongly lipophilic properties with little or no hydrophilic properties. FF CP 91. Because toluene has very little hydrophilic properties, most water included in the Profarmaco process is associated with the surface of the sodium carbonate base particle. FF CP 92.

The '035 process is one in which the inorganic base particles (potassium base particles) are surrounded by a solvent-water mixture, wherein the concentration of water is greatest at the surface of the particle and decreases with distance from the particle. Some water is dissolved in the bulk organic phase. FF CP 100.

Building on the existence of this solvent-water mixture, complainants have propounded a theory of reaction which they call a "surface solvent phase," allegedly applicable to the '035 patent and respondents, including Profarmaco and Abic. However, complainants' expert, Dr. Gokel, has carried out no experiments and is unaware of any experiments carried out by others, comparing a surface solvent phase formed in the '035 process with a surface

solvent phase formed in any of the respondents' processes. Indeed, Dr. Baldwin would expect to find more dissolved base in the solvent system of the '035 process than he would in the toluene phase of the Profarmaco process. FF CP 102.

The pH of the carbonate buffer contained in the aqueous phase of the Profarmaco process is the same, whether sodium carbonate or potassium carbonate is used as the base. Because a dramatic difference is obtained in the '035 process when using a sodium base instead of a potassium base, this indicates that the '035 reaction system is a mixed solvent system, comprising water, organic solvents and potassium base. This mixed solvent system is further evidenced by the knowledge that potassium bases are more soluble than sodium bases in the '035 carbonyl solvents, due to the ability of the carbonyl solvents to solvate potassium ions more efficiently than sodium ions. FF CP 103.

The ratio of water to organic solvent in the '035 process is a gradient or continuum extending outward from the solid base particles of the '035 patent. FF CP 104. In the '035 system, there exists a "phase boundary" between the ethyl acetate and water phases "which is on the ethyl acetate side more like ethyl acetate; on the water side, more like water. And in the middle there is a progression from one to the other. FF CP Id. Complainants' expert Dr. Gokel "would certainly expect" that the difference between toluene and ethyl acetate would alter the phase boundary present in the respective systems. FF CP 105.

The particular base/solvent combinations of the '035 patent result in the reactants coming together in solution and thus allow the reaction to proceed at relatively low temperatures with good yields. FF CP 108. The TZP in the

'035 process is depronated by carbonate or hydroxide ions and the resulting amide anion reacts with the aziridinium ion to yield the alkylated product. FF CP 106. However, no direct experimental evidence exists that the claimed N-alkylation process of the '035 patent using potassium carbonate as a base is hydroxide-mediated. FF CP 107. In fact, there are indications that it is not hydroxide-mediated. Id.

Complainants' expert, Dr. Gokel, was unsure whether the actual alkylating agent in either the Profarmaco or the '035 processes is the aziridinium ion. Specifically, the only thing Dr. Gokel knows is that in both reactions some aziridinium ion is formed, but he does not know whether the aziridinium ion is the actual alkylating agent or not. Although he "think[s], it is reasonable that it could be. . . . [he] can't rule out the other possibility." That the alkylation of TZP occurs predominantly through the aziridinium ion would be a "guess" for Dr. Gokel. FF CP 109. Dr. Gokel also agreed that the aziridinium ion would likely be involved in the '257 process, in addition to its likely involvement in both the '035 and Profarmaco processes.[23] FF CP 110.

Profarmaco's expert testified that in the Profarmaco reaction, the aziridinium ion acts as a phase transfer agent between the thin water layer surrounding the inorganic base particle and the bulk toluene phase. See FF CP 112.

Although the precise activity of the molecules has not been proved, there are differences between the '035 process and the Profarmaco process that are known definitively, and which have a direct bearing on the way in which the Profarmaco process works. In the Profarmaco process, the amounts of water

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[23] Dr. Baldwin's labeling experiments in JEB1-JEB4 do not prove that the aziridinium ion is the alkylating species. FF CP 111.

present are substantially smaller than the amounts of water present in the '035 process. Specifically, in Example 3 of the '035 patent, the amount of water associated with potassium carbonate is about 1.1 moles of water per mole of potassium carbonate. FF CP 113. In contrast, in the Profarmaco process wherein the water concentration of the water-extracted toluene is C %, the molar ratio of water to sodium carbonate is about C % or C times less than in the '035 process. Id.

The small amount of dissolved water in the toluene of the Profarmaco process exists in aggregates of molecules. FF CP 114. The minuscule amounts of water in the toluene associate with the surface of the sodium carbonate base in the Profarmaco process, whereas in the process of the '035 patent significant amounts of water are dissolved in the carbonyl solvent and the water participates in the solvation and dissolution of the inorganic potassium base. FF CP 115.

No mention is made of azeotropic removal of water in any of the examples of the '035 patent. Instead, the '035 patent teaches in the examples that the reaction is carried out under reflux conditions, meaning that the vapors of solvent released from the reaction mixture during boiling are condensed to a liquid in a reflux condenser and returned to the reaction vessel. FF CP 116.

In many ways, the Profarmaco process is much more like the '257 process than the '035 process because where reversible deprotonation of the TZP starting material occurs in the '035 process, the TZP starting material in the Profarmaco process is directly alkylated after deprotonation occurs. Thus, no equilibrium (or reversibility) exists in the Profarmaco process between the TZP starting material and its anion. FF CP 117.

A higher amount of energy is required for the reaction occurring in the

Profarmaco process than for the reaction occurring in the process of the '035 patent, as reflected by the higher reaction temperatures required for obtaining good yields in the Profarmaco process. FF CP 118. The Profarmaco process is carried out at a temperature of C °C versus 77°C or less in the '035 process. FF CP 119.

Because of the higher reaction temperatures necessary to carry out the Profarmaco process, carbon dioxide is evolved during the Profarmaco process, thereby also producing sodium hydroxide. FF CP 120. Nothing in the '035 patent indicates that carbon dioxide is evolved during the '035 process. FF CP 121.

The fact that the evolution of carbon dioxide in the Profarmaco process coincides with the production of product indicates that the hydroxide ion formation, which occurs simultaneously with carbon dioxide evolution, is important to the Profarmaco process. FF CP 122.

While the pH in the '035 process drops from an initial pH of 11.5 to 8.5, the pH in the Profarmaco process is maintained at a minimum level of 11.5. FF CP 123. One pH interval level represents a difference in hydroxide ion concentration of a factor of 10. Thus, there is 1000 times more hydroxide ion present in the Profarmaco process than in the '035 process. FF CP 124.

Thus, the Profarmaco process operates at a much higher pH level than the process of the '035 patent, due to the higher hydroxide ion concentration and significantly lower amount of water present in the Profarmaco process. FF CP 125.

Dr. Baldwin's experiments also demonstrated the importance of water removal during the Profarmaco process. See FF CP 155.

In Experiment JEB2 (which sought to mimic the Profarmaco process), Dr.

Baldwin's assistants failed to follow his instruction that steps be taken to remove water during the reaction. FF CP 156. Without taking steps to remove water in JEB2, a yield of only 32% was obtained. FF CP 157.

When Dr. Baldwin repeated Experiments JEB2 with azeotropic water removal, the yield increased from 32% to 98%. FF CP 158.

Complainants' expert, Dr. Gokel, agreed that "an effort was made to remove water" during Dr. Baldwin's repeat of JEB2,[24] including transferring the reaction mixture to a clean Wheaton vile after the neutralization step, as well as using a heat gun to heat the distillation head to ensure that any water adhering to its walls was driven over into the condenser. In addition, a clean condenser was attached to the reaction system prior to completing the reaction. The effort made to remove water in the repeat of Experiment JEB2 was consistent with Profarmaco's effort to remove water during its process by azeotropic distillation. FF CP 159.

In addition to performing the N-alkylation of diltiazem in a different way from that of claim 1 of the '035 patent, the Profarmaco process performs a substantially different function and achieves a substantially different result than the process of the claim 1 of the '035 patent.

The examples of the '035 patent teach that the N-alkylated TZP obtained as the product of claim 1 of the '035 patent must be isolated, purified, and transferred to another reaction vessel before the manufacture of diltiazem can proceed. FF CP 182. The product of Profarmaco's sodium carbonate/toluene N-alkylation process provides commercial advantages, for example, convenience,

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[24] Complainants' expert, Dr. Gokel, had no idea whether Dr. Baldwin's Experiment Nos. JEB1-JEB20 had been optimized; in other words, they may have been or they may not have been. FF CP 161. Assuming Dr. Baldwin's experiments were not already optimized, they could have been optimized if complainants' chose to do so. FF CP 162.

unobtainable using the product of the N-alkylation process claimed in the claim 1 of the '035 patent. FF CP 183.

Because claim 1 of the '035 patent does not include a recovery step, the function of the process of claim 1 of the '035 patent is to produce an organic reaction mixture containing N-alkylated TZP in a carbonyl solvent-water mixture. This product will contain water, dissolved base and salts along with alkylated TZP. To utilize the solubilized N-alkylated TZP, the reaction mixture must be (i) extracted, (ii) washed, (iii) filtered, (iv) concentrated, (v) redissolved, and (vi) transferred to another reactor prior to the subsequently applied steps, including, inter alia, the acetylation and salt-forming steps. FF CP 185.

In contrast, the Profarmaco process produces a solution of N-alkylated TZP in toluene. FF CP 181. Because toluene is immiscible with water, the solution of N-alkylated TZP in toluene produced from the N-alkylation step of the Profarmaco process can be directly washed with water to remove byproducts and unreacted DMC, leaving behind a solution in which one can directly carry out the subsequent acetylation reaction. FF CP 184.

Profarmaco's sodium carbonate/toluene process cannot be found within any range of equivalents of claim 1 of the '035 patent given the differences between the bases and solvents used in the '035 patent and the Profarmaco process, and because complainants have failed to show that the Profarmaco process performs substantially the same function in substantially the same manner to achieve substantially the same result. In summary, the elements of the Profarmaco process are not equivalents of the elements of claim 1 of the '035 patent.

Tanabe's Claim of Equivalents Would Involve the Prior Art

Among the relevant prior art are U.S. Patent Nos. 3,895,006 and Patent 3,455,902 to Krapcho. These patents are discussed in the section on obviousness mainly for their teachings that benzothiazepinones could be alkylated in hydrous conditions without serious side reactions.

Both the '006 and '889 patents teach the N-alkylation of benzothiazepinones using a sodium base (sodium hydroxide) and toluene (the same base/solvent combination used by Profarmaco) in a system that generates water. See FF D 143. Thus, if claim 1 of the '035 patent were applied broadly enough to cover the accused Profarmaco process, and therefore open the door to sodium bases and toluene, the '006 and '902 patent would assume greater weight, thereby strengthening the invalidity case presented by respondents and OUII.

The Federal Circuit has held that "a patentee should not be able to obtain, under the doctrine of equivalents, coverage which he could not lawfully have obtained from the PTO by literal claims." Wilson Sporting Goods Co. v. David Geoffrey & Assoc., 904 F.2d 677, 684 (Fed. Cir.), cert. denied, 498 U.S. 992 (1990). Thus, there can be no infringement under the doctrine of equivalents if the asserted scope of equivalency would encompass the prior art. Indeed, "the burden is on the [plaintiff] to prove that the range of equivalents which it seeks would not ensnare the prior art . . . ." Id. at 685. Complainants have not demonstrated that the scope of equivalents they seek in this investigation would stay clear of the prior art, especially with respect to the '006 and '902 patents, which teach the use of a sodium and toluene base/solvent combination in the N-alkylation of benzothiazepinones.

Sanctions

Alternatively, if the Commission finds infringement of the '035 patent by

the Profarmaaco process, then the sanctions in paragraphs 2 and 3 of Order No. 52 should apply, and complainants would be precluded from adducing evidence that toluene as a solvent and sodium carbonate as a base are equivalent to the bases and solvents of the '035 process. Complainants' would thus have failed to prove infringement. Thus, for this alternative reason the Profarmaco process does not infringe the '035 patent.

C. The Abic Process Does Not Infringe Claim 1 of the '035 Patent

The Development of the Abic Process

In 1982 Abic decided to market a calcium channel blocker, and chose diltiazem as its goal. FF CA 106. Although there was no patent on diltiazem in Israel, Abic sought a license from Tanabe for sale to other countries. FF CA 107. Tanabe refused to license Abic, or to supply raw material. FF CA 108. Consequently, Abic began research and development of the overall process for synthesizing diltiazem hydrochloride in December 1982 or very early in 1983. FF CA 109. By early 1983, Abic knew of the '257 patent and its foreign counterparts, but not of the '035 patent or any foreign counterpart of it. FF CA 110.

There are about seven or eight steps in Abic's procedure to manufacture diltiazem hydrochloride, and the N-alkylation is the fifth or sixth step. FF CA 111. Therefore, it was not until May of 1983 that Abic had the starting material in hand to enable it to begin working on the N-alkylation step. FF CA 112. Based on the literature, Abic believed that alkylating the nitrogen on the seven-membered ring would be a straightforward procedure. FF CA 114.

Because Abic needed diltiazem precursor for study of the acetylation step, and for further pharmaceutical testing, Abic began alkylating TZP under

the conditions already reported in the '257 patent and the Kugita publications, i.e., with the base/solvent combination of sodium hydride/DMSO. FF CA 115. Abic quickly moved away from the base/solvent combination of sodium hydride/DMSO by replacing DMSO with DMF. FF CA 116. Abic then began to look for alkylation processes which did not employ sodium hydride. FF CA 117.

It was known at that time, that one could alkylate carbon atoms (C-alkylation) using either harsh conditions or the milder conditions of phase transfer catalysis, in the presence of water. It was felt that those milder phase transfer catalysis methods would be ideal for the task confronting Abic. FF CA 118.

Abic believed that alkylating under milder conditions would minimize the possibility of side reactions. Although there is a large amount of water present in classical phase transfer conditions, Abic was not concerned with potential hydrolysis of the TZP. Similarly, Abic was not concerned with the potential retro-Michael reactions under phase transfer catalyzed conditions because of the particular structure of the TZP molecule. FF CA 120, 121.

Because Tanabe had not observed O-alkylation at the 3-hydroxyl group of TZP under the harsher conditions of the '257 patent, Abic was not concerned that such O-alkylation was likely to take place under the milder phase-transfer conditions. FF CA 122. Abic was not concerned about the potential for alkylation at the carbonyl oxygen because in the presence of a base, alkylation occurs almost exclusively at the nitrogen. FF CA 123.

Abic was not concerned that DMC would be unstable under Abic's phase transfer conditions because, as with all alkylating agents, conditions can be modified to minimize instability. FF CA 124.

In August, 1983, Abic tried two phase transfer catalyzed processes, one using potassium hydroxide/methylene chloride-water and the other using potassium hydroxide/toluene-water, both with TEBA bromide as the phase transfer catalyst. In August, 1983, Abic still was not aware of the '035 patent or any of its foreign counterparts. FF CA 125, 126.

The phase transfer catalyzed reaction in toluene did not work at low temperatures; and at high temperatures, there was some hydrolysis of the lactam. FF CA 127. However, the phase transfer catalyzed reaction in methylene chloride worked well, and at low temperature, so that hydrolysis was not a problem. FF CA 128.

Although Abic tried a number of other solvents, none was as good as methylene chloride. Abic also experimented with several phase transfer catalysts, but rapidly settled on TEBA because it gave the best results. Therefore, beginning in August, 1983, Abic concentrated on developing the methylene chloride-water phase transfer catalyzed process. FF CA 129, 130.

The product of the alkylation using potassium hydroxide as the base was somewhat impure. FF CA 131. Therefore, in August 1983, Abic tried sodium hydroxide as the base, since it was the most similar base to potassium hydroxide. FF CA 132. Sodium hydroxide gave a purer product, but it still contained about 10% of the unidentified impurity. FF CA 133. Abic continued using sodium hydroxide as a base for two to three months to make precursor for use in studying the subsequent acetylation, hydrochlorination and purification processes. FF CA 134.

Eventually Abic discovered that the impurity obtained with potassium hydroxide and sodium hydroxide was "dimer", which was formed by an alkylation reaction between the solvent methylene chloride and two molecules of TZP. FF

CA 135.

Abic was aware of British Patent No. 1,236,467, a counterpart of the '257 patent, as well as other counterparts, claiming alkylation processes employing alkali metal salts. In an effort to avoid the formation of dimer, and in an attempt to develop a process using bases other than alkali metal bases (so as to avoid infringing the '257 foreign counterpart process patents), Abic began experimenting in December 1983 with ammonium hydroxide, magnesium hydroxide and calcium hydroxide. FF CA 136, 137.

Abic also apparently became aware in December of 1983, for the first time, of the European patent application that was the counterpart of the '035 patent. Abic was not concerned with potential infringement in Europe, because the European application was restricted to potassium bases, and Abic at the time was using sodium hydroxide. FF CA 138, 139.

Abic tested various bases that did not work well in the reaction. FF CA 140-142. Then in February 1984, Abic tested barium hydroxide with its methylene chloride-water-TEBA system and found that barium hydroxide gave good yields, practically no formation of dimer, and fewer side reactions with DMC. FF CA 143.

Abic repeated tests of other bases in the methylene chloride-water system with a phase transfer catalyst, and confirmed that potassium hydroxide and potassium carbonate yielded large amounts (20%-30%) of the dimer under those conditions. FF CA 144. For comparative purposes, Abic also tried some of the base/solvent combinations of the EPO 81234 application, but Abic did not pursue those combinations because Abic has a policy of not infringing valid patents. FF CA 145.

Abic tried numerous bases in the methylene chloride-water-TEBA system,

including, in chronological order, potassium hydroxide, sodium hydroxide, potassium carbonate, sodium bicarbonate, calcium carbonate, magnesium hydroxide, ammonium hydroxide, triethylamine, and alumina. However, in every case Abic obtained either low yields of N-alkylated product or high yields of the unwanted dimer formation. FF CA 146.

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FF CA 147.

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FF CA 151.

The evidence adduced at the hearing in this investigation demonstrates that Abic's process is not a copy of the Tanabe process. Furthermore, Abic's effort to develop its own process was wholly independent, and was not guided by knowledge of the '035 patent or of any counterpart. See FF 152, 153.

Abic obtained patents on its process in the United States, Israel, Japan, Canada and Europe. In the United States, Abic's patent application was examined by Examiner Bond, who cited the '257 patent and the '035 patent as prior art, and concluded that Abic's process was patentable over those references. FF CA 154, 155.

Abic's Use of Barium Hydroxide As a Base

The Abic process does not use either of the two bases or either of the two organic solvents or any of the five specific base/solvent combinations identified in the '035 patent. FF CA 1. Abic's commercial process uses barium hydroxide octahydrate as a base, a biphasic solvent system of methylene chloride and water, and triethylbenzylammonium chloride (TEBA).[25] FF CA 2.

Barium is an alkaline earth metal. As an alkaline earth metal, barium forms divalent cations. FF CA 6. Among the differences between barium and the potassium disclosed in the '035 patent is the fact that barium hydroxide is less soluble than potassium hydroxide in carbonyl solvents such as acetone and lower alkyl acetates. FF CA 7.

If one of ordinary skill in the art were investigating the interchangeability of other bases with the potassium bases of the '035 patent, one would likely try sodium hydroxide (NaOH) first because sodium hydroxide is more common and substantially less expensive than potassium hydroxide. FF CA 8. Tanabe tried and abandoned sodium hydroxide in combination with DMSO. FF CA 9.

Barium hydroxide would be expected to be less effective than sodium hydroxide in the '035 process because barium is even less soluble than sodium

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[25] Abic's commercial process is similar to the process described in example 4 of its United States Patent No. 4,466,995 ("the '995 patent"). FF CA 2.

in the carbonyl solvents acetone or ethyl acetate of the '035 patent. FF CA 11. Consequently, if sodium hydroxide were found to be not as good as potassium hydroxide, one of ordinary skill in the art would not be led to try barium hydroxide, since, barium hydroxide would be expected to be even worse in the '035 process, which discloses solvation of the solid base in a carbonyl solvent. FF CA 12. Accordingly, one of ordinary skill in the art, knowing that even sodium hydroxide was not interchangeable with potassium hydroxide would not have expected that barium hydroxide would be interchangeable with either potassium hydroxide or potassium carbonate. FF CA 13.

Abic's Use of Methylene Chloride As a Solvent

The organic solvent in Abic's process is methylene chloride. FF CA 14. The '035 patent does not teach the use of methylene chloride as an organic solvent to be used in the N-alkylation of the '035 process. FF CA 15. The '035 patent discloses chloroform (a chlorinated hydrocarbon like methylene chloride) for certain purposes, but did not disclose its use or the use of any other chlorinated hydrocarbon solvent in its N-alkylation process. FF CA 16.

One of ordinary skill in the art investigating the scope of potentially interchangeable solvents to replace acetone in the '035 process would have sought solvents which shared the important structural and functional characteristics of the carbonyl solvents of the '035 patent, i.e., one would have looked at oxygen-containing, cation-solvating, water-miscible solvents. FF CA 18.

Some common solvents which one might have investigated include methyl ethyl ketone, dioxane, methanol, and DMSO. FF CA 19. However, methylene chloride would not be one of the solvents one would first try, since it does not solvate cations well, has no oxygen atoms to act as donors, and is nearly

totally immiscible with water. FF CA 20.

If solvents such as dioxane, methanol, and methyl ethyl ketone were not as effective as acetone in a reaction, one would not be led to try methylene chloride, since that would be going in the "wrong direction," to even more inferior water-immiscible solvents.[26] FF CA 21.

The Abic Process is Substantially Different from the '035 Patent Process

The evidence received at the hearing demonstrates that the Abic process does not perform substantially the same function in substantially the same way to achieve substantially the same result as the process claimed in claim 1 of the '035 patent.

Each of the organic solvent-water mixtures of the '035 patent forms a single liquid phase, i.e., it is a solution of water in the acetone or lower alkyl acetate organic solvent. FF CA 26. However, Abic's solvent system is a "biphasic solvent system." In other words, Abic's solvent is of two distinct liquid phases, one of methylene chloride and another of water. FF CA 27. There is no solid phase present in the Abic process. FF CA 28.

Liquid-liquid phase transfer catalyzed systems such as that used by Abic and the simple solid-liquid processes such as those of the '035 patent are not generally thought of by those skilled in the art as being chemically

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[26] Tanabe itself tried various bases and solvents other than those disclosed in the '035 patent. Tanabe tried sodium carbonate instead of potassium carbonate, but it did not work as well. FF CA 22. Tanabe tried structurally and functionally similar solvents, such as dioxane, methyl ethyl ketone, methanol, and DMSO, and they did not work as well. FF CA 23. In fact, Tanabe tested and abandoned the base/solvent combination of potassium carbonate/methyl ethyl ketone (the combination currently employed by Fermion) because Tanabe could not get that combination to work. FF CA 24.

In accordance with testimony of Abic's expert, Dr. Taylor that, starting from the five base-solvent combinations of the '035 patent, one would not get to Abic's process, Tanabe never tried barium hydroxide as a base, methylene chloride as a solvent, or the combination of barium hydroxide and methylene chloride. FF CA 25.

equivalent. FF CA 29.

In the Abic liquid-liquid biphasic solvent process, the TZP and the DMC are in the organic phase (the methylene chloride layer), while the barium hydroxide remains dissolved in the aqueous phase. TEBA, the phase transfer catalyst, is soluble in both phases. The aziridinium ion, which, as a cation, is insoluble in methylene chloride, remains in the aqueous layer. FF CA 40. The hydroxide ion in the water layer cannot efficiently deprotonate the TZP in the methylene chloride layer, because they are in separate layers, organic and aqueous. The TEBA phase transfer catalyst carries the hydroxide ion as TEBA hydroxide into the methylene chloride layer, where it deprotonates the TZP. The TZP anion can then react with DMC to N-alkylate the TZP N-aryl amide. FF CA 41.

Abic carried out a series of experiments, which were originally suggested by complainants' expert Dr. Liotta, to show the differences between the Abic process with and without the use of TEBA. The results of the experiments indicate that the phase-transfer catalyzed reaction was at least twice as fast as the uncatalyzed reaction. FF CA 31-39. Catalysis selectively increases the rate of hydroxide ion transfer, while heating would indiscriminately speed up everything that is going on, and increase the potential for side reactions. FF CA 61.

The methylene chloride phase has an additional function in the Abic process beyond the function of acetone in the '035 process. FF CA 42. The water-immiscible solvent methylene chloride keeps the TZP and DMC separated from dissolved aqueous barium hydroxide. FF CA 42, 43. Tanabe's own published research Kugita I discloses that TZP can hydrolyze in the presence of aqueous sodium hydroxide, especially at higher temperatures. Furthermore,

with biphasic toluene-aqueous hydroxide processes Abic itself has observed hydrolysis of TZP at higher temperatures. FF CA 44, 45. In the accused Abic process, the methylene chloride, operating at 40°C, protects the TZP and DMC from hydrolysis by aqueous barium hydroxide. FF CA 46. Because there is no aqueous hydroxide in the '035 solid-liquid potassium hydroxide-acetone process, hydrolysis is not a problem in the '035 process. FF CA 47.

In Abic's process, dimer formation is inhibited by use of a phase transfer catalyst. FF CA 62, 63. Use of a phase transfer catalyst in Abic's system also enables a reduction in the volume of solvent used. Complainants and Abic agree on this point. FF CA 64. See, e.g., Complainants' Rebuttal to Abic's Proposed Findings of Fact at 48a (Abic Proposed Finding of Fact No. 323).

Complainants do not agree that Abic's process proceeds through phase transfer catalysis. Rather, complainants assert that the small amount of water present in the base-solvent combinations of the '035 patent is present as a "surface solvent phase" which complainants attempt to liken to the aqueous phase of Abic's biphasic solvent process. FF CA 91.

The so-called "surface solvent phase" is postulated by complainants to be a very thin layer, approximately 100 angstroms (Å) thick, of indeterminate composition associated with the solid FF CA 93. The surface solvent phase would be invisible to the naked eye It would take 50,000 of the postulated 100 Å surface solvent phases laid one on top of the other to make up the thickness of a pencil line. FF CA 94.

Professor Wrighton of M.I.T., an expert witness for Abic on surface chemistry, testified that the term "surface solvent phase" was not customarily used in surface chemistry, and had no recognized meaning. FF CA 96. Indeed,

before this investigation, complainants' expert, Dr. Liotta, had never used the term "surface solvent phase" in any publication. FF CA 97. Before this investigation, Dr. Liotta had never called a surface solvent phase a "biphasic solvent system." FF CA 98. The postulated surface solvent phase film, of indeterminant composition, and only 1/50,000th of the thickness of a pencil line, is not the chemical equivalent of the aqueous phase of the Abic methylene chloride-water biphasic solvent system. FF CA 99.

Dr. Liotta performed experiments attempting to prove the presence of a surface solvent phase when water was added to a mixture of potassium carbonate and ethyl acetate. FF CA 100. Dr. Liotta's experiments established that the potassium carbonate and water did not form a "surface solvent phase", but formed the well-known solid compound potassium carbonate sesquihydrate ($K_2CO_3 \cdot 1.5H_2O$). FF CA 101. Potassium carbonate sesquihydrate is not a surface solvent phase. FF CA 102.

Abic repeated Dr. Liotta's experiments, and tested the products by differential scanning calorimetry (DSC). FF CA 103. Dr. Wrighton testified that the DSC results established that when potassium carbonate was treated with water in ethyl acetate as Dr. Liotta had done, the products were potassium carbonate sesquihydrate, or potassium carbonate sesquihydrate with some residual potassium carbonate FF CA 104. Dr. Ronald Jenkins of the International Center for Diffraction Data, another expert witness for Abic, testified as to analyses he had performed on the same material about which Dr. Wrighton testified. Dr. Jenkins concluded that the products were potassium carbonate sesquihydrate, or potassium carbonate sesquihydrate with some residual potassium carbonate. FF CA 105. The Abic process does not work

as a "surface solvent phase," or in the same way as the '035 process.[27]

The Abic commercial process does not represent insubstantial changes from the '035 patent. The Abic process represents major changes from both the '257 and '035 processes and is based on Abic's own experimental work.

As shown above, the bases and solvents disclosed in the '035 patent must be given a narrow interpretation and a narrow range of equivalents. Barium is not an equivalent to the potassium bases claimed in the '035 patent, and methylene chloride is not an equivalent to the solvents claimed in the '035 patent. Even if there is a surface solvent phase in the '035 process (although this has not been proven) the '035 and Abic processes are substantially distinct in the way they work, and there is not infringement under the doctrine of equivalents.

Alternatively, if the Commission finds infringement of the '035 patent, the sanctions in paragraph 1 of Order No. 52 should apply, and would require that all of the scientific expert testimonial evidence adduced by complainants to show equivalence of the Abic process should be stricken, because none of it has any support in the '035 patent. Thus, complainants' would have failed to prove infringement and for this alternative reason the Abic process does not infringe claim 1 of the '035 patent.

D. The Fermion Process Does Not Infringe Claim 1 of the '035 Patent

In February 1983, Dr. Lindholm (a Fermion development manager) assigned the project of developing a process for manufacturing diltiazem to Mr. Hytönen (who was then a product development chemist). FF CF 1. In early September

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[27] Dr. Atwood disputed Dr. Jenkins' opinions. The administrative law judge accepted Dr. Jenkins' opinions because Dr. Atwoods' expertise is in a different field. Nevertheless, resolution of this dispute in Dr. Atwood's favor would not change the administrative law judge's conclusion.

1983, Mr. Hytönen began working on the N-alkylation step of the process to manufacture diltiazem. FF CF 4.

Mr. Hytönen conducted many tests with various base/solvent combinations for about one year. Then, in September and October 1984, Fermion experimented with 2-butanone or methy ethyl ketone (or "MEK"), as well as several other solvents. FF CF 6. In October 1984, Fermion conducted a pilot plant test on the N-alkylation process using potassium carbonate/MEK as the base/solvent combination. This pilot plant test was a failure. FF CF 13.

After the October pilot plant failure with MEK, Fermion conducted additional experiments with a mixture of various bases and solvents. However, in 1985, Mr. Hytönen also conducted further experiments with the potassium carbonate/MEK process to determine why it had failed in the pilot plant. FF CF 14-16.

In late 1985, Mr. Hytönen thought he had solved the problem with the MEK and potassium carbonate system, and conducted a second pilot plant test. However, the second MEK and potassium carbonate pilot plant test was also a failure. FF CF 21-22.

Fermion conducted further experiments with the MEK and potassium carbonate process, and conducted a third pilot plant test in January 1986 which was a success. FF CF 23.

Fermion conducted over C N-alkylation experiments between October 1983 and early 1986 in developing its process. FF CF 36.

Today in the accused Fermion process, the N-alkylation step uses TZP, DMC·HCl, K_2CO_3, butanone and water. FF CF 24.

Complainants contend that Fermion used the '035 patent (or its foreign counterpart) in the development of its accused process. See, e.g.,

Complainants' Post-Trial Brief at 37-38. Complainants take the position that Fermion infringes claim 1 of the '035 patent under the doctrine of equivalents. Id. at 44-51.

Fermion denies having the '035 patent (or its foreign counterpart) before October 11, 1983. Fermion takes the position that even after obtaining the '035 patent, it had to develop its process independently. Furthermore, Fermion denies that it infringes the '035 patent. See, e.g., Fermion's Proposed Findings of Fact at 7-13.

The principal difference between the Fermion N-alkylation process and the process disclosed by the '035 patent is Fermion's use of MEK as the solvent rather than acetone.

The '035 patent does not mention the use of any solvent in the N-alkylation reaction other than acetone and lower alkyl acetates (sometimes with added water) for use in the N-alkylation process. In fact, with respect to the choice of acetone it is noted that although the '035 patent disclosed a subclass of "lower alkyl acetates," it did not disclose a class or subclass of lower alkyl ketones. For these and other reasons one of ordinary skill in the art reading the '035 patent in conjunction with the file history would conclude that the only solvents taught by the '035 patent as suitable for the claimed N-alkylation reaction are acetone and lower alkyl acetates. See, supra at 16, 23-24.

The burden in this investigation was on Tanabe to show that the substitution of MEK for acetone was an insubstantial change, i.e., one that was within the narrow range of equivalents that was left for the '035 patent after the representations that Tanabe made to the PTO.

There is evidence that MEK and acetone, although different chemicals, are

close to one another at least for some purposes.

Methyl ethyl ketone is a ketone, and is not a lower alkyl acetate. MEK is a homolog of acetone. A homolog is defined as a:

> Member of a series of compounds whose structure differs regularly by some radical, e.g., $=CH_2$, from that of its adjacent neighbors in the series.

FF CF 8. Thus, in this case, MEK has an additional methylene group as compared with acetone. However, MEK does not have exactly the same properties as acetone.

Normally, if one of ordinary skill in the art wanted to see how far one could extend the N-alkylation of the '035 patent, one would try another ketone besides acetone, possibly 2-butanone (another name for MEK). By the same token, one of ordinary skill in the art familiar with a range of ketones would read the '035 patent, and would notice the specificity and exclusivity of the claim to the use of acetone. Therefore, one would conclude that other ketones were not included because they did not work. FF CF 9. Indeed, Mr. Hytönen read the '035 patent to exclude MEK. FF CF 7.

Furthermore, as seen from the extensive testing conducted by Fermion, Tanabe, and complainant's expert, the use of MEK as a solvent could not be simply substituted for acetone in the '035 process. In 1981, Tanabe attempted to use MEK as the solvent in the N-alkylation of TZP. In 1981, Tanabe's experiments with MEK either resulted in no product or impure product.[28] FF CF 39.

Fermion duplicated examples found in the '035 patent, and compared the results obtained with the '035 patent solvent to those obtained when MEK was

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[28] This failure on Tanabe's part may explain why MEK was not claimed in the '035 patent.

used as the solvent. FF CF 47. With the exception of '035 patent Example 2 (in which case the reaction proceeded a little faster with MEK), the substitution of MEK for the solvent of the patent Examples provided substantially different, and worse results.[29] FF CF 48-55.

Similarly, Professor Baldwin's tests demonstrate that the mere substitution of MEK for the '035 patent's solvents did not result in an N-alkylation process which achieved yields and/or productivity comparable to that achieved in the Examples of the '035 patent. FF CF 57, 60.

Fermion presented evidence as to why it decided to invest resources in a potassium carbonate/MEK process despite the teachings, or lack of teachings, in the '035 patent. While at university, Mr. Hytönen tried alternatives to acetone in an alkylation with potassium carbonate. One of the substitutions he tried was MEK for acetone. He later had better success with another chemical. Although he tried these substitutions, Mr. Hytönen believes that many researchers (including his professor) think that certain alkylation reactions are specific to acetone FF CF 10. Mr. Hytönen had experience with MEK at Fermion before starting his diltiazem development work. FF CF 11.

During the course of experimentation with MEK, Fermion learned that the

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[29] In patent Example 3, the use of ground potassium carbonate in combination with ethyl acetate resulted in an N-alkylation reaction which proceeded to completion as described in the patent i.e., within six hours. In contrast, with MEK and ground potassium carbonate, after six hours roughly 60% of the starting TZP remained. FF CF 50.

In patent Example 4, Fermion was able to duplicate the results reported for acetone and powdery potassium carbonate, essentially complete TZP conversion within nine hours. However, when MEK was substituted for the acetone, the reaction did not proceed at all, essentially all TZP remained unreacted. FF CF 51.

Patent Example 5 did not proceed as written. FF CF 52.

In patent Example 6, the substitution of MEK for the methyl acetate of the example resulted in an N-alkylation which proceeded to completion in two hours, while with methyl acetate the reaction took thirty hours. FF CF 53.

amount of C present in the potassium carbonate/MEK process was critical. FF CF 25. Fermion learned that the process did not work with either too much or too little added C . FF CF 28. After Fermion's success with a potassium carbonate/MEK N-alkylation process in the pilot plant, Mr. Hytönen began to experiment with making the process less sensitive to the amount of C present, and therefore "more reliable." FF CF 29.

Mr. Hytönen discovered that by reducing the ratio of C C it was possible to reduce the sensitivity of the MEK and potassium carbonate to the amount of C present. FF CF 30. Fermion discovered that its present process is extremely reliable, always proceeding to completion, i.e., all the TZP is consumed. FF CF 32.

The '035 patent contains no teaching that the amount of C in the process is critical. FF CF 33. Indeed, the '035 patent provided no guidance to Fermion and Mr. Hytönen in solving the problems encountered with the MEK and potassium carbonate process. FF CF 34.

The question presented in this investigation is not whether respondents have misappropriated a method to make diltiazem in any yield whatsoever. Rather, the question is whether respondents have misappropriated an invention for an improved method of making diltiazem efficiently, safely and in high yield, and the question of infringement under the doctrine of equivalents should be reviewed in this context In view of Tanabe's decision to use restrictive language in the claims of the '035 patent, specifying only acetone and no other keytone solvent, and given the admissions made to the PTO about the specificity of the claimed invention, and the further admissions Tanabe made to the EPO and other foreign patent offices, it has not been shown that Fermion's use of MEK is equivalent to the acetone covered by claim 1 of the

'035 patent. Therefore, it has not been demonstrated that the accused Fermion process infringes claim 1 of the '035 patent.

Alternatively, if the Commission finds that the Fermion process infringes the '035 patent, the sanctions in numbered paragraph 1 of Order 52 should apply,[30] and the scientific expert testimony adduced by complainants to show that MEK is an equivalent of acetone should be stricken because it is not based on material in the '035 patent. Complainants would then have failed to prove that the Fermion process infringes the '035 patent. Thus, for this alternative reason, Fermion could not be found to infringe the '035 patent.

IV. CLAIM 1 OF THE '035 PATENT IS INVALID UNDER 35 U.S.C. § 103

A. General Law Applicable to Section 103 of the Patent Act

Section 103 of the Patent Act provides in pertinent part as follows:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains.

35 U.S.C. § 103. Thus, the claims of a patent must fall if it is determined that the differences between them and the pertinent prior art would have been obvious to a person reasonably skilled in that art. Graham v. John Deere Co., 383 U.S. 1, 37 (1966). However, the Patent Act provides that a patent is presumed to be valid. 35 U.S.C. § 282. Consequently, the presumption of validity can only be overcome by clear and convincing evidence. Loctite Corp.

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[30] It does not appear that Fermion joined in the sanctions motion. However, OUII as the party representing the public interest supported the motion. If the sanctions are appropriate, it is not in the public interest to bar imports which would reward complainants' sanctionable conduct. Thus, Fermion should have the benefit of the sanctions even if it did not join in the motion.

v. Ultraseal Ltd., 781 F.2d 861, 872 (Fed. Cir. 1985).

Although the ultimate question of patent validity is one of law, a determination on the question of validity under section 103 requires several factual determinations. Graham v. John Deere Co., 383 U.S. at 17. The Supreme Court has held that:

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or nonobviousness, these inquires may have relevancy.

Id.

The Federal Circuit has held that "[t]he person of ordinary skill is a hypothetical person who is presumed to be aware of all pertinent prior art." Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc., 807 F.2d 955, 962 (Fed. Cir. 1986). Accord In re Wood, 599 F.2d 1031 (C.C.P.A. 1979).

When prior art references require selective combination to render an invention obvious, the combination must not be based on the hindsight gleaned from the invention itself. Instead, "[s]omething in the prior art as a whole must suggest the desirability, and thus the obviousness, of making the combination." Uniroyal, Inc. v. Rudkin-Wiley Corp., 837 F.2d 1044, 1050 (Fed. Cir.), cert. denied, 488 U.S. 825 (1988). Prior art references need not explicitly suggest combining their teachings. The knowledge generally available to one of ordinary skill in the art may lead one to combine the relevant teachings. In re Nilssen, 851 F.2d 1401, 1403-04 (Fed. Cir. 1988); Ashland Oil, Inc. v. Delta Resins & Refractories, Inc., 776 F.2d 281, 297 n.24 (Fed. Cir. 1985), cert. denied, 475 U.S. 1017 (1986). The Federal Circuit has

held that "[o]bviousness does not require absolute predictability of success." In re O'Farrell, 853 F.2d 894, 903 (Fed. Cir. 1988). Rather, "all that is required is a reasonable expectation of success." Id. at 904. The reasonable expectation of success may be derived from the combination of prior art references. Id.

When prior art relied on by the party attacking the patent was previously considered by the patent examiner, deference is due the decision to issue the patent. American Hoist and Derrick Co. v. Sowa and Sons, Inc., 725 F.2d 1350, 1359 (Fed. Cir.), cert. denied, 469 U.S. 821 (1984). However, when an attacker produces prior art or other evidence not considered by the PTO, there is no reason to defer to the PTO so far as the effect of the new evidence on validity is concerned. Id. Indeed, reliance on prior art that is "more pertinent than the art considered by the PTO may facilitate meeting the burden of proving invalidity." Uniroyal, 837 F.2d at 1050. In any event, "[a]ll evidence bearing on the validity issue, whether considered by the PTO or not, is to be taken into account by the tribunal in which validity is attacked." Id. at 1360.

The '035 patent has been subject to reexamination.[31] The fact that it

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[31] On May 3, 1993, respondent Abic filed with the PTO a Request for Reexamination of the '035 patent, accompanied by the Declaration of Dr. Taylor. RX 1086.

On June 25, 1993, the PTO granted Abic's Request for Reexamination stating in part. Id.

On September 1, 1993, Tanabe filed with the PTO an Information Disclosure Statement identifying 145 references, including non-confidential versions of the Answers filed by each respondent in this investigation which discussed the prior art and its purported relevance to the '035 patent. Included also were declarations from Messrs. Gambrell and Adelman. RX 1690. On November 3, 1993, Tanabe filed with the PTO a Supplemental Information Disclosure Statement identifying an additional 27 references. RX 1691.

On November 18, 1993, the PTO issued an Office Action in which all the claims of the '035 patent were rejected as unpatentable under § 103. RX 1603. (continued...)

has survived reexamination should be taken into account when making a subsequent determination as to patent validity or invalidity. The Federal Circuit has held that the burden of proving the non-patentability of claims in a patent is made heavier when the patent has survived a reissue or reexamination proceeding in light of the same prior art later presented to a court. Custom Accessories, 807 F.2d 955. Nevertheless, the PTO's decision on reexamination is not binding on the Commission. For example, in addition to relying on prior art not considered by the examiner, it may be shown that the Examiner adopted an erroneous position during reexamination. Certain Stabilized Hull Units and Components Thereof and Sonar Units Utilizing Said Stabilizing Hull Units, 218 U.S.P.Q. 752 (U.S. Int'l Trade Comm'n 1982)(the examiner adopted an erroneous position on the scope of the prior art).[32]

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[31](...continued)
The November 18, 1993 Office Action rejected all claims "over Kugita et al. '257 taken in view of the British Patent, Pachter et al., Johnstone et al., and Nagarajan et al." Id.
On December 9, 1993, Tanabe conducted an interview with Examiner Robert T. Bond. CX 638.
On January 18, 1994, Tanabe filed a Response to the Office Action attaching the Declarations of Drs. Jack E. Baldwin and Andrew S. Kende, and selected pages from the deposition transcripts of certain witnesses. CX 638.
On February 4, 1994, Tanabe conducted a second interview with Examiner Bond, at which Drs. Baldwin and Krapcho were present. CX 638.
On February 28, 1994, and while the first request was still pending, respondent Plantex and third party American Cyanamid Co. filed a second Request for Reexamination of the '035 patent, accompanied by a Second Declaration of Dr. Taylor, as well as additional pages from the deposition transcripts of certain witnesses. Id.
On May 2, 1994, the PTO granted Plantex's and American Cyanamid's second Request for Reexamination of the '035 patent. Id.
On July 26, 1994, the PTO issued Reexamination Certificate No. B1 4,438,035. Id.

[32] The Federal Circuit has considered the effect of a reissue proceeding on the presumption of patent validity. Like the reexamination proceeding, the reissue proceeding does not allow for cross-examination or many of the other procedural safeguards required by the trial-type hearing provided for in the ITC Rules. The Federal Circuit has held that the examination procedure which (continued...)

B. Analysis Under Section 103

1. Scope and Content of the Prior Art

The Federal Circuit has set forth the following general test to determine whether the subject matter of a reference should be considered prior art to the claimed invention:

> First, we decide if the reference is within the field of the inventor's endeavor. If it is not, we proceed to determine whether the reference is reasonably pertinent to the particular problem with which the inventor was involved.

In re Deminski, 796 F.2d 436, 442 (Fed. Cir. 1986)(quoting In re Wood, 599 F.2d at 1036). Accord Orthopedic Equip. Co., Inc. v. United States, 702 F.2d 1005, 1009 (Fed. Cir. 1983)("In determining the relevant prior art of the claims in suit one looks to the nature of the problem confronting the inventor.").

The '035 patent involves the alkylation of a benzothiazepinone (TZP) through the use of particular base/solvent combinations. A benzothiazapinone is within a class of compounds denominated as N-aryl amides, and is denominated as such because the N-aryl functional group is included within the TZP compound. An N-aryl amide is a further subtype in the general class known as amides.

The stated endeavor of the inventor was to alkylate TZP under mild, non-

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[32](...continued)
results in a reissue application "should be given appropriate consideration and due weight," and further that the examiner's decision on an original or reissue application is evidence that must be considered in determining whether a party asserting invalidity has met its statutory burden by clear and convincing evidence. However, the Federal Circuit has also held that an examiner's decision is never binding on a court, even a decision to allow a reissue application that was subject to a supplemental internal review at the PTO by three examiners. Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 1139 (Fed. Cir. 1985).

ydangerous conditions, in high yield, above 87%.[33] CX 1 and 2. The problem facing the inventor was to find the right base/solvent combinations to provide mild, non-dangerous conditions, high yield and easy solvent recovery.

The reactive part of the TZP molecule is known as an N-aryl amide. Chemists would commonly look to the reactive portion of the molecule in searching the literature for information concerning the prior art. FF D 20. They will also search for prior art in closely analogous molecules. If a prior art process is discovered that may prove useful the literature would be searched for all uses of that process.

The wide scope and content of the prior art to the '035 patent is illustrated by the 170 references actually cited by the patentee and Abic during the reexamination. FF D 10. Although other prior art references are discussed in this Initial Determination, the following are the principal prior art references relied on by respondents and OUII during the hearing in this investigation that were also before the examiner during reexamination:

1. U.S. Letters Patent 3,562,257 to Kugita et. al. , which the examiner characterized as showing "the conventional process for production of benzothiazepinones such as diltiazem by alkylation. . . ." FF D 27. The '257 patent teaches the N-alkylation of the identical substrate of the '035 patent, TZP, with the alkyl halide DMC·HCl using as a base an alkali metal, alkali metal hydride, or alkali metal amide, and as a suitable solvent, for example, dioxane, toluene, xylene or DMSO, to yield the identical alkylated product as that of the '035 patent. FF D 27, 29, 30.

2. Pachter and Kloetzel, "Methylation of Some Amides in

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[33] For many years prior to the application for the '035 patent Tanabe had utilized a process in Japan and had sold the products of that process in the United States which provided for alkylation of TZP under mild, non-dangerous conditions in high yield. This was the KOH/DMSO process. The '035 process was superior to KOH/DMSO in that it facilitated easy recovery of the solvent so that it could be reused, thus reducing the cost of producing diltiazem. See discussion, infra, at 114.

Acetone," 74 J. Am. Chem. Soc. 1321-22 (1952) ("Pachter reference"), which discloses the N-alkylation of several N-aryl amides using the base/solvent combination KOH/acetone, with good yield. FF D 49.

3. Worley et al., "2-Dialkylphosphonyl- and 2-Alkylidene-3,4-dihydro-3-oxo-2H-1,4-benzothiazepines," 40 J. Org. Chem. 1731-34 (1975) ("Worley"), which describes the successful N-alkylation of an N-aryl amide lactam under Pachter conditions, using the alkylating agents methyl iodide and ethyl bromo acetate, and reporting a 73% yield. FF D 80.

4. Johnstone et al., "A Rapid Method of N-alkylation of Amides," 16 J. Chem. Soc. 2223-24 (1969) ("Johnstone"), which reported the use of Pachter conditions, in this case the base/solvent combination potassium hydroxide/acetone, to alkylate a substrate that is not an N-aryl amide. FF D 93.

5. Nagarajan et al., "Condensed Heterotricycles: Amino & Aminoalkyridibenz[b,f][I,4] oxazepin-II(IOH)-ones," 12 Indian J. Chem. 236-46 (1974) ("Nagarajan"), which shows the N-alkylation of a lactam[34] structurally similar to TZP, using conditions similar to those used in the '257 patent. FF D 104.

6. U.S. Letters Patent 3,895,006; 3,948,889; 3,075,967; and 3,455,902, which issued to John Krapcho, and describe the N-alkylation of benzothiazepinones. FF D 144.

The following references were not of record before the PTO examiner:

1. U.S. Letters Patent 4,377,522, which issued to Quirico Branca in 1983, is prior art based on its filing date before the Japanese counterpart to the '035 patent.[35] The '522 patent discloses an alkylation reaction of a seven-member ring N-aryl amide using DEC, DMC or methyl iodide, with potassium carbonate and acetone as the base/solvent combination. FF D 130.

2. U.S. Letters Patent 3,910,887, which issued to Walter von Bebenburg in 1975, discloses alkylation of a seven-member N-aryl amide ring using DMC as the alkylating agent, and potassium carbonate/acetone as the base/solvent

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[34] Lactams, including TZP, are cyclic amides. FF D 81, 82.

[35] The application for the '035 patent was filed on December 1, 1982, based on a foreign application priority filing date of December 7, 1981, in Japan. CX 1.

combination. FF D 133.

3. U.S. Letters Patent 3,644,338, which issued in 1972 to Karl Schenker, discloses the alkylation of a compound which, although not an aryl amide, is an amide with a seven-member ring. The reaction uses DMC as one of the possible alkylating agents, potassium carbonate as a possible base, and acetone as a possible solvent. FF D 135.

Additional prior art to the '035 patent is found in the process used by Tanabe prior to its use of the '035 process to manufacture diltiazem. The process in question used potassium hydroxide (KOH) as the base and dimethylsulfoxide (DMSO) as the solvent during the N-alkylation step. FF D 227. It is undisputed that from approximately 1976 through 1984, i.e., more than one year prior to the priority filing of the application for the '035 patent, complainant Tanabe sold diltiazem manufactured by the KOH/DMSO process in the United States. FF D 262. By reason of section 102(b) of the Patent Act, the diltiazem sold in the United States during that period constitutes prior art to the '035 patent.[36]

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[36] Complainant contends that the KOH/DMSO process is not prior art for the reasons among others that this process is a two-step process, that DMSO is a super base, and that the administrative law judge has recognized that this process is not equivalent to the '035 process. Complainant's Post-Trial Brief at 32-33. None of these points is well taken.

Claim 1 of the '035 patent contains no limitation as to the number of stages or steps in the process, or concerning the order of adding the reagents. There is some indication in some of the experiments in the body of the patent that the reagents are mixed together simultaneously, but there is no explicit teaching in the patent of the importance of the order of mixing reagents. Nor is there any limitation in the claim or teaching in the patent about superbases with a pk of over 18.

Finally, the administrative law judge in Order No. 41, discussed the deposition testimony of one of complainants' experts in finding no dispute as to the material facts in the Summary Determination Motion at issue. That deposition testimony also contained the expert's views concerning DMSO. However, the administrative law judge found only that there was no dispute as to material facts concerning the motion, and gave no substantive credence to the testimony. The complainants confuse the nature of a ruling on Summary Determination with a factual determination on the merits based on all the evidence.

Section 102 of the statute provides in part as follows:

A person shall be entitled to a patent unless --

* * *

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for a patent in the United States . . . .

35 U.S.C. § 102 (emphasis added). Furthermore, if a sale is sufficient to effect an on-sale bar under 35 U.S.C. § 102(b), it also constitutes prior art under 35 U.S.C. § 103. In re Kaslow, 707 F.2d 1366, 1374 (Fed. Cir. 1983). A product placed on sale may create a section 102(b) on-sale bar to patentability either alone, if the product is an anticipation of the later claimed invention, or in conjunction with section 103, if the claimed invention would have been obvious in combination with other prior art. LaBounty Mfg., Inc. v. United States Int'l Trade Comm'n, 958 F.2d 1066, 1071 (Fed. Cir. 1992).

Complainants contend that Tanabe's KOH/DMSO process cannot be prior art to the '035 patent because Tanabe practiced this process only in Japan. However, the fact that the process in question was carried out in Japan is irrelevant inasmuch as the products made by that process were sold in this country.

The Federal Circuit has held that:

> [S]ales or offers by one person of a claimed invention will bar another party from obtaining a patent if the sale or offer to sell is made over a year before the latter's filing date.
>
> An exception to this general rule exists where a patented method is kept secret and remains secret after a sale of the unpatented product of the method. Such a sale prior to the critical date is a bar if engaged in by the patentee or patent applicant, but not if engaged in by another.

In re Caveney, 761 F.2d 671, 675 (Fed. Cir. 1985)(citations and footnote omitted). In this case, the patentee is also the party that made the sales more than one year prior to the filing of the patent application, and the principle of on-sale bar applies as against Tanabe.

Under Caveney it is immaterial whether the product on sale was made in the United States or abroad, as long as the sale or offer to sell was made in the United States (as in this case), or even to a company with its place of business in the United States. Id. 676-77. Although the patent at issue in Caveney was a product patent, the language employed by the Federal Circuit explicitly contemplates the use of a method to produce a product put on sale or offered for sale.[37]

Complainants contend that in order for the on-sale bar to apply to a process patent the process must itself be carried out in the United States. They rely principally on Shurie v. Richmond, 699 F.2d 1156 (Fed. Cir. 1983), in which the Federal Circuit construed the meaning of 35 U.S.C. 102(g), which provides in part as follows:

> [A person shall be entitled to a patent unless --]
>
> (g) before the applicant's invention thereof the invention was made in this country by another who had not abandoned, suppressed, or concealed it.

35 U.S.C. § 102(g).

Shurie involved an interference proceeding at the PTO. The senior party claimed priority of invention based on its sale in the United States of products produced by the claimed process. The Federal Circuit denied the

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[37] This is not as complainants contend, a question of first impression. Rather, the statutory language clearly covers sales which are made in this country, and the place where the process is performed is irrelevant under § 102(b).

claim to priority, holding that "because [Shurie] never performed that process in the United States, Shurie is restricted to his filing date." 699 F.2d at 1158.

The principal difference between § 102(g) and § 102(b) is that § 102(b) bars a patent if the product of the process was sold in this country prior to the critical date, whereas § 102(g) bars a patent if another made it in this country prior to the applicant's invention. Complainants' reliance on Shurie to show that the on-sale bar provision of section 102(b) must apply only to processes performed in the United States has no support in the statute or in the Shurie decision. While the plain language of 102(g) applies to inventions "made in this country," section 102(b) does not specify where the invention is to have been made. Indeed, section 102(g) applies strictly to the assignment of priority among would-be inventors. The Federal Circuit's holding in Shurie that "the importation into the United States of a product produced by a particular process is not equivalent, for patent entitlement purposes, to the performance of the process in the United States" lends no support to complainants' views. Shurie, 699 F.2d at 1159 (emphasis added).[38]

Not only is the statutory language of the two provisions essentially different, the on-sale bar provision of section 102(b) has several underlying policies which differ from those of section 102(g). The Federal Circuit has held that the on-sale bar serves many purposes, including "a policy against removing inventions from the public domain which the public justifiably comes to believe are freely available due to commercialization. . . ." Caveney, 761 F.2d at 676. Furthermore, "[o]ne policy underlying the bar is to obtain

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[38] See also LaBounty, 958 F.2d at 1071 n.3 ("A section 102(b)/103 bar obviously concerns a device which is not a reduction to practice of the claimed invention. Nevertheless, such an on-sale device is prior art.")

widespread disclosure of new inventions to the public via patents as soon as possible; another is to prevent the inventor from commercially exploiting the exclusivity of his invention substantially beyond the statutorily authorized 17-year period." RCA Corp. v. Data Gen. Corp., 887 F.2d 1056, 1062 (Fed. Cir. 1989). Consequently, the purposes of the 102(b) on-sale bar (as reflected in its language) are not served by restricting application of the bar only to sales of products produced by claimed processes carried out in the United States, but rather by finding the existence of an on-sale bar when a sale or offer to sell occurred in this country, despite the fact that the process may have been carried out abroad.

Inasmuch as the sale of diltiazem made by Tanabe's KOH/DMSO process was sufficient to effect an on sale bar,[39] the KOH/DMSO process is prior art to the '035 patent.

2. Differences Between the Prior Art and the Claim at Issue

Background

As required under Graham v. John Deere, the differences between the prior art and the claim at issue must be determined. The focus must be on the differences between hypothetical combinations of prior art and the claimed

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[39] In rebuttal to respondents' findings concerning Tanabe's KOH/DMSO process, complainants indicate that importations of diltiazem made by that process occurred in connection with clinical trials in the United States. However, complainants' proposed findings of fact state that Tanabe used its KOH/DMSO process for approximately 10 years, and further contrast the commercial use of the KOH/DMSO process with the supposed commercial success of the '035 patent process. See CFF 454, 456. Therefore, it is clear that in addition to any clinical trials that took place in the United States using diltiazem made by the Tanabe KOH/DMSO process, commercial sales of the product were also made.

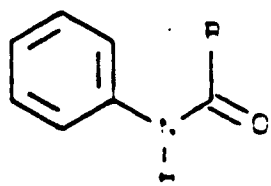
If complainant seeks to rely on sale or transfers of diltiazem for FDA clinical trials as an exemption from the 102(b) on sale bar, it has failed to point out the law, or adduce evidence to support such a conclusion. Further, this issue was not included in the complainants' Prehearing Brief and complainants are barred from including it now.

invention as a whole. Kaslow, 707 F.2d at 1374.

The N-alkylation process described in the '035 patent is typical of the types of projects that process development chemists would have undertaken in 1981. FF D 12. The inventors of the '035 patent knew prior to 1981 that the N-alkylation reaction worked and that commercially feasible methods existed. The only question faced by the inventors was whether cheaper, easier-to-handle bases or solvents giving high yield could be used. FF D 21.

The chemistry of organic compounds revolves around the chemistry of functional groups. FF D 17. Functional groups are more important than ring structure in determining chemical reactivity. FF D 18. A chemist can choose reaction conditions by focusing on the functional group on which one wishes to carry out the chemical transformation. The ring framework to which the functional group is attached plays a minor role, if any, in the functional group chemistry. Thus, in organic chemistry, synthetic reactions depend upon and are focused on the properties of the functional group. FF D 20.

The functional group known as an "N-aryl amide," is part of the structure of the substrate N-alkylated in the '035 patent, i.e., TZP. An N-aryl amide has the following general structure:



FF D 19.

The process claimed in the '035 patent involves the conversion of an N-aryl amide, i.e., TZP or acetyl-TZP, to an N-alkylated amide. FF D 22.

In attempting to improve on the '257 patent, the person of ordinary skill

in the art would have first looked for art related to benzothiazepinones and N-aryl amides, because both contain the reactive part of the TZP molecule for alkylation. FF D 23. Second, the person of ordinary skill in the art would have looked to alkylation of amides in general. This is precisely what Dr. Pachter did. In fact, he found the solution to his problem in the work of Gabriel who worked with amides. FF D 39.

The hypothetical person of ordinary skill would have found references such as Pachter[40] et al., "Methylation of Some Amides in Acetone," 74 J. Am. Chem. Soc. 1321-22 (1952)("Pachter reference"); Worley et al., "2-Dialkylphosphonyl- and 2-Alkylidene-3,4-dihydro-3-oxo-2H-1,4-benzothiazepines," 40 J. Org. Chem. 1731-34 (1975)("Worley"); Clark et al., "Synthesis and Analgesic Activity of 1,3-Dihydro-3-(substituted phenyl) imidazo[4,5-b]pyridin-2-ones and 3-(Substituted phenyl)-1,2,3-triazolo[4,5-b]pyridines," 21 J. Med Chem. 965-78 (1978)("Clark"); Nagarajan et al., "Condensed Heterotricycles: Amino & Aminoalkyridibenz[b,f][I,4] oxazepin-II(IOH)-ones," 12 Indian J. Chem. 236-46 (1974)("Nagarajan"); and Latif and Sattar, "A Note on the Alkylation of Amides," 32 J. Indian Chem 489-90 (1955) ("Latif"). FF D 23. These references, and many others, were part of the reexamination of the '035 patent.

Reexamination of the '035 patent was requested by respondent Abic, and supported by a declaration of its expert, Dr. Taylor. The examiner initially agreed with Dr. Taylor, and rejected all the claims of the '035 patent. FF D 7, 8. The bases for the initial rejection included:

> (a) The '257 patent showed a conventional method of N-alkylation;

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[40] Dr. Magnus found the Pachter reference in five minutes. Magnus Tr. 3156.

(b) Pachter and subsequent references showed the "widely used" N-alkylation of N-aryl amides with the same bases (potassium hydroxide, potassium carbonate) and the same solvent (acetone) as the '035 patent;

(c) British '119 and Nagarajan showed dimethylaminoethylation (i.e., reaction with DMC) of dibenzoxazepinones;

(d) Johnstone "further illustrat[ed] the value of the Pachter et al. technique."

FF D 8.

In response to the examiner's rejection of the claims of the '035 patent, Tanabe submitted declarations by its experts, Drs. Baldwin and Kende, who argued that:

(a) The Pachter technique was not widely known;

(b) Pachter did not render the '035 patent obvious because it (i) disclosed only amides which were not cyclic and (ii) did not disclose DMC as an alkylating agent;

(c) British '119 and Nagarajan were limited to "nitro-substituted" amides, and thus not relevant to N-alkylation of TZP which had no nitro substituent;

(d) Johnstone was not pertinent;

(e) A number of potential side reactions, including retro-Michael reaction, ring-cleavage, O-alkylation, and carbonyl O-alkylation might occur, and might prevent high yields of the '035 patent.

FF D 9.

In his final consideration, the examiner issued the reexamination certificate stating that the prior art then of record did not establish the obviousness of the '035 patent. FF D 11. The principal prior art of record during the reexamination and other prior art not of record before the examiner is discussed below.

The Prior Art

a. The Kugita '257 Patent

During the Reexamination of the '035 patent, the examiner issued an Office Action wherein he stated that "Kugita ['257] show the conventional process for production of benzothiazepinones such as diltiazem by alkylation...." FF D . In determining to accept Abic's petition for reexamination the examiner concluded that:

> It would be obvious for one of ordinary skill in the art to use the Pachter et al technique in the Kugita et al. ['257] process. Since the desirability of Pachter's technique has been long established, it would be obvious to use it in a process such as that of Kugita et al. One would be motivated to do so in the desire that superior results would be achieved. The chances for success would be excellent.

FF D 28.

The '257 patent discloses a process for the N-alkylation of the identical substrate as the '035 patent, i.e., TZP, using the alkyl halide DMC·HCl to yield the identical alkylated product. As a base, the '257 uses an alkali metal, alkali metal hydride, or alkali metal amide, and as a suitable solvent, for example, dioxane, toluene, xylene, or DMSO. FF D 30.

Thus, the '257 patent (the only patent cited in the '035 patent) teaches that benzothiazepinones, can be alkylated under rigorous conditions (e.g., NaH/DMSO) using somewhat dangerous bases that can result in explosions, and solvents that are inconvenient, and which result in relatively low yields. FF D 34. In seeking to improve upon the '257 process, a process development chemist would rapidly realize that the reactive portion of the TZP molecule is what is known as an "N-aryl amide". FF D 33.

b. The Pachter Reference

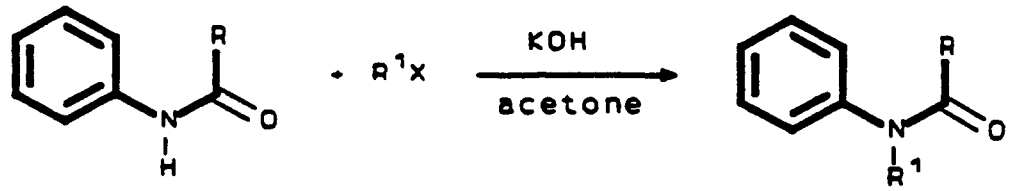
The Pachter reference was published in 1952 as a result of work done by Dr. Pachter towards his Ph.D. thesis under the tutelage of Dr. Kloetzel. FF D

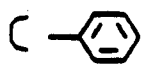
The N-aryl amide structure, which is part of TZP, is also a part of each

of the substrates alkylated by Dr. Pachter in 1952. FF D 36.

The Pachter reference applied the known Gabriel synthesis conditions to N-aryl amides. FF D 39. Pachter's process used the same base/solvent combination as the '035 patent, namely, potassium hydroxide and acetone. FF D 40.

Pachter disclosed the following N-alkylation of an N-aryl amide using KOH and acetone:



R^1X above represents an alkyl halide. FF D 42. Pachter disclosed successful N-alkylations using methyl iodide as the alkyl halide, in which R was methyl ($-CH_3$) or phenyl  . FF D 43.

Pachter decided to use potassium hydroxide and acetone based upon the teachings of the prior art that alkylation of an amide, in what is known as the Gabriel synthesis, succeeded with potassium hydroxide, yet failed under '257 conditions. FF D 55 According to Pachter, it was important to have as much of the base as possible in solution in order for the reaction to take place rapidly. Therefore, he chose potassium hydroxide as the base because potassium bases are more soluble in acetone than sodium bases. FF D 45. He chose acetone as the solvent because he knew he could get his compounds into the acetone solution quite readily and because it would provide a good medium for the reaction. FF D 46.

The person of ordinary skill in the art would do exactly what Dr. Pachter

did. If one wants to carry out a reaction on a substrate, one looks at what has been done that is analogous, to see whether it can be applied to the system at hand. The closer the analogy, and the closer the example from the literature, the greater confidence of success one has. FF D 57.

The Pachter reference itself has become part of the art, to be used in the same manner by other organic chemists. FF D 59. Some of the compounds alkylated by Pachter were complex. The (N-methylbenzamido)diphenylamine compounds that Pachter alkylated had two possible sites for alkylation, the amide nitrogen and the amine nitrogen. Alkylation of the amine did not interfere with alkylation of the amide. FF D 50, 51. Each of the N-alkylated amides has an aryl, or benzene ring, and a carbonyl. The benzene ring and the carbonyl flank the nitrogen, which is to be alkylated. FF D 47.

The process taught in the Pachter reference was an improvement over earlier processes because it achieved the N-alkylation reaction by switching the known bases and solvents (later disclosed in the '257 patent) to potassium hydroxide/acetone (those later described in the '035 patent). In his paper, Dr. Pachter showed that in relatively short reaction times, and under very convenient conditions, one could rapidly and in good yield produce the necessary compound. Dr. Pachter's paper teaches that some compounds are inactive under '257 conditions, but easily alkylated under Pachter conditions. FF D 73. The Pachter reference disclosed that the usual method for alkylating N-aryl amides until his publication included the use of dangerous metals, metallic sodium, or sodium hydride in inert solvents (i.e., '257 conditions). FF D 74. Thus, in 1952, Pachter taught that the substitution of KOH/acetone for the base/solvent combinations later used in the '257 patent would avoid the dangers and inconveniences of such bases and solvents and could actually

increase yields.[41] FF D 74.

The specification of the '035 patent is similar to the first few paragraphs of the Pachter reference, e.g., both describe previous methods as inconvenient, dangerous, and resulting in low yields. Indeed, Dr. Pachter initially thought the '035 patent drafters "copied paragraph 1" of his paper. FF D 76.

Pachter recognized the problem that the '035 patent purports to solve. Pachter disclosed in his 1952 article that, "[t]he usual method for the alkylation of amides, involving metallic sodium and an inert solvent is at best a rather inconvenient and somewhat dangerous procedure." Pachter then suggested replacing the sodium, i.e., a '257 base, with the KOH/acetone system, the same substitution proposed by the '035 patent.[42] FF D 77.

In the five specific examples described by Pachter, the yields of N-alkylated amides were from 81% to 90%. FF D 50. Although certain of the N-aryl amides alkylated by Dr. Pachter had potential alternative reaction sites, they did not interfere with the desired reaction of the amide. FF D 51.

In explaining why the N-alkylation reaction occurs at one nitrogen rather than another, Dr. Pachter stated that with respect to one of the amides discussed in his paper, under neutral conditions both of the amide's nitrogens are extremely weak bases. However, under basic conditions, only the nitrogen

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[41] The Pachter reference teaches one of ordinary still in the art that one can alkylate an amide under hydrous conditions. FF D 78. In Pachter's process, water is formed in the reprotonation step. FF D 68. The alkylation of an amide under Pachter conditions produces water as a side product. FF D 69.

[42] We do not know if the inventors of the '035 patent had knowledge of the Patcher reference in doing the work which led to the '035 patent.

of the N-aryl amide is sufficiently acidic to be deprotonated and form an anion. FF D 63. In fact, every attempt known to Dr. Pachter to N-alkylate an N-aryl amide using Pachter conditions has succeeded. Dr. Pachter knows of about 100 such N-alkylations. FF D 64.

In 1952, Dr. Pachter concluded that the alkylation procedure with potassium hydroxide and acetone seems to have "general application." FF D 39. Pachter investigated the N-alkylation of N-aryl amides over a range of conditions, including those in which the amide was activated toward alkylation, deactivated, and neither activated nor deactivated, thus demonstrating the general applicability of his reaction procedure. FF D 48.

Following the publication of the Pachter reference, the Pachter base/solvent combination of KOH/acetone for the N-alkylation of N-aryl amides became well-known and well-recognized by those of ordinary skill in the art as a generally applicable procedure for the N-alkylation of N-aryl amides. FF D 59.

The examiner in initially rejecting the patent during the reexamination stated that "Pachter et al. show the widely used alkylation of aryl amides." FF D 8. In his declaration submitted to the PTO during the reexamination, complainants' expert Dr. Baldwin argued that a paper by Yamawaki suggested that the Pachter method is not general. FF D 60. However, the Yamawaki experiments mentioned by Dr. Baldwin were not limited to N-aryl amides. FF D 60. By contrast, respondents presented over a dozen references in this investigation which describe Pachter-type N-alkylations of N-aryl amides. FF D 62.

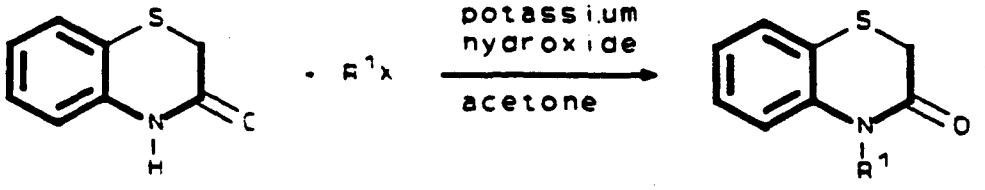
The prior art at the time of the reexamination, and at the time the '035 patent issued, showed that Pachter conditions worked for the N-alkylation of

all N-aryl amides and some other amides. FF D 65. In 1981, no reference was known of in which Pachter's conditions did not work for the alkylation of an N-aryl amide. Today, no reference is known in which Pachter's conditions have been reported not to work for the alkylation of an N-aryl amide. FF D 66. Also, several references, which are mentioned below, describe the Pachter conditions in general terms, e.g., Worley (RPX 1094), Johnstone (RX 1137), Latif and Sattar (RX 1605), Clark (RPX 1093). See FF D 72.

Given only the '257 patent and the Pachter reference, a person of ordinary skill in the art would have had an "excellent" chance (90 percent) of success, of N-alkylating TZP although there is the possibility of side reactions. See FF D 35.

c. Worley

In 1975, Worley used KOH/acetone as the base/solvent combination in the following N-alkylation reaction, stating that the procedure used was the "general procedure of Pachter and Kloetzel for the alkylation of [N-aryl] amides with potassium hydroxide in acetone" (the N-aryl amide structure shown in bold type):



FF D 87.

Worley describes the successful N-alkylation of an N-aryl amide lactam under Pachter conditions using the alkylating agents methyl iodide and ethyl bromo acetate, reporting a 73% yield. FF D 80.

The Worley compound is a very good model for TZP. Both compounds are

N-aryl amides; both compounds have heterocyclic ring systems; both compounds are aromatic; and both compounds have sulfur in the same position.[43] FF D 88.

Worley's compound is a six-member ring. In terms of ease of alkylation, a distinction between the six-member ring of Worley and the seven-member TZP ring is not significant for our purposes. On the size of the ring alone, even complainants' expert would not draw any distinction between six-member rings and seven-member rings. FF D 86. Furthermore, Worley does not report any reaction (or side reaction) of the sulphur atom. FF D 90.

The amide group in Worley has approximately the same acidity as the amide group in TZP. FF D 85. The compound alkylated by Worley had a sulfur atom which, like the sulfur atom of TZP, can transmit its effects through the aromatic ring down to the nitrogen. If the sulfur atom of TZP were to affect the N-alkylation reaction of Pachter, such a deleterious effect would have been seen in Worley. However, Worley obtained a good yield when using Pachter conditions. FF D 83. Worley taught that Pachter conditions can be applied to a lactam (a cyclic amide) as well as to Pachter's N-aryl amides. FF D 82. Thus, Worley provided assurance that the sulfur atom in the TZP ring would not inhibit the N-alkylation reaction. FF D 84.

By adding Worley to the '257 patent and the Pachter reference, it would have been even more obvious that one could alkylate TZP under the general Pachter conditions. FF D 92. The expectation of success would have increased to 95% with the addition of Worley because the Worley compound is more similar to TZP in that it is a lactam and it also contains a sulfur atom in the same

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[43] Abic's expert, Dr. Taylor believes that Worley, which uses a substrate having a six-member heterocyclic ring, is closer prior art to the '035 patent than Nagarajan, discussed below, which uses a substrate with a seven-member heterocyclic ring (like TZP) but is an oxazepinone. FF D 91.

position as TZP. FF D 92.

d. Johnstone

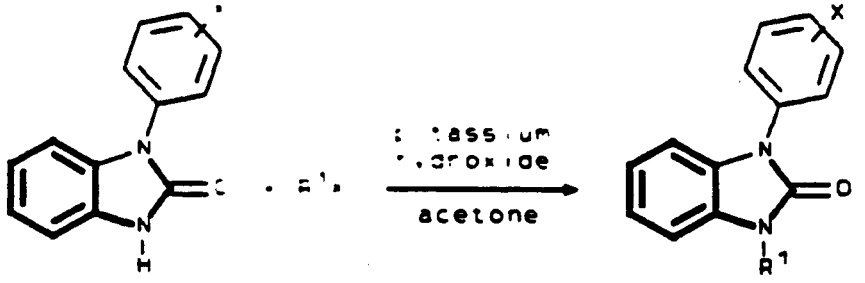
In 1969, a technical article, Johnstone et al., "A Rapid Method of N-alkylation of Amides," 16 J. Chem. Soc. 2223-24 (1969)("Johnstone"), reported the use of Pachter conditions to alkylate a substrate that is not an N-aryl amide, calling Pachter "a singular example of easy alkylation of an amide...." FF D 93.

In Johnstone, a base/solvent combination of potassium hydroxide/acetone was successful, whereas sodium carbonate/acetone did not work. FF D 94. The Johnstone use of the Pachter reference and the use of Pachter conditions is one further indication that people working on amides looked to reactions performed on other amides, even if they involved very different substrates. FF D 95.

Specifically, Johnstone shows an appreciation of the potential generality of the Pachter technique, and that the Pachter technique was used as a general technique. FF D 96.

e. Clark

In 1978, Clark et al. reported the following N-alkylation reaction, in which the N-aryl amide "was alkylated with alkyl halide and refluxing acetone solution in the presence of powdered potassium hydroxide according to the method of Pachter and Kloetzel" as follows:



FF D 97.

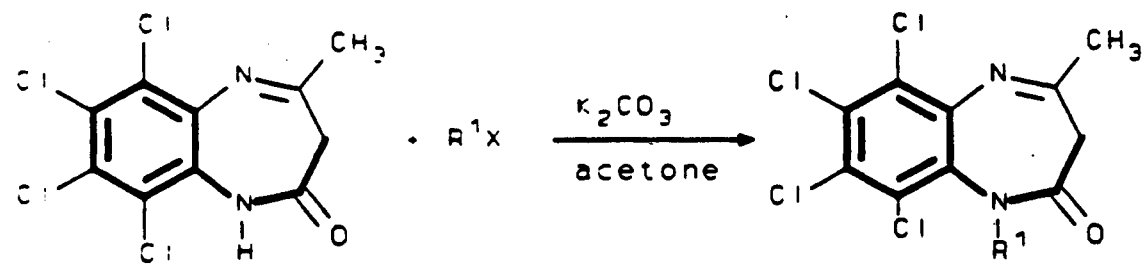
Clark discloses 40 examples of hydrous reactions on 40 compounds using Pachter conditions (a base/solvent combination of potassium hydroxide/acetone), and reports satisfactory yields. FF D 98. Clark reports the use of Pachter conditions with dialkylaminoethyl chloride in many of the reactions. FF D 100.

f. Latif

Latif refers to Pachter as a general process for the alkylation of amides that is applicable for almost all types of alkyl halides. FF D 101. Although Latif observed some limitations for use of the Pachter technique, Latif records no limitation with respect to any N-aryl amide. FF D 102.

g. Burton

The N-alkylation of N-aryl amides using the base/solvent combination K_2CO_3/acetone was taught as early as 1968, by Burton et al., "Halogeno-o-phenylenediamines and Derived Heterocycles Part I. Reductive Fission of Benzotriazoles to O-Phenylenediamines," 10 J. Chem. Soc., 1268-73 (1968)("Burton"). FF D 120. Burton disclosed the following N-alkylation reaction using K_2CO_3/acetone:



FF D 120.

b. Nagarajan

In the May 31, 1994 Notice of Intent to Issue Reexamination Certificate, the examiner stated:

> Perhaps the most pertinent references are the British Patent and Nagarajan et al. Both of these references show the aminoalkylation of lactams which bears some structural relationship to those of Kugita et al. using a process similar to Pachter et al. However, all of the compounds which are amino alkylated contain an activating nitro group when the Pachter-type process is employed. Nagarajan et al. shows that where no activating nitro group is present that the more harsh methods, similar to those of Kugita et al., must be employed. This indicates that where, activating nitro group is not present, the Pachter et al. technique is not operable. This teaches away from the process of Gaino et al. the patent being reexamined here.[44]

FF D 103.

This statement of the PTO examiner is incorrect. It is a singular example of his being misled by the declaration filed by complainants' expert, Dr. Kende. In his experiments, Nagarajan started with '257 conditions and then switched to Pachter conditions. FF D 109. Nagarajan went to Pachter conditions because certain alkylations did not proceed under '257 conditions. Id.

Nagarajan used '257 conditions on the unsubstituted, i.e., no nitro-substitution, compounds because these were the conditions commonly used at the time. However, as Pachter taught, under '257 conditions, a nitro group is a deactivating group. FF D 104. Nagarajan found that while he was unable to alkylate nitro-substituted compounds under '257 conditions, the Pachter conditions worked well. FF D 108, 109, 115.

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[44] While British patent 1,106,119 was not a principal reference used at the hearing in this investigation, considerable evidence was adduced about the Nagarajan reference.

Contrary to the examiner's statement, the Nagarajan paper does not teach that N-alkylation under Pachter conditions will not work with compounds that are unsubstituted with the nitro substituent. FF D 117. Nagarajan simply used '257 conditions to alkylate, and (as taught by Pachter) those compounds that contained an activating nitro group did not proceed. Nagarajan could have used Pachter conditions to alkylate all the compounds.

Thus, the PTO examiner's conclusion on reexamination that the Pachter reference does not have general application in view of the literature is plainly incorrect.

Complainants' expert, Dr. Baldwin, stated in his declaration submitted to the examiner during the reexamination that "the Nagarajan reference suggested that ring cleavage was a distinct possibility under Pachter base/solvent conditions of seven-member oxazepines. (See, Experimental, page 245(d)). This too would have taught away from the process of the '035 patent." FF D 111. Also, Dr. Kende, in his declaration referred to Nagarajan's discussion of ring cleavage. FF D 110.

The statements of both experts, Drs. Baldwin and Kende are incorrect.[45] Nagarajan did not report ring cleavage with potassium carbonate and acetone. Nagarajan reported ring cleavage with '257 conditions, and no ring cleavage with Pachter conditions. FF D 115. If there is no nitro group, as there is none with TZP, there is no problem of ring cleavage. As expressly stated in Nagarajan, the ring cleavage noted in that reference depends upon the presence of the nitro group. Under Pachter conditions there is no problem of ring cleavage. FF D 116.

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[45] At the hearing, Dr. Kende stated that he did not see the connection between Nagarajan and the '035 substrate. FF D 111. Although he contributed substantially during the tutorial, Dr. Baldwin did not testify at the trial.

i. The Branca '522 Patent

Based upon Dr. Baldwin's declaration, the examiner stated that the Pachter reference would have provided little if any guidance, regarding the use of DMC or its hydrochloride salt in the N-alkylations of the '035 patent using a Pachter-type base/solvent combination. In his order of May 2, 1994 granting the request for reexamination the PTO examiner stated that the equivalents of methyl iodide and DMC has not been demonstrated using the conditions of the '035, but only under the harsher conditions employed in the '257 patent.[46] FF D 121.

This statement of the examiner is also incorrect and appears to be the result of misleading statements in the Baldwin declaration to the PTO. The prior art which was not of record during the reexamination shows that the equivalents that the examiner thought were missing, i.e., the equivalence of methyl iodide and DMC using the conditions of the '035 patent, actually exist. FF D 123. Also as Dr. Pachter testified methyl iodide is routinely used as a scouting or probing alkylating agent. If there is success in the reaction DMC or some other more complex agent is used. FF D 203, 204, 205.

The '522 patent discloses the alkylation of a seven-member ring lactam using DMC with a weak inorganic base, such as alkali metal carbonate (e.g., potassium carbonate) in a solvent such as a lower alkanone (e.g., acetone). FF D 126.[47] The substrate in the '522 patent is an N-aryl amide seven-member ring structure, which is a benzodiazepinone. Indeed, it is a seven-member

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[46] This matter was not addressed by the examiner in the notice to issue the reexamination certificate. See RX 1654.

[47] U.S. Letters Patent 4,377,522, issued to Quirico Branca in 1983, is prior art based on its filing date before the Japanese counterpart to the '035 patent.

ring benzodiazepinone where the N-aryl amide linkage is the same as it is in TZP. FF D 127.

Benzodiazepines are related to benzothiazepines in that they have a six member ring fused to a seven member ring and they have the amide; however, they lack the sulfur. FF D 129.

The Branca patent provides an example of the kind of art the examiner said was not before him, showing the equivalence of methyl iodide and DMC. Branca provides an example of a substrate similar to TZP that is alkylated under '035 conditions with a dialkylaminoethyl halide and methyl iodide. FF D 131. See supra at 112 (Tanabe's use of methyl iodide).

j. The Bebenburg '887 Patent

U.S. Letters Patent 3,910,887, which issued to Walter von Bebenburg in 1975, was not of record during the reexamination on the '035 patent. It discloses a seven member N-aryl amide ring alkylation using DMC as the alkylating agent, and potassium carbonate/acetone as the base/solvent combination. FF D 133.

The '887 patent suggests that one can N-alkylate a seven-member ring using either methyl iodide or DMC and a base/solvent combination of potassium carbonate/acetone. FF D 134.

k. The '338 Schenker Patent

U.S. Letters Patent 3,644,338, which issued in 1972 to Karl Schenker, is not of record in the reexam. FF D 135. Schenker discloses the alkylation of a compound which, although not an aryl amide, is an amide with a seven-member ring. The reaction uses DMC as one of the possible alkylating agents, potassium carbonate as a possible base, and acetone as a possible solvent. Id.

The Schenker substrate has the nitrogen and the carbon double bond oxygen reversed in position from that of an N-aryl amide, so now the C double 10 group is attached to the aromatic ring and the nitrogen is not. The substrate is called a benzamide, which is an amide. FF D 136. Dr. Pachter testified that benzamides were substrates with which his conditions did not always work. FF D 137.

The Schenker patent teaches that:

> The reaction is advantageously performed in the presence of a solvent such as a polar solvent, for example in a lower alkanol such as methanol or ethanol or in a lower alkanone such as acetone and especially in the presence of a condensing agent such as a weak inorganic base such as sodium or potassium carbonate, or in weak organic base such as a tertiary amine . . . .

Id.

The solvents referred to in Schenker are the kind of solvents that are capable of solvating potassium, such as a polar solvent. FF D 138.

Schenker also teaches that one should avoid strong bases (such as those found in the '257 patent) because their use results in low yields. FF D 139. Indeed, Example 2 of Schenker discloses finely grounded potassium carbonate in acetone, with DMC·HCl. FF D 140. Example 5 of Schenker discloses finely ground potassium carbonate in acetone, with DMC·HCl. FF D 141.

Schenker is closer art to the '035 patent than the Nagarajan article. FF D 142. In fact, Abic's expert is of the opinion that Schenker is closer to the '035 patent than any reference of record. FF D 143. Schenker discloses the same base/solvent combination and alkylating agent disclosed in the '035 patent, whereas Nagarajan used sodium hydroxide (a different base) and acetone in a homogenous solution. FF D 142.

Thus, Schenker is prior art to the '035 patent disclosing Pachter-like conditions to perform an N-alkylation reaction of a compound having

similarities to TZP, including a seven-member ring.

1. The Krapcho '006, '889, '967 and '902 Patents

During the reexamination of the '035 patent, the examiner relied upon the testimony of Dr. John Krapcho, which was included in Tanabe's response to the November 18, 1994 Office Action, stating:

> Dr. Krapcho is virtually the founder to the entire field of 1,5-Benzothiazepine-4-ones (as well as other closely related compounds ... Contrary to requestor's argument Dr. Krapcho's testimony is seen as relevant. This relevancy is shown by the pioneering nature of Dr. Krapcho's work as evidenced by the Krapcho patents of record and Reexam 90/003,044. The fact that such an expert in this field should be surprised that the process in Gaino et al. '035 should work with a dramatic and consistent increase in yields is entitled to considerable weight. If such an expert should be surprised, just how would such a process be so obvious to one or ordinary skill in the art (as requestor would have us believe)?

FF D 182.

Indeed, Dr. Krapcho testified that he was extremely surprised, at the success of the hydrous N-alkylation of TZP. He stated he had worked solely with anhydrous alkylating conditions, that it is surprising to him that alkylation could take place under hydrous conditions such as the '035.[48] FF D 183.

Respondents and OUII rely on four patents issued to Dr. John Krapcho as prior art, and to address the issue of his alleged surprise.

The Krapcho patents (U.S. Letters Patent 3,895,006; U. S. Letters Patent 3,948,889; U.S. Letters Patent 3,075,967; U.S. Letters Patent 3,455,902) describe the N-alkylation of benzothiazepinones, and are relevant to the alkylation of benzothiazepinones in general. FF D 179, 181. TZP is a 2,3-

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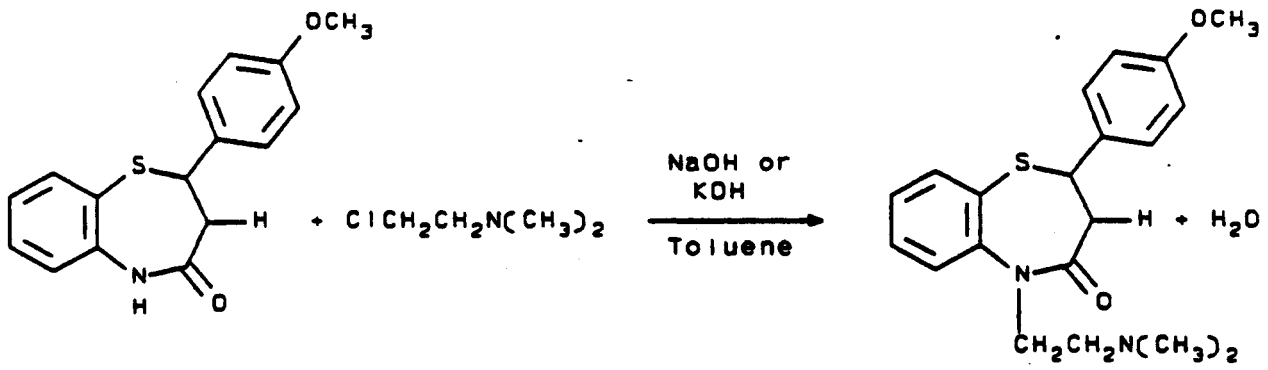
[48] Complainants used the term "hydrous" during the hearing to include a system having a base or solvent that contains a small amount of water. Complainants' expert, Dr. Kende, defined anhydrous as completely free of water and hydrous as not completely free of water. FF D 184.

dihydrobenzothiazepinone. FF D 180. The '967 patent was the principal reason for the initial rejection of the '035 patent by the European Patent Office, and other foreign patent offices. The general Formula II of the '967 patent includes the following 2,3-dihydrobenzothiazepinone (shown in the '967 N-alkylation reaction):



FF D 145.

Contrary to Dr. Krapcho's expression of surprise, the Krapcho patents teach the use of hydrous systems for the N-alkylation of benzothiazepines.[49] FF D 144, 146. The '006 and '889 patents, which contain an identical Example 1B, teach the N-alkylation of benzothiazepinones using sodium hydroxide and toluene in a system that generates water. FF D 144.

The reaction described in Example 1B of the '006 and '889 patents is illustrated as follows:

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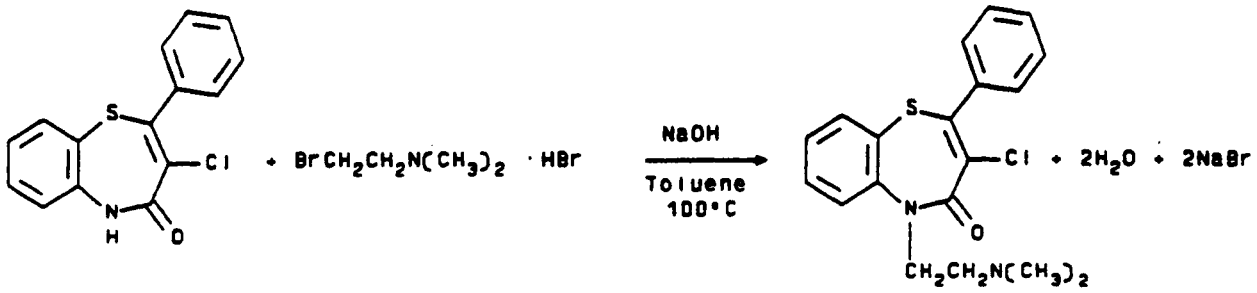
[49] Dr. Krapcho did not specifically bring any of his patents to the attention of the patent examiner during the reexamination proceeding. FF D 187.



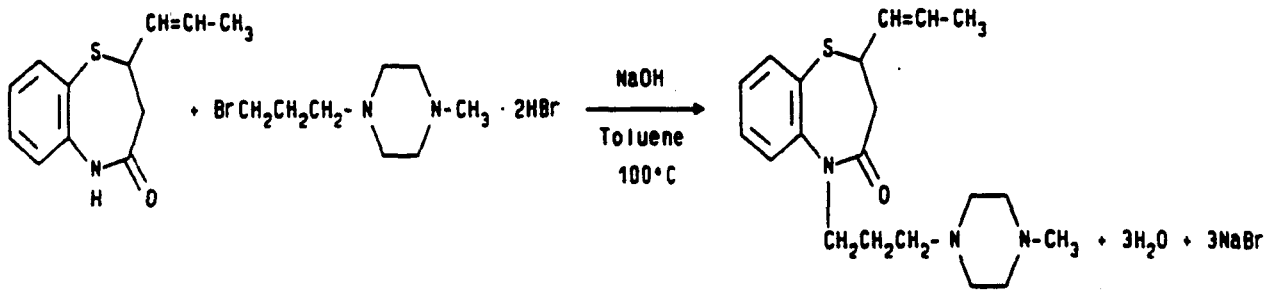
FF D 145.

An organic chemist of ordinary skill in 1981 would have recognized that the N-alkylation reaction in Example 1B of the '889 and '006 patents was carried out in a hydrous system as opposed to an anhydrous system. This is true even if "great pains" were taken to dry the toluene, glassware and other equipment of the reaction system. FF D 146.

The starting material in Example 1B of the '006 and '889 patents contains a phenyl group at the two position of the benzothiazepine molecule, and column 1 of those patents also describes a methoxyphenyl at the two position, which is the identical substituent contained at the two position of TZP. FF D 147. The reaction system in Example 1B of the '006 and '889 patents is a "reversible" reaction system. FF D 152. The alkylating agent used in Example 1B of the '889 and '006 patents, dimethylaminoethyl hydrobromide, is one of the alkylating agents encompassed by claim 1 of the '035 patent, specifically because claim 1 of the '035 patent broadly states "dimethylaminoethyl halide." FF D 153. Complainants' expert, Dr. Baldwin, believes that if TZP was used as the starting material in the N-alkylation process of Example 1B of the '006 and '889 patents, that process would be equivalent to the process of the '035 patent. FF D 148.

The '902 patent describes the use of sodium hydroxide and toluene in a

hydrous system for the N-alkylation of a 2,3-dihydrobenzothiazepinone.[50] FF D 157. The N-alkylation reaction described in Example 4 of the '902 patent may be illustrated as follows:



FF D 158.

The substrate for the N-alkylation reaction of the '967 patent differs from TZP (the substrate of the '035, '257, and the accused processes) only by the substitution of hydrogen (H) for hydroxyl (OH) at the 3 position of the TZP molecule. FF D 165.

The N-alkylation reactions disclosed in the Krapcho '967, '889, '006 and '902 patents are hydrous reactions, for at least two reasons. First, when the base, sodium hydroxide, deprotonates TZP, water is produced. Second, hydrogen chloride or hydrogen bromide from the alkylating agent will react with the sodium hydroxide to produce water.[51] FF D 176.

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[50] The Krapcho '902 patent, example 4, describes N-alkylating the N-aryl amide of a benzothiazepinone with an aminopropyl halide with sodium hydroxide and toluene. FF D 159. The '967 patent teaches the use of an "alkali metal hydroxide" in combination with toluene to N-alkylate a 2,3-dihydrobenzothiazepinone. An alkali metal hydroxide would include sodium hydroxide or potassium hydroxide. FF D 163. The definition of the alkylating agent provided in the '967 patent includes dimethylaminoethyl chloride (DMC). FF D 168. The substrate in example 4 of the '902 patent is a 2,3-dihydrobenzothiapinone, like the structure of TZP. FF D 159.

[51] None of the Krapcho patents contains any comment regarding possible negative side-reactions, or that the alkylating agent, DMC, is unstable. Example 1B of the '889 and '006 patents teaches that the alkylating agent used

(continued...)

A chemist who understood the teaching of Pachter, Worley, and Nagarajan could not be surprised that N-aryl amides could be alkylated under Pachter-type hydrous conditions of potassium hydroxide and acetone or potassium carbonate and acetone. To the extent that Dr. Krapcho's alleged surprise at the successful N-alkylation of TZP using hydrous conditions affected the decision of the examiner, that surprise on Dr. Krapcho's part must be discounted by the teachings of Dr. Krapcho's own patents, which show the hydrous N-alkylations of substrates similar to TZP. Thus, the examiner if he had properly examined Dr. Krapcho's patents would not have been surprised that TZP could be alkylated under hydrous conditions particularly if he had been informed of complainants' and Dr. Kraphcho's definition of "hydrous." FF D 186, 191.

m. Kugita I, II, III and IV

During the reexamination of the '035 patent, complainants' expert, Dr. Baldwin, submitted a declaration to the PTO in which he speculated that the following side reactions might occur (i) the so-called "retro-Michael reaction," (ii) alkylation of the amide oxygen, (iii) alkylation of the 3-hydroxyl, (iv) dehydration between that 2 and 3 position, (v) hydrolysis of the amide bond, and (vi) alkylation at the 1 and 2 positions under "certain

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[51](...continued)
in the N-alkylation reaction was sufficiently stable under the hydrous reaction conditions to alkylate the benzothiazepinone substrate and obtain a yield of N-alkylated product. FF D 177, 156. There is no suggestion or warning in the '967 (RX 3125), '889 (RX 3673), '006 (RX 3669), or '902 (RX 3647) Krapcho patents, which disclosed N-alkylation of benzothiazepinones in hydrous reactions, or that amide carbonyl O-alkylation would occur under hydrous conditions using sodium hydroxide and toluene. FF D 178. Nothing in the '902 patent suggests that side reactions will occur during N-alkylation. FF D 162. In the N-alkylation reactions described by Krapcho in the '967, '889, '006, and '902 patents, each of which occurred in hydroxide bases under hydrous conditions, no hydrolysis of the amide bond was reported. FF D 175.

conditions." Dr. Baldwin also speculated that dimethylaminoethyl halide alkylating agents might have been unstable under '035 conditions, thus reducing the yield of the reaction. FF D 209.

Many of the possible side reactions raised by Dr. Baldwin are described in a separate section of the Findings of Fact in this Initial Determination. FF D 265-331. Significant, individual prior art references which contradict Dr. Baldwin's declaration concerning side reactions are to be found in the published writings of Tanabe scientists, which are discussed immediately below.

i. Kugita I

In 1970, Tanabe scientists, in a paper referred to during the hearing as "Kugita I," H. Kugita et al., "Synthesis of 1,5-Benzothiazepine Derivatives. I," Chem. Pharm. Bull., 18(10) 2028-37 (1970), reported treating TZP with hot aqueous hydroxide to the destruction of the molecule. From the results reported in Kugita I, it could be concluded that the stereochemistry of TZP was not disrupted even under these conditions. FF D 194.

Kugita I, a paper of which both Drs. Baldwin and Kende were not aware, clearly shows that under aqueous alkaline conditions a retro Michael reaction does not result. FF D 211.

In Kugita I (which cites the Mills and Whitworth retro Michael paper) Tanabe was investigating whether it could get retro Michael like Mills using TZP. However, no retro Michael occurred. FF D 212. A chemist who was aware of Kugita I would "absolutely not" have expected a retro Michael reaction using Pachter conditions to alkylate TZP using DMC. FF D 213. Indeed, none of the Kugita papers reported a retro Michael. FF D 214.

ii. Kugita II

In his declaration submitted to the patent examiner during the reexamination proceeding, Dr. Baldwin stated:

> [I]n Pachter, only methylation with methyl iodide is performed on non-lactam substrates. Pachter does not alkylate with any amide with the highly reactive and unstable DMC or any closely related alkylating agent. Alkylation conditions used for methyl iodide could not have been extrapolated to dissimilar alkylating agents such as DMC because of the differences in the structure stability and reactivity of the different alkylating agents.

FF D 195. The examiner during reexamination then found that the equivalence of methyl iodide and DMC had not been demonstrated under '035 conditions. FF D 196. However, the prior art demonstrates that methyl iodide provides a reasonable model for alkylation with DMC. Methyl iodide is routinely used as a probing agent. FF D 199, 200, 203, 204.

For example, Tanabe scientists first used methyl iodide as the alkylating agent followed by using DMC as the alkylating agent, both with a 20 percent excess of alkylating agent, thus indicating that Tanabe scientists believed there to be no difference between the two for the purpose of conducting test reactions. FF D 205. Using conditions other than those of the '035 patent, Kugita II (H. Kugita et al., "Synthesis of 1,5 Benzothiazepine Derivatives. II," Chem. Pharm. Bull., 18(11) 2284-89) used methyl iodide as the alkylating agent, and Kugita III (RX 3809) used DMC as the alkylating agent. The results in these cases were comparable.[52] FF D 206.

The mechanism of alkylation is almost irrelevant to the expectation that methyl iodide and DMC will both act as appropriate alkylating agents. Differences between the mechanism of alkylation with DMC and methyl iodide are not important for determining whether the '035 processes are obvious. FF D

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[52] Nagarajan (RX 3820) methylated (N-alkylated) with methyl iodide. After succeeding with methyl iodide, Nagarajan used DMC. FF D 119.

199.

When medicinal chemists begin to develop reactions for their compounds, the first alkylating agent they usually use is the simplest alkylating agent, namely methyl iodide or methyl sulfate. This methylation reaction serves as a model. Chemists work out reaction conditions with the simplest compound possible. After working out reaction conditions, medicinal chemists then use DMC or other related alkylating agents using the same procedures as used with methyl halide to make the desired compound. FF D 200.

DMC is used to alkylate TZP in order to allow the compound to dissolve in water and thus enter the bloodstream either orally or by way of injection. FF D 201. DMC and related alkylating agents are among the most common of side chains put on drug molecules. Thousands of examples exist in the literature of alkylation with DMC and related dialkylaminoalkyl halides. FF D 202. Chemists use the same conditions for alkylating with methyl iodide and DMC, and, at least for the purposes of experimentation and development, DMC and related compounds have been used in medicinal chemistry for over 50 years. FF D 203. In fact, Dr. Pachter knows of no examples related to a pharmaceutical compound where a chemist started the alkylation reaction by using methyl iodide and then switched to DMC and the desired result was not obtained. FF D 204.

iii. Kugita III

Eleven years before the priority date of the '035 patent, Tanabe scientists had concluded that when sodium hydride was used as a base in the N-alkylation reaction, low yields and numerous side reactions resulted. H. Kugita et al., "Synthesis of 1,5-Benzothiazepine Derivatives. III," Chem. Pharm. Bull., 19(3), 595-602 (1971)("Kugita III"), states that "[r]eaction of

2-aryl-3-hydroxy-2,3-dihydro-1,5-benzothiazepin-4(5-ones (I) with dialkylaminoethyl halides and dioxane using sodium hydride as a base afforded the N-dialkylaminoalkyl derivatives (II) in low yields." FF D 207.

Table I in Kugita III reported the result of numerous N-alkylation reactions, and in those in which sodium hydride was used as the base, the yields were low. Id. By contrast, it is further stated in the Kugita III article that "[t]he reaction in the presence of dimethylsulfinyl carbanion and dimethylsulfoxide resulted in a remarkable increase in the yields (Table I)." FF D 208.

iv. Kugita IV

In Kugita IV (H. Inoue et al., "Synthesis of 1,5 Benzothiazepine Derivatives. IV," Yakugaku Zashhi, 93(6) 729-32 (1973)), N-alkylation of TZP with DMC was reported with a very high yield, thereby indicating that no major side reactions occurred. FF D 210.

n. Tanabe's KOH/DMSO Process

During the time Dr. Baldwin was present at the interview with the patent examiner, the examiner was never told about the KOH/DMSO process. FF D 239. The examiner also was not told during the interview that Tanabe regarded alkylation processes that used bases and solvents other than those specifically identified in the '035 patent to be equivalent to those in the '035 patent. Id.

During reexamination of the '035 patent, the examiner was presented with about 172 prior art references. FF D 240. Rather than expressly disclosing the KOH/DMSO process to the Examiner during Reexamination, Tanabe submitted a book, entitled, Diltiazem from Birth to Today, that contained over 250 pages, of which one sentence on one page referenced the KOH/DMSO process. That page

was not pointed out to the examiner. FF D 241.

In the "Information Disclosure Statement Under 37 C.F.R. §1.555," submitted to the PTO by Tanabe's counsel, Tanabe requested that the examiner take particular note of specified patents and publications. The book Diltiazem from Birth to Today was not one of those references. FF D 242.

The one page of Diltiazem from Birth to Today which allegedly disclosed the KOH/DMSO process, reads in pertinent part as follows:

> The N-alkylation of the lactam was also studied through close collaboration between the Organic Chemistry Research Laboratory, Onoda Factory and the Pharmaceutical Technics Division. They found that the reaction proceeds easily by the use of potassium carbonate and ethyl acetate in place of potassium hydroxide and dimethylsulfoxide. These two improvements were accomplished at the same time that diltiazem was being introduced overseas and greatly contributed to a plan for a plant with increased output and more efficient production.

FF D 243.

That sentence does not disclose that the material made by the KOH/DMSO process had been imported into the United States. Rather it leaves the impression that Tanabe was building a plant for potassium carbonate/ethyl acetate to make the compound to send to the United States. Furthermore, it does not explain that the KOH/DMSO process, like the '035 process, was hydrous. FF D 244.

In any event, it cannot be assumed that the examiner read that sentence. As a matter of PTO practice, the placement of examiner's initials next to a cited reference indicates that the reference was expressly considered by the examiner. (Manual of Patent Examining Procedure ("MPEP") § 609). The examiner placed his initials next to the reference, Diltiazem From Birth To Today. However, without knowing what he was looking for, that one page would have been extremely difficult to find. Even if the examiner had found it, it

would not disclose the essential facts that largely make the KOH/DMSO process prior art; namely, that the product of the KOH/DMSO process was sold in the U.S. more than one year prior to the application which led to the '035 patent. See FF D 243.

During the reexamination of the '035 patent, complainants also did not inform their expert, Dr. Baldwin, about Tanabe's KOH/DMSO process. Dr. Baldwin first learned about the KOH/DMSO process in May 1994, four months after he had prepared and signed his declaration. FF D 245.

Assuming the KOH/DMSO process was conducted under hydrous conditions, Dr. Baldwin agreed that it was relevant to his declaration. FF D 255. In fact, Dr. Baldwin believes that the patent examiner would have wanted to know that Tanabe had used the KOH/DMSO process for a number of years prior to the '035 process, and if Dr. Baldwin had known about the KOH/DMSO process, he would have told the patent examiner about it. FF D 256, 257.

Despite the initials of the examiner that he had considered the book, Diltiazem: From Birth to Today, it appears that the PTO examiner was not aware of the Tanabe KOH/DMSO process, and thus the reexamination proceeding was conducted with a serious deficiency as to the contents of the prior art.

The KOH/DMSO process is highly relevant prior art to the '035 patent. The production of diltiazem using the base/solvent combination KOH/DMSO is a hydrous system, like the '035 process, and the yields obtained by KOH/DMSO and KOH/acetone were, in the words of a Tanabe witness, "about the same." FF D 250. A May 1981 Tanabe report stated that the yield using the KOH/DMSO method was 85%. FF D 251.

In 1981, the inventors of the '035 patent sought to find a solvent to replace DMSO because it was difficult to recover. They kept KOH as the base

and quickly settled on acetone. FF D 252. In May 1981, Tanabe scientists reported that the reaction using acetone as a solvent proceeds to the same degree as it did using DMSO. FF D 253. In June 1981, Tanabe scientists reported that "alkylation can take place in the same manner when KOH/DMSO is replaced with KOH/acetone." Id.

The KOH/DMSO system used by Tanabe for the commercial manufacture of diltiazem falls somewhere between '257 and '035 conditions in terms of reactivity. The KOH/DMSO system thus falls in the middle of the reactivity of c disclosed the KOH/DMSO process, reads in pertinent part as follows:

> The N-alkylation of the lactam was also studied through close collaboration between the Organic Chemistry Research Laboratory, Onoda Factory and the Pharmaceutical Technics Division. They found that the reaction proceeds easily by the use of potassium carbonate and ethyl acetate in place of potassium hydroxide and dimethylsulfoxide. These two improvements were accomplishompounds tested by Dr. Pachter. Thus, in Dr. Pachter's opinion, because KOH/DMSO and '257 conditions succeeded, so should '035 conditions. FF D 259.

The KOH/DMSO process and the '035 process work in the same way. See FF D 261. Both the KOH/DMSO process and the '035 process use the TZP substrate. The base and solvent of the KOH/DMSO process are interchangeable with the '035 bases and solvents. DMC and the aziridinium ion[53] are present in both the KOH/DMSO process and the '035 proces conditions on TZP because the KOH/DMSO process showed success using the identical substrate under aqueous, KOH basic conditions. FF D 264.

3. Instances in Which the PTO Examiner Was Mislead

The PTO examiner reached a number of erroneous conclusions on his own or due to the errors and misrepresentations of Tanabe and its experts. The

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[53] An explanation of the aziridinium ion is contained, infra, in the findings of fact on the tutorial session.

examiner was incorrect in concluding that the Pachter reference does not have general application to the alkylation TZP. Clearly, it is well established in the art as a method for alkylating N-aryl amides, including TZP. The examiner was incorrect in concluding that Nagarajan shows that where no nitro group is present '257 conditions must be used. Nor did Nagarajan report ring cleavage under Pachter conditions. The examiner was incorrect in concluding that DMC and methyl iodide (used by Pachter) are not equivalent. The equivalent use of DMC as an alkylating agent for methyl iodide is well known to one of ordinary skill in the art and had been demonstrated with '035 conditions. The use of hydrous conditions for the N-alkylation of TZP had been demonstrated by Kraphco and Tanabe. Many possible side reactions raised by Tanabe's experts, including the retro-Michael, were not of concern to one of ordinary skill in the art, having in some cases been shown not to occur with TZP under aqueous alkaline conditions. Finally, highly material prior art showing the N-alkylation of TZP with potassium hydroxide and DMSO was withheld from the PTO examiner.

4. Additional Evidence Concerning the Issue of Possible Side Reactions

As stated above, complainants' experts, Drs. Baldwin and Kende, argued to the examiner that the claimed '035 process was nonobvious, in part, because of the possibility of side reactions that would have prevented high yields. In granting the request for reexamination, the examiner stated in part as follows:

> The arguments concerning the possibility of side reactions by Taylor, Baldwin in [sic] Kende are not seen as having great weight in this particular case one way or another. Nor are the arguments concerning the use of DMC·HCl.

FF D 16. The issue of side reactions should not play a major role now in determining whether the claim 1 of the '035 patent is obvious.

Furthermore, the evidence adduced at the hearing demonstrates that side reactions frequently occur in the course of experimentation, and avoidance of side reactions is not necessary in order for one of ordinary skill in the art to try a reaction or to consider it successful. In addition, there is strong evidence that one of ordinary skill in the art would have known that the specific side reactions raised by complainants would not occur in large proportions or could not occur at all in the N-alkylation of TZP, especially under Pachter conditions. See FF D 265-331.

5. Conclusion on the Differences Between the Prior Art and the Claimed Invention of the '035 Patent

The only difference between the prior art as a whole and the claimed invention of the '035 patent is that there was no previously reported N-alkylation using Pachter conditions specifically on TZP. There had, however, been numerous and successful reported N-alkylations of other N-aryl amides and benzothiazepines (with the same functional groups as TZP), as well as complex molecules sharing structural features with TZP using Pachter conditions.

C. Level of Ordinary Skill in the Art

The level of ordinary skill in the art was very high in 1981, at the time of the alleged invention claimed in the '035 patent. A person of ordinary skill in the art had a Ph.D. with process development experience, or the equivalent. FF D 335.

The person of ordinary skill would be an industrial, process development chemist, in contrast to a discovery or "bench" chemist. Bench chemists had different objectives than those of a process development chemist. Bench chemists had as their objective the preparation of small quantities of material, without concentrating initially on the yield. Once a product showed

promise, it was given to process development chemists whose objective was to develop procedures that would provide a more practical synthesis. FF D 333.

Organic process development was a sophisticated field of technology in 1981. Thus, the person of ordinary skill would be familiar with the literature of organic chemistry and would be especially familiar with the patent literature in his or her field of study. FF D 336.

D. Objective Indicia of Nonobviousness

Complainants take the position that objective indicia of nonobviousness (secondary considerations of nonobviousness) confirm the validity of the '035 patent. Complainants' Post-Hearing Brief at 22-23; Complainants' Proposed Findings of Fact 454-457.

Complainants contend that the '035 patent has been commercially successful in that it allows Tanabe to produce diltiazem less expensively and in sufficient quantity to meet MMD's increasing demands then it could using its previous KOH/DMSO process. Complainants further contend that a long felt need for the process of the '035 patent is demonstrated by the fact that Tanabe used what it terms "harsh, inefficient reaction conditions of the KOH/DMSO process" for nearly ten years before it discovered and used the mild, efficient conditions of the '035 patent.

As discussed above in connection with the KOH/DMSO process as prior art, the Tanabe scientists developed the '035 process as an improvement over the KOH/DMSO process, particularly with respect to cost. It appears that the Tanabe scientists were successful in that regard because they could replace the DMSO with another, more easily recovered, solvent. However, the yields obtained with the '035 process are comparable to those of the KOH/DMSO. FF D 250. Furthermore, the mild conditions of the '035 process do not stand in

contrast to the KOH/DMSO process as much as they would to the dangerous '257 process, which used sodium hydride. FF D 259, 260.

Complainants allege that a failure of others to develop a commercial process to manufacture diltiazem is demonstrated by the activities of the various respondents and the vast amount of testing required, over many years, for them to develop their commercial processes. Complainants also contend that it may be inferred that all respondents copied the invention disclosed in the '035 patent.

One respondent, Profarmaco, designed around the '035 patent when it obtained a copy of the patent or its foreign counterpart. FF D 20-26. Another, Abic, developed its own process, independently.

The objective indicia of nonobviousness are not strong enough to overcome the clear and convincing evidence of obviousness presented by respondents and OUII.

E. Conclusion on Obviousness

The respondents and OUII have presented clear and convincing evidence that claim 1 of the '035 patent is invalid due to obviousness under section 103 of the Patent Act. The prior art taught one of ordinary skill in the art the ease and desirability of performing the N-alkylation of a benzothiazepine such as TZP under the mild, hydrous conditions disclosed by the Pachter and other references. The applicability of Pachter conditions for the N-alkylation in high yield of N-aryl amides and other compounds similar to TZP was also well known.

There is strong evidence that the examiner was misled during the reexamination of the '035 patent into erroneous reasoning by the incorrect and misleading assertions of complainants' experts. Also, some of the examiner's

conclusions are shown to be incorrect by prior art which was not of record before him.

V. THE '035 PATENT IS UNENFORCEABLE

A. General Legal Standards Applicable to the Issue of Patent Unenforceability; Duty of Disclosure During a Patent Reexamination

During reexamination of the '035 patent, Tanabe and its counsel, and all those substantively involved on behalf of Tanabe had a duty to disclose to the PTO all information known to them to be material to patentability, and an uncompromising duty of candor to the Patent and Trademark Office.[54] See 37 C.F.R. § 1.555.

The general rule concerning materiality is that information is material if there was a substantial likelihood that a reasonable examiner would have considered it important in deciding whether to allow the application to issue as a patent. However, a patentee has no obligation to disclose a reference that is cumulative or less pertinent than those already before the examiner. Halliburton Co. v. Schlumberger Technology Corp., 925 F.2d 1435, 1439-40 (Fed. Cir. 1991). Accord 37 C.F.R. § 1.56(b). During a reexamination, the PTO considers information to be material if: (1) it is in the form of a patent or printed publication that establishes (by itself or in combination with other patents or printed publications) a prima facie case of unpatentability of a claim, or (2) if the information refutes, or is inconsistent with, a position a patent owner takes in either opposing an argument of unpatentability relied upon by the PTO, or asserting an argument of patentability. 37 C.F.R. § 1.555(b).

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[54] FMC Corp. v. Manitowoc Co., Inc., 835 F.2d 1141 (Fed. Cir. 1987)(actions of applicant's attorney are chargeable to applicant).

Materiality does not depend upon whether the claimed subject matter is patentable over the withheld prior art. Driscoll v. Ceballo, 731 F.2d 878, 884 (Fed. Cir. 1984). See also Merck & Co., Inc. v. Danbury Pharmacal, Inc., 873 F.2d 1418, 1421 (Fed. Cir. 1989)(there is no "but for" standard of materiality).

While reexaminations are based on new questions of patentability over prior printed publications, "[a]n admission relating to any prior art (i.e., on sale, public use, etc.) established in the record or in a court may be used by the examiner in combination with patents or printed publications in a reexamination proceeding. The admission must stand on its own." Manual of Patent Examining Procedure ("MPEP"), § 2217 (1992).[55] See Quad Environmental Technologies Corp. v. Union Sanitary Dist., 946 F.2d 870, 875 (Fed. Cir. 1991); Ex parte Seiko Koko Kabushiki Kaisha, 225 U.S.P.Q. 1260 (P.T.O.B.P.A.I. 1984); Ex parte Kimbell, 226 U.S.P.Q. 688 (P.T.O.B.P.A.I. 1985); Ex parte McGaughey, 6 U.S.P.Q.2d 1334 (P.T.O.B.P.A.I. 1988). Furthermore, the MPEP provides, as follows:

> Where the subject matter for which a patent is being sought is, or has been involved in litigation, the existence of such litigation and any other material information arising therefrom must be brought to the attention of the Patent and Trademark Office; such as, for example, evidence of possible prior public use or sales, questions of inventorship, prior art, allegations of "fraud", "inequitable conduct" or violation of duty of disclosure. Such information might arise during litigation in, for example, pleadings, admissions, discovery including interrogatories, depositions and other documents, and testimony.
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> . . . As a minimum, the applicant should call the attention of the

[55] The MPEP is entitled to notice as an official interpretation of statute and regulations, to the extent that it is not in conflict with them. Litton Sys., Inc. v. Whirlpool Corp., 728 F.2d 1423, 1439 (Fed. Cir. 1984). No conflict is noted between the MPEP and the relevant statutes and regulations.

> Office to the litigation, the existence and the nature of any allegations of validity and/or "fraud", or "inequitable conduct" relating to the original patent, and the nature of the litigation materials relating to these issues. Enough information should be submitted to clearly inform the Office of the nature of these issues so that the Office can intelligently evaluate the need for asking for further materials in the litigation.

MPEP § 2001.06(c) (emphasis added). This section applies to applications for a patent as well as reexaminations. MPEP § 2014.

A patent is unenforceable if the patentee failed to disclose material information to the PTO, or submitted false material information, with an intent to deceive. Kingsdown Medical Consultants, Ltd. v. Hollister Inc., 863 F.2d 867, 872 (Fed. Cir. 1988), cert. denied, 490 U.S. 1067 (1989). Both materiality and intent to deceive must be proven by clear and convincing evidence. Id.

In cases of inequitable conduct before the PTO, "direct proof of wrongful intent is rarely available, but may be inferred, from clear and convincing evidence of the surrounding circumstances." LaBounty Mfg. v. U.S. Int'l Trade Comm'n, 958 F.2d 1066, 1076 (Fed. Cir. 1982). The conduct at issue must be viewed in light of all the evidence, including evidence of good faith. Kingsdown, 863 F.2d at 876.

B. Discussion

In September, 1993, complainants made the following admission in this proceeding:

> Diltiazem prepared by Tanabe in Japan using KOH and DMSO, then a trade secret, was sold to MMD more than one year prior to the filing of the '035 patent.

FF E 1.

On September 30, 1993, the Fermion respondents filed a motion for summary determination of patent invalidity based on the Tanabe KOH/DMSO process and

allegations of an on-sale bar. FF E 25.

Respondents and OUII assert that Tanabe, and those involved on Tanabe's behalf during the reexamination of the '035 patent at the PTO, engaged in intentional concealment of the Tanabe KOH/DMSO process, the sales of products manufactured by that process, and the on-sale bar issue raised in this investigation. Respondents and OUII take the position that the '035 patent is unenforceable.

Complainants deny those allegations, claiming that the Tanabe KOH/DMSO process is not prior art to the '035 patent, and that it was in fact disclosed to the PTO during reexamination of the '035 patent.

A reference need not render a patent invalid in order to be considered material. The Tanabe KOH/DMSO process (and sales of products manufactured by that process) is prior art to the '035 patent as shown above. At least claim 1 of the '035 patent is invalid in view of the prior art, including the Tanabe KOH/DMSO process.

Tanabe and its counsel were aware that the Tanabe KOH/DMSO process was a possible impediment to the patentability of the claimed invention of the '035 patent, and also stood in direct opposition to specific arguments in favor of patentability that Tanabe made during reexamination. For example, Tanabe repeatedly argued that the solvent systems disclosed and claimed in the '035 patent were hydrous and directly contrary to the strictly anhydrous systems of the '257 patent. FF E 30, FF D 183. However, the Tanabe KOH/DMSO is also "hydrous" as complainants have used that term. FF E 8.

At the time Tanabe filed its Japanese counterpart application to the '035 patent, Tanabe had used its KOH/DMSO N-alkylation process for several years to make commercial bulk diltiazem hydrochloride which was sold to, inter alia,

MMD in the United States. FF E 7, FF D 226, FF D 234. Tanabe also had drafted a patent application for the KOH/DMSO process claiming that it possessed the same advantages over the '257 patent as those ascribed to the process of the '035 patent. FF E 3. In fact, the introductory sections of the Japanese KOH/DMSO and '035 patent applications, setting forth the background of the invention, are strikingly similar, differing in only a few words. FF E 5. The Japanese application on the KOH/DMSO commercial process described that invention, in particular the benefits derived from it, in language virtually identical to that of the '035 patent:

> The above method of the present invention uses less expensive potassium hydroxide that is easier to use compared with the conventional sodium hydride. Another advantage is that it is free from the worry of explosive accidents. It is safe and excellent for industrial use.

FF E 6. Tanabe withdrew its Japanese application on the KOH/DMSO patent, and maintains that it did so in order to keep the process a trade secret. Nevertheless, Tanabe was well aware of the advantages of the KOH/DMSO over the '257 patent during the original '035 patent application and the reexamination of the '035 patent.

Thus, by December 7, 1981, when Tanabe filed its two Japanese N-alkylation applications, Tanabe was well aware that the prior commercial KOH/DMSO process had, some ten years earlier, solved the disadvantages of yield and danger of explosion occurring with the '257 process. Nevertheless, when Tanabe filed its application for the '035 patent in December 1982, Tanabe asserted that it was the '035 base/solvent combination which solved these problems. FF E 9.

Internal Tanabe documents, which were produced to respondents in this investigation through Tanabe's counsel, further illustrate that Tanabe knew of

the similarity of the KOH/DMSO process to that of the '035 patent. FF D 253.

Tanabe argued that "the '035 patent discloses the 'dramatic improvement' of its processes over those in the '257 patent," but did not tell the examiner that the Tanabe KOH/DMSO secret prior process had provided Tanabe with the same "dramatic improvement" and the same yield as the KOH/acetone process of the '035 patent. FF E 27. A Tanabe report from June 1981 states that "[i]t became clear that alkylation can take place in the same manner when KOH/DMSO is replaced with KOH-acetone in the reaction." FF E 28. Another Tanabe report from 1981 states that "[n]ormally DMSO is used as a solvent, however, the reaction proceeds to the same degree (y. 70 - 86%) with acetone. Acetone is considered advantageous since the reaction fluid has a light coloring, and the collection and disposal of the solvent is simple." FF E 29.

Tanabe repeatedly argued that the solvent systems disclosed and claimed in the '035 patent are hydrous and directly contrary to the strictly anhydrous systems of the '257 patent, yet Tanabe did not tell the examiner that the KOH/DMSO process also was hydrous. FF E 30. Tanabe also asserted during reexamination that "[t]o [Dr. Krapcho] the aqueous processes of the '035 patent that resulted in a 90 percent yield were 'a total surprise' and 'violated all that [he] knew.'" Yet, Tanabe did not tell the examiner that the prior Tanabe KOH/DMSO process was aqueous. FF E 31.

Tanabe argued that "the chemoselective alkylation of the processes of the '035 patent is critical to the industrial scale production of diltiazem," while failing to advise the examiner that the same chemoselective alkylation was possessed by its prior KOH/DMSO process for the "industrial scale production" of diltiazem hydrochloride, which was then sold in this country prior to the critical date. FF E 32.

In addition, under the provisions of the MPEP, discussed above, the materiality of the Tanabe KOH/DMSO process is underscored by the fact that Tanabe had a duty to disclose not only the existence of this litigation, but also material information pertaining to it, such as the fact that a Summary Determination motion had been filed alleging that the Tanabe KOH/DMSO process constituted an on-sale bar under § 102(b) rendering the '035 patent invalid. See MPEP §§ 2001.06(c), MPEP § 2014.

The evidence of record shows that Tanabe and its counsel were aware of the high level of materiality of the KOH/DMSO process to the reexamination of the '035 patent, and proceeded in the reexamination in such a calculated manner as to be sure that the existence, details and import of the Tanabe KOH/DMSO process would be concealed from the examiner.

In connection with the reexaminations, Tanabe submitted to the PTO declarations of patent experts, James Gambrell Esq. and Martin Adelman Esq., concerning transfers of diltiazem to MMD before the critical date of the '035 patent. Both declarations referred generally to the process used by Tanabe which "differed from the '035 process" (Gambrell at ¶ 11) or "is not disclosed in" the '035 patent (Adelman at ¶ 9). However, neither the Gambrell declaration nor the Adelman declaration identified the process as the commercial Tanabe KOH/DMSO process, or the fact that it was a hydrous process.[56] FF E 21. Both declarations indicated that Tanabe sold or provided diltiazem made by another process not disclosed in the patent to MMD for the

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[56] Tanabe also apparently withheld the identity of its prior commercial process from its experts until after the reexamination certificate was issued. FF E 22. Complainants' expert, Dr. Baldwin, conceded that this process should have been disclosed to the PTO. FF E 23. Another of complainants' experts, Dr. Liotta, testified on deposition that he considered the Tanabe KOH/DMSO process to be equivalent to the process of the '035 patent. FF E 24. He later changed his opinion.

purpose of obtaining FDA approval of the drug. However, neither declaration identified the KOH/DMSO process or referred to any commercial sales.

Tanabe's counsel sent a draft declaration to James Gambrell, which stated that diltiazem manufactured by Tanabe in Japan by a trade secret process was sold or provided free of charge to MMD for the purposes of obtaining FDA approval, and included the conclusion that such sales could not fall under the public use and on-sale provisions of 35 U.S.C. § 102 (b). FF E 33.

Mr. Gambrell revised his declaration. Although he retained the ultimate conclusion that Tanabe's transfers to MMD did not effect an on-sale bar, he added the caveat "this is not necessarily true if the product produced by the foreign process is used or sold in the United States without restriction. In re Caveney, 751 F.2d 671 (Fed. Cir. 1985)." FF E 34, 35.

After consultation with counsel for Tanabe, Mr. Gambrell revised his draft of the declaration, again. He deleted, among other things, the citation to In re Caveney, and the sentence immediately preceding the citation. Thus, his declaration now stated that "the language of § 102(b) does not apply to the practice of a process in a foreign country (whether secret or otherwise); hence it cannot be prior art against a U.S. patent." FF E 35. The declaration of James Gambrell went through a series of modifications by which the declarant's original concerns about the possibility of use or sales effecting an on-sale bar under In re Caveney were edited out, leaving the erroneous impression that no sales of diltiazem made in this country could possibly effect an on-sale bar if the patented process is performed overseas, despite the fact that the declarant in his earlier draft had stated that In re Caveney represents the applicable law.

Despite the fact that the Gambrell and Adelman declarations were written

in an indefinite manner so as not to reveal the base or solvent used in Tanabe's "different" process, complainants contend that they did in fact disclose the Tanabe KOH/DMSO process to the examiner during the reexamination because they cited a Tanabe book entitled Diltiazem From Birth to Today and provided the examiner with a copy.

Diltiazem From Birth to Today, a book of over 260 pages, was one of some 172 references in a September 1993 Information Disclosure Statement ("IDS"), and a November 1993 Supplemental IDS. FF E 17, E 19. Although the examiner placed his initials next to the citation of the book, there is no assurance that he read the entire book in order to find the single, obscure reference to the Tanabe KOH/DMSO process.[57] FF D 248, D 249.

The only mention of the Tanabe KOH/DMSO process in the book is a brief, one-sentence reference to the secret potassium hydroxide/DMSO process at page 33. FF E 11. The sentence reads as follows:

> They found that the reaction proceeds easily by the use of potassium carbonate and ethyl acetate in place of potassium hydroxide and dimethyl sulfoxide.

FF E 17.

No effort was made to point out this sentence. Furthermore, if the examiner read this sentence, it would not have revealed the information necessary for the examiner to consider the process as prior art. Other written sources, such as the pleadings in this investigation, would have informed the PTO of Tanabe's prior use of the process, and the sale of product of the process in the United States, as well as the fact that the process contained features which Tanabe claimed as arguments for patentability of the

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[57] The book Diltiazem From Birth to Today, is not listed in the reexamination certificate. FF E 12.

'035 process. The sale in the United States, prior to the critical date, of diltiazem hydrochloride made using the Tanabe KOH/DMSO process is not described in the book. FF E 20, E 13. Nor was an effort made to point out that the Tanabe KOH/DMSO process was "hydrous," as contrasted with the "strictly anhydrous" conditions of the '257 patent. FF E 13.

Thus, having only the book, which Tanabe asserted was not prior art, the examiner had no way of learning of the critical prior art sales.

Counsel's conduct with regard to the Tanabe book is analogous to the situation in Imperial Chem. Indus., PLC v. Barr Labs., 795 F. Supp. 619 (S.D.N.Y. 1992), in which the court stated:

> . . . ICI finally cited to the PTO, without discussion and buried in a list of references an article by Harper & Walpole . . . which referred to the mouse test results on the products. Absence of discussion of this far-from-highlighted item is more indicative of an intent to protect ICI's position than to call the matter to the attention of the PTO. The Harper & Walpole article was not cited in the patent specifications disclosed to the public.

Id. at 625. The same is true here. The manner in which the book was cited by Tanabe counsel is more indicative of an intent to conceal the KOH/DMSO process, than to disclose it to the PTO.

The actions of Tanabe and its representatives with respect to the non-disclosure of the Tanabe KOH/DMSO process are part of a larger pattern of misconduct. There is further misconduct which is exemplified by (1) events concerning the Krapcho '967 patent, and (2) arguments made to the examiner about supposed side reactions.

During the patent prosecution that led to the issuance of the '035 patent Tanabe did not disclose the '967 patent. During reexamination, Tanabe and its representatives mischaracterized the '967 patent.

The '967 patent discloses and claims the drug "thiazesim," a "parent" of

diltiazem. FF E 47. In fact, Tanabe's application for its '257 patent, which claims diltiazem, expressly acknowledges thiazesim as prior art. FF E 49. The '967 patent which claims thiazesim also discloses that alkali metal hydroxides, a class which includes potassium hydroxide, can be used in the N-alkylation of benzothizepines. FF E 48. In March 1983, while the application for the '035 patent was pending, the European Patent Office identified the '257 patent and the '967 patent as relevant prior art to the EPO counterpart of the '035 patent. FF E 51. The EPO subsequently rejected the European application as unpatentable over the '257 patent in view of the Krapcho '967 patent.[58] FF E 53. Furthermore, certain claims to an N-alkylation process which were presented in the application for the '257 patent were rejected by the PTO in the United States over, inter alia, the Krapcho '967 patent, and the claims were then cancelled by Tanabe. FF E 50. Nevertheless, at no time during the patent prosecution did Tanabe or its representatives cite the Krapcho '967 patent to the PTO. FF E 52.

Inasmuch as the Tanabe patent department in Japan was not knowledgeable about the disclosure requirements of the PTO, it was the policy of Tanabe to submit all potentially relevant information to their attorneys in the United States, so that the U.S. attorneys could determine what should be disclosed. FF E 54. Nevertheless, Tanabe did not submit the '967 patent to its attorneys in the United States. FF E 55.

Tanabe takes the position that it did not notify its attorneys in the United States about the '967 patent because it believed the '257 patent to be more relevant inasmuch as it disclosed a process for the manufacture of

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[58] The Israeli and the Finnish patent offices also rejected the respective '035 counterparts as unpatentable over the '257 and Krapcho '967 patent. FF E 53.

diltiazem. FF E 57. However, that explanation was not universal among the Tanabe witnesses. See FF E 56.

Furthermore, it is debatable whether in the context of the '035 patent which claims particular base/solvent combinations, that the '257 is more relevant. Tanabe knew that unlike the '257, the '967 discloses the use of one of the exact bases claimed by the '035 patent (i.e., potassium hydroxide), as well as an "aqueous" reaction. There has been no explanation as to why Tanabe took the initiative to evaluate for itself the degree of relevance of the '967 patent to the United States prosecution of the '035 patent, especially since the '967 was clearly so highly material to the '035 patent prosecution. Rather, an inference can be drawn that Tanabe knew that the '967 patent was material to its '035 patent application, and intentionally withheld it.

During reexamination, Tanabe distinguished the '035 process from that of the '257 patent on the grounds that the processes of the '035 patent were "aqueous," and thus "diametrically opposed to the anhydrous systems of the '257 patent." FF E 40. Tanabe also represented that Dr. Krapcho used only anhydrous processes, while concealing from the examiner the fact that Krapcho used alkali metal hydroxides as bases in combination with aprotic solvents, a system which complainants here assert is not anhydrous. FF E 41. Tanabe twice told the PTO that the '967 patent disclosed N-alkylations of benzothiazepines using "anhydrous" conditions. However, complainants here assert that the reference also discloses aqueous conditions. FF E 42. Indeed, the '967 patent conditions are "hydrous" conditions, as complainants use that term.[59] FF E 44.

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[59] British Patent No. 1,106,119 ("the British '119 patent") published in 1968, discloses alkali metal hydroxides generally, including potassium

(continued...)

Tanabe also made at least two misleading arguments regarding side reactions. They were the arguments that (1) ring cleavage or (2) the retro-Michael reaction of TZP might take place under Pachter ('035 conditions). FF E 60.

Complainants' expert, Dr. Baldwin, stated in his declaration submitted to the examiner, at paragraph 47, as follows:

> In addition, the Nagarajan reference suggested that ring cleavage was a distinct possibility under Pachter base/solvent conditions of seven-membered oxazepines (see Experimental,p. 245(d)). This too would have taught away from the processes of the '035 patent.

FF E 61. Later in his declaration, Dr. Baldwin stated as follows:

> Fifth, British '119 and Nagarajan, viewed together, also taught the distinct possibility of ring cleavage in using a Pachter-type base/solvent system, and for this reason, would have suggested that this system be avoided in the N-alkylation reactions of the '035 patent. Indeed, when a substrate was N-alkylated which was not highly activated, the Pachter system was changed to a system similar to that of the '257 patent.

FF E 62.

The passage referred to by Dr. Baldwin (at ¶ 47 of his declaration) as occurring at p. 245(d) of Nagarajan does not in fact refer to Pachter base/solvent conditions, rather to '257-type conditions of sodium amide and DMF. FF E 63. Complainants' attorneys submitted a letter to the PTO, in which they attempted to "amend" Dr. Baldwin's declaration, changing "Pachter base/solvent combination" to "Pachter-like base solvent combination" and changing the page reference to page 244(iii). FF E 64. However, Dr. Baldwin never submitted an amended declaration to the PTO. FF E 65.

Aside from any typographical error which may have occurred in the Baldwin

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[59](...continued)
hydroxide, and also discloses the use of acetone-water mixtures as the solvent. FF E 46.

declaration, the substance of the issue raised by Dr. Baldwin, i.e., that Nagarajan reported a ring cleavage of concern to one using Pachter conditions on TZP, is itself spurious.

The Nagarajan ring opening (which one would never see with TZP) occurs under '257 conditions but not under '035 conditions. Nagarajan expressly reported that ring cleavage occurred only with nitro-substituted N-aryl amides. FF E 69. Nagarajan cannot be fairly read to suggest that ring cleavage was a distinct possibility under Pachter base/solvent conditions. FF E 70, E 72. It was therefore misleading for Dr. Baldwin to suggest to the examiner that Pachter base/solvent conditions led to ring cleavage. FF E 73.

Both the Kende and Baldwin declarations suggest that the possibility of retro-Michael reaction of TZP might deter chemists from attempting the N-alkylation under Pachter/'035 conditions. FF E 74. In particular, Dr. Kende testified that an article by Mills and Whitworth suggested that retro-Michael reaction might take place with TZP. FF E 75. However, in 1970, Tanabe scientists published their experiments showing that TZP did not undergo retro-Michael reaction in the same conditions in which it was suggested by Mills and Whitworth that other benzothiazepinones might undergo retro-Michael reaction. FF E 76. Tanabe should have known from its own 1970 publication that there was no retro-Michael reaction of TZP under the conditions of Mills and Whitworth, and Tanabe and its counsel should not have raised the possibility of such a reaction as an argument to the examiner. FF E 77.

C. Conclusion on Unenforceability

The totality of the evidence in this investigation pertaining to respondents' and OUII's allegations that the '035 patent is unenforceable demonstrates that Tanabe's KOH/DMSO process and the sales of products

manufactured by that process were material to the reexamination proceedings, and further that Tanabe, its counsel, and others acting on Tanabe's behalf, intentionally concealed the Tanabe KOH/DMSO process from the PTO during reexamination of the '035 patent. Therefore, the '035 patent is unenforceable.

VI. IMPORTATION AND SALE

Each of the respondents imports diltiazem hydrochloride made by an accused process, sells such diltiazem for importation into the United States, or sells such diltiazem after importation into the United States. FF F 1-9.

VII. DOMESTIC INDUSTRY

In accordance with the Notice of Investigation, complainants allege that respondents have committed and are committing acts which are deemed unlawful pursuant to subsection (a)(1)(B)(ii) of section 337. The availability of relief to complainants from alleged unlawful acts, shall "apply only if an industry in the United States, relating to the articles protected by the patent, copyright, trademark, or mask work concerned, exists or is in the process of being established." 19 U.S.C. § 1337(a)(2).

Paragraph (a)(3) of section 337 (which was added as part of the Omnibus Trade and Competitiveness Act of 1988) provides the definition of an "industry in the United States" (referred to herein as a "domestic industry") as follows:

> For purposes of paragraph (2), an industry in the United States shall be considered to exist if there is in the United States, with respect to the articles protected by the patent, copyright, trademark, or mask work concerned --
>
> (A) significant investment in plant and equipment;
>
> (B) significant employment of labor or capital; or

(C) substantial investment in its exploitation, including engineering, research and development, or licensing.

The domestic industry requirement may be satisfied by meeting the criteria of any one of the three factors of paragraph (a)(3). Certain Concealed Cabinet Hinges and Mounting Plates ("Cabinet Hinges"), Inv. No. 337-TA-289, Commission Opinion at 19-20 (1990). Complainants bear the burden of establishing that the required domestic industry exists. See Id. at 22.

Respondents take the position that complainants do not satisfy the domestic industry requirement thereby making it impossible for an unlawful act to be found in this investigation. Complainants and OUII take the position that complainants' activities and investments satisfy the statutory requirement.

At the core of the dispute among the parties is the fact that complainants admittedly do not practice the process of the '035 patent in the United States. Rather, Tanabe practices an N-alkylation process covered by claim 1 of the '035 patent in Japan. FF G 23, 26, 95. Then, at least one additional step (i.e., the acetylation step), which is not covered by the '035 patent, is carried out on the product of the N-alkylation.[60]

Bulk diltiazem HCl is subsequently exported from Tanabe in Japan to MMD in the United States for further processing and for sale. FF G 14-16, 40.

The legislative history of the 1988 amendments concerning the definition of domestic industry directly addresses the issue of overseas manufacturing by a complainant. With respect to the three factors enumerated by the statute

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[60] As discussed in detail above in the section on claim interpretation, complainants (in opposition to the other parties, including OUII) take the position that the acetylation step is covered by the '035 patent. Respondents contend that even if Tanabe's acetylation step were covered by the '035 patent, a domestic industry could not be found to exist.

the legislative history states in pertinent part:

> The first two factors in this definition have been relied on in some Commission decisions finding that an industry does exist in the United States. The third factor, however, goes beyond ITC's recent decisions in this area. This definition does not require actual production of the article in the United States if it can be demonstrated that significant investment and activities of the type enumerated are taking place in the United States.

H.R. Rep. 40, 100th Cong., 1st Sess. 157 (1987); S. Rep. No. 71, 100th Cong. 1st Sess. 129 (1987)(emphasis added).[61] Therefore, Congress contemplated foreign production under the patent at issue coupled with domestic activities that satisfy one or more of the factors enumerated in the statutory definition of domestic industry.

The legislative history quoted above does not specifically address the question of whether a domestic industry may be found in the case of foreign manufacture under process patents as well as product patents. This lack of a distinction between the two circumstances is not surprising given the context in which the legislative history was written. The 1988 amendments included subparagraph (B) of paragraph (a)(1),[62] which served to bring process patents

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[61] It is clear that the sentence emphasized above applies to all three factors enumerated in paragraph (a)(3), inasmuch as the term "significant" is found in the first and second factors, and the term "investment" is found in the third factor. Furthermore, it is stated in the emphasized sentence that "this definition" does not require actual production in the United States, without limitation to any particular "factor," as is the case in the sentences that immediately precede it.

[62] Subparagraph (B) provides as follows:

> The importation into the United States, the sale for importation, or the sale within the United States after importation by the owner, importer, or consignee, of articles that --
>
> (i) infringe a valid and enforceable United States patent, or a valid and enforceable United States copyright registered under Title 17; or

(continued...)

to an equal footing with product patents. Congress, therefore, contemplated both process and product patents when it discussed the "article" in the legislative history.

The "article" or "the article protected by the patent" is the linchpin of the definition of a domestic industry of paragraph (a)(3), with "respect" to which all relevant activities are performed and all relevant investments are made. Especially in light of subparagraph (B) of paragraph (a)(1), which in 1988 expressly extended the protection of section 337 to unfair acts committed in connection with "articles" made overseas by a process covered by a valid and enforceable United States patent, it is reasonable to assume that in this portion of the 1988 amendments dealing with domestic industry, an "article protected by the patent" is an article made overseas by a process covered by a valid and enforceable United States patent.[63]

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[62](...continued)

> (ii) are made, produced, processed, or mined under, or by means of, a process covered by the claims of a valid and enforceable United States patent.

19 U.S.C. § 1337(a)(1)(B).

[63] Senator Lautenberg, an original author of the Section 337 amendments, stated that "process patent reform, and Section 337 reform are complementary. The two measures are a reflection of the breadth of the problem posed by the infringement of intellectual property rights, and the need for [a] variety of solutions." 131 Cong. Rec. S16003 (November 20, 1985).

Congress expressed special concern for the products of processes used in biotechnology and the pharmaceutical industry. See, e.g., 134 Congress Rec. H5520, H5528-29 (July 13, 1988) (remarks of Rep. Fish): 133 Cong. Rec. S10275, S10355 (July 21, 1987) (remarks of Sen. Hatch). The products under consideration in this investigation are pharmaceuticals and are certainly encompassed by these concerns.

In the House Report submitted by Representative Kastenmeier, the Committee on the Judiciary noted that "[p]rocess patent protection today is of central importance to the pharmaceutical industry." H.R. Rep. No. 60, 100th Cong., 1st Sess., at 5 (1987). Denying process patent protection "ignores the

(continued...)

Furthermore, although section 337 uses separate provisions to proscribe unfair acts related to patents on products as opposed to process patents, the domestic industry provision, quoted above, makes no such distinction. The statute directs the domestic industry inquiry toward investment and activities with respect to the "articles protected by the patent," without any reference to where those articles are produced.

Whether, in view of the 1988 amendments, a domestic industry may be found to exist in the case of a process patent that is practiced overseas will be a matter of first impression on the Commission level. However, in an earlier investigation governed by the 1988 amendments, the issue was raised before the administrative law judge. Based on the facts in that investigation, the administrative law judge found that, all things being equal, a domestic

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[63](...continued)
reality that the offending act is the importation of a product made through the use of a protected process patent or its subsequent sale within the United States." H.R. Rep. No. 60, *supra*, at 6. The President's Commission on Industrial Competitiveness also found that "the failure to extend such protection diminishes the economic value of United States process patents." *Id.*

In its recommendation to strengthen process patent protection, the Senate Judiciary Committee stated:

> Once the patent on a brand-name drug has expired, anyone is free to make, use or sell the product (assuming the FDA clearance), but if there is an unexpired patented process for making the drug, then other parties must find a different way to make it. Again, in order to obtain a patent, the process must be novel, useful and unobvious, an invention whose disclosure would benefit the public as envisioned in the Constitution. To obtain a process patent on a useful, new way to make a medicine is not to prolong or "evergreen" the product patent on the medicine itself, even if the patentholder for the process and original product is the same inventor. No responsible critic of S. 1200 has ever maintained that goods made abroad by a process patented in the United States should be allowed to come into the United States to benefit competitors of the process patent owner.

S. Rep. No. 83, 100th Cong., 1st Sess., at 47 (1987).

industry could exist even if the chemical process covered by the patent in suit were performed overseas by the foreign complainant. No domestic industry was found however, and the issue was not reached by the Commission on appeal because the Commission affirmed the administrative law judge's finding that the foreign complainant was not using the claimed invention of the patent at issue in that investigation. See In re Certain Doxorubicin, 20 U.S.P.Q.2d 1602, 1610 (U.S. Int'l Trade Comm'n 1991)(citing Beloit Corp. v. Valmet Oy, 742 F.2d 1421 (Fed. Cir. 1984).

The application of the domestic industry requirement in section 337 investigations, both before and after the 1988 amendments, supports protection of industries in which the patent is practiced overseas but is further exploited by domestic activities and investments.

In Schaper Mfg. Co. v. United States Int'l Trade Comm'n, 717 F.2d 1368 (Fed. Cir. 1983), the Federal Circuit held that "the relevant domestic 'industry' extends only to articles which come within the claims of the patent relied on."[64] The production of accessories for the articles protected by the patent, which in Schaper were certain toy vehicles, was held not to be part of a domestic industry.[65] Nevertheless, the Federal Circuit held that "in proper cases 'industry' may encompass more than the manufacturing of the patented item . . . ." Id. at 1371

The Federal Circuit cited other instances in which activities other than

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[64] Although Schaper was decided before the 1988 amendments, as seen in the legislative history quoted, supra, the new provision was intended to build upon existing Commission decisions as they related to investment and equipment, as well as employment of labor or capital.

[65] It was found that "[t]he accessories are not a necessary part of the vehicles, nor are they integral to them," and further that "[t]here is simply not enough significant value added domestically to the toy vehicles by Schaper's activities in this country." Schaper, 717 F.2d at 1371.

the manufacture of the patented item were sufficient to constitute a domestic industry, i.e.: Certain Cube Puzzles, USITC Pub. 1334 (Jan. 1983), in which the domestic industry was found to be based on quality control, repair and packaging of imported cube puzzles which added half of the puzzle's value, and Certain Airtight Cast Iron Stoves, USITC Pub. 1126 (Jan. 1981) and Certain Airless Paint Spray Pumps and Components Thereof, USITC Pub. 1199 (Nov. 1981), "in which substantial domestic repair and installation activities necessarily associated with imported stoves (Stoves), and frequent domestic product servicing under warranties as well as some domestic production (in Spray Pumps), were found by the Commission sufficient to warrant determinations that the 'industry' requirement was met." Schaper, 717 F.2d at 1372-73.

The Commission has consistently held that relief in a patent-based investigation under section 337 is dependent upon whether a complainant "is exploiting or practicing the patent in controversy." Certain Plastic Encapsulated Integrated Circuits, Inv. No. 337-TA-315, Commission Opinion at 16 (1992). The variety of circumstances in which a domestic industry has been found to exist, as noted by the Federal Circuit in Schaper, reflects the fact that the domestic industry is not determined by a rigid formula, but by an examination of the facts in each investigation, the article of commerce, and realities of the marketplace. Certain Double-Sided Floppy Disk Drives and Components Thereof, Inv. No. 337-TA-215, 227 U.S.P.Q. 982, 989 (United States Int'l Trade Comm'n 1985)(Commission Opinion on temporary relief).

In this investigation additional steps are performed on the product of the chemical process covered by the '035 patent (e.g. N-alkylated TZP) before the product is made available to consumers. One of those steps is not covered by the '035 patent and is performed overseas (i.e., acetylation), while other

steps which are also not covered by the patent, are carried out by MMD in the United States and create a valuable product ready for the consumer marketplace.

In Floppy Disks, only the head assemblies incorporated in the disk drives were covered by the claims of the patent-in-suit. The head assembly was used every time a disk drive was used; and the disk is useless without a head assembly. Consequently, the Commission affirmed the finding of the administrative law judge that the domestic industry should be defined as domestic production of disk drives, and not merely the patented head assemblies. See Initial Determination (on permanent relief) at 49-56. See also Certain Modular Structural Systems, Inv. No. 337-TA-164 (1984) ("[I]t may happen that the article resulting from the exploitation of the involved intellectual property is not itself an actual article of commerce, but is physically incorporated in an article of commerce.").

In Certain Personal Computers and Components Thereof, Inv. No. 337-TA-140, 224 U.S.P.Q. 270, 284 (United States Int'l Trade Comm'n 1984), the patented and copyrighted elements were manufactured overseas yet were essential components of the personal computers assembled in the United States. The article of commerce was found to be the complete personal computer, thus requiring that the domestic industry be defined in terms of such computers.

More recently and after the 1988 amendments, in the Cabinet Hinges investigation, a complainant's product was manufactured overseas, and a domestic industry was found to be lacking. It was determined that "[t]he only domestic addition to the completed product is the addition of imported dowels, which is optional and, because the patent covers the completed imported hinge, not the dowel feature, [the addition] does not bear directly on the

'exploitation' of any claim of the . . . patent." Commission Op. at 22-23. However, it is significant that in Cabinet Hinges, complainant's investment in the United States was not totally discounted. Rather, it was held that "[b]ecause of its indirect bearing on the patented features . . . we reduce the weight we otherwise would accord complainant's investment in plant and equipment." Id. at 23 (emphasis added).

In this instance, it is clear that without the work carried out by MMD, Tanabe's diltiazem HCl would be worthless as a pharmaceutical product. Diltiazem is a very short-acting product.[66] Bulk diltiazem must be formulated into dosage forms for human consumption before it can be effectively administered to patients.[67] FF G 29. MMD converts Tanabe's bulk diltiazem into a variety of dosage forms.[68]

Therefore, the article of commerce protected by the patent is diltiazem HCl which has been converted into dosage forms.

Respondents have taken the position that, inter alia, because Tanabe does not need MMD, in particular, to convert its diltiazem HCl into dosage forms, and because MMD could source its bulk diltiazem HCl elsewhere or because Tanabe could change its method of preparing diltiazem, there is no nexus

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[66] Cardizem products made from diltiazem HCl are channel blockers which inhibit the influx of calcium into a cell. FF G 31. Cardizem products are taken by people who have angina (restricted blood flow in the coronary arteries) and hypertension (high blood pressure). FF G 32.

[67] It is not apparent from the evidence adduced at the hearing whether sales of bulk diltiazem occur in what could properly be called a "bulk diltiazem market." However, it is clear that a competitive consumer market exists for diltiazem HCl which has been finished into consumer pharmaceutical preparations.

[68] MMD's Cardizem products include Cardizem CD, Cardizem tablets, Cardizem SR and Cardizem IV which are different dosage forms of Cardizem. Cardizem CD is MMD's most significant diltiazem preparation. FF G 14-16, 18, 30. Cardizem CD is produced in Kansas City and Puerto Rico. FF G 2, 15, 16.

between the article protected by the '035 patent and MMD's domestic activities.

The evidence shows that hypothetically Tanabe could change its method of preparing diltiazem (e.g. Tanabe could change back to its KOH/DMSO process or to a novel process), and that technologically MMD would be able to accommodate such a change without substantial modification to its domestic operations. FF G 6, 8. There is no evidence that from a technological standpoint MMD must use Tanabe's bulk diltiazem.

However, almost any change to the Tanabe process could have unknown effects in the quality or characteristics of the bulk diltiazem. Because of FDA requirements, MMD's processes and equipment are carefully qualified to work in combination with Tanabe's formulated bulk diltiazem. FF G 41. MMD conducts research and development related to its Cardizem products in order to comply with FDA requirements. FF G 42. Any change in the process for making the bulk diltiazem would require evaluation, qualification, validation, and stability tests by MMD in order to comply with FDA requirements. FF G 44. If the process to make bulk diltiazem used in MMD's Cardizem preparations were changed, MMD would have to amend its NDA, submit a new Drug Master File to the FDA, and wait for approval, an overall process that would take somewhere between one and a half and four years. Problems would, of course, also exist if MMD sourced bulk diltiazem from a company other than Tanabe.

Tanabe and MMD have had a long-term exclusive supply relationship regarding bulk diltiazem. FF G 28. Tanabe can only supply bulk diltiazem to MMD; and MMD can only purchase bulk diltiazem from Tanabe. FF G 27. MMD and Tanabe have developed a relationship over the years throughout which Tanabe has consistently supplied MMD with high quality product in the quantities

necessary for MMD to maintain a supply of product in the marketplace. FF G 39. After MMD receives Tanabe's imported bulk diltiazem, it is sampled, tested, and released to manufacturing upon meeting specification criteria. FF G 40. Because of FDA requirements, MMD's processes and equipment are carefully qualified to work in combination with Tanabe's formulated bulk diltiazem. FF G 41.

Therefore, although hypothetically Tanabe and MMD could cease to do business with each other or to use the '035 patent's process, it would come at a heavy commercial price. Furthermore, the prior holdings by the Federal Circuit and the Commission on domestic industry do not require that activities and investments may be considered part of a domestic industry only if permanently committed to the patent at issue.[69] Rather, the relationship between the complainants in this investigation exemplifies the kind of investment that satisfies the policies behind the domestic industry requirement, especially when the patented process is carried out overseas. In particular, Tanabe has chosen to exploit a United States patent by contracting with MMD, a United States company whose activities give value to the Tanabe bulk diltiazem in the United States consumer market. MMD makes investments and provides employment in the United States in carrying out its contract with Tanabe.

MMD has been receiving bulk diltiazem from Tanabe since the late 1970's. FF G 38. Today, Cardizem products constitutes MMD's largest product line. FF

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[69] This question of whether activities and investments must be unalterably dedicated to the patent at issue should not be confounded with the Commission's holding in Cabinet Hinges to the effect that in order to be relevant, investments in plant and equipment, for example, must be irrevocable and binding. Comm'n Op. at 21-22 (equipment to be delivered in the future under a contract that complainant could rescind on payment of unspecified cancellation fee not "investment" in plant and equipment).

G 30.

MMD has made significant investments in plant and equipment, as well as in the employment of labor and capital. Because of the sizeable amount of resources and employment devoted to the commercial exploitation of the '035 patent through the making of dosage forms of diltiazem these investments are significant. They allow the assignee of the '035 patent to increase the value of the bulk diltiazem by converting it into a valuable pharmaceutical product.[70]

MMD's Kansas City facilities occupy over C square feet. FF G 2. Currently, MMD has over C square feet of its Kansas City facilities dedicated to Cardizem products made from bulk diltiazem supplied by Tanabe. FF G 3. In 1992, MMD employed approximately C full-time associates in Kansas City, of which approximately C were devoted full-time to the production of Cardizem products. FF G 11.

MMD has also invested C million in plant and equipment at Roche Products, Inc. ("RPI") in Puerto Rico where Cardizem products are produced. FF G 5. Furthermore, MMD leases C square feet from RPI in Puerto Rico; approximately C square feet are used for the production of Cardizem products. MMD leases C direct labor employees from RPI; C of these individuals are working on the production of Cardizem CD and SR. FF G 7, 9.

In addition, evidence has established that MMD has made substantial investment in the exploitation of the '035 patent through research and development linked to the diltiazem HCl in dosage form. Aside from the research and testing necessary to meet the FDA requirements, MMD's research

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[70] Complainants' expert presented evidence showing that MMD's activities add roughly C of the value of the finished diltiazem HCl. FF G 91.

and development on Tanabe's diltiazem has led to the development of Cardizem CD and Cardizem SR. FF G 86.[71]

Complainants and OUII have presented evidence sufficient to demonstrate that the activities and investments of MMD in the United States with respect to the article protected by the patent are sufficient to satisfy the domestic industry requirement of section 337.

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[71] MMD provides extensive marketing and promotion related to its Cardizem product line through a trained sales force, and through educational information and product information based on comparative test studies. FF G 87.

FINDINGS OF FACT

I. TUTORIAL

A. Dr. Baldwin

FF A 1. A molecule is the smallest constituent of matter. Atoms make all matter, but atoms can join together to form certain shapes or organizations called molecules. Tutorial Tr. 13-14.

FF A 2. The synthesis of a molecule is the construction of the molecule by bringing together constituent atoms that are required to make up the structure of that molecule. That construction is done by chemists through the processes of chemical synthesis, in particular by the use of chemical reactions. Tutorial Tr. 12.

FF A 3. Diltiazem is a man-made molecule, in that as far as we know, it never existed in nature, but was discovered by Tanabe workers in the course of their research activities. Tutorial Tr. 12.

FF A 4. All molecules can, in principle, be synthesized by chemical reactions carried out by chemists. Tutorial Tr. 12

FF A 5. Organic chemistry is the part of chemistry that deals with the molecules and reactions of the element carbon. Tutorial Tr. 13.

FF A 6. Different atoms have different ability to form bonds. Hydrogen can only form one bond, so its bond is shown in notation by a single line. Carbon can form four different bonds to other atoms. Tutorial Tr. 14.

FF A 7. A molecule which bears either a positive or a negative charge is called an ion. Tutorial Tr. 15.

FF A 8. Anything that substitutes for hydrogen is called a substituent group. Tutorial Tr. 16.

FF A 9. Benzene consists of six carbons and six hydrogens. Tutorial Tr. 14.

FF A 10. Benzene is a liquid that boils at about 80 degrees (centigrade), and is used as a common organic solvent and a starting material for other reactions. Tutorial Tr. 15. FF A 1. A benzene ring is shaped like a hexagon. Tutorial Tr. 18.

FF A 11. A 7-membered ring structure that exists in organic chemistry, and which contains a sulfur atom and a nitrogen is called a dihydrothiazepine. Tutorial Tr. 18.

FF A 12. A certain combination of a benzene molecule and a dihydrothiazepine molecule is a benzothiazepine molecule structure. It is a benzene ring joined together with a thiazepine. Tutorial Tr. 18-19.

FF A 13. The positions around the benzothiazepine, as with other molecules, are numbered to show places where certain substituent groups may be placed. By convention, 1 is at the sulfur. Tutorial Tr. 19.

FF A 14. TZP, the starting material for the N-alkylation at issue in the '035 patent, is made by adding certain substituents to benzothiazepine. The OH, is called a hydroxyl group; and on atom 4, the oxygen with 2 bonds, is called a carbonyl group.
Tutorial Tr. 20.

FF A 15. The molecule diltiazem has the same benzothiazepine structure as in TZP, but now instead of the hydroxyl group it has another group we called acetoxyl (written in a short form as OAc), and instead of the hydrogen at a certain position, it has a different group which consists of two carbons linked together terminating in a nitrogen which bears two methyl groups. Tutorial Tr. 23-24.

FF A 16. In order to perform a chemical reaction, and to create one structure from another, a chemist develops ways of breaking and creating bonds, one hopes in a controlled and predictable way. Tutorial Tr. 25.

FF A 17. An acid is a compound or a molecule that can give out or donate to another molecule an entity called a proton. So an acid is a proton donor. Tutorial Tr. 29.

FF A 18. A proton may be considered the simplest of all molecules. A proton is the core of the hydrogen atom, and is referred to as H+. It has a positive charge. It is an ion, not an uncharged molecule. Acids are therefore those molecules or compounds that can deliver this H+ to others. Tutorial Tr. 29.

FF A 19. The recipients of the H+, the acceptors of it, are called bases. Tutorial Tr. 29.

FF A 20. Acids and bases are two sides of something called an acid/base reaction. The base is the acceptor of the H+. Tutorial Tr. 29.

FF A 21. It may be said that the most fundamental of all chemical reactions that relate to organic chemistry is the very simple acid/base reaction. Tutorial Tr. 29.

FF A 22. Not all bases have to be negatively charged. However, most negatively charged entities or ions have basic properties. Tutorial Tr. 30.

FF A 23. The idea of strength of acids and bases as a general term relates to the ability of a base to take the proton from an acid. So if a base has an extremely high affinity for a proton, it is called a strong base. Tutorial Tr. 31.

FF A 24. Sodium hydride is a very strong base that can take a proton off of most things relevant to this investigation. Tutorial Tr. 31.

FF A 25. Potassium carbonate is a weaker base than sodium hydride. Tutorial Tr. 31. T

FF A 26. The degree to which a process occurs is generally less with a weaker base. It is not simply a question of the reaction taking longer. Tutorial Tr. 31-32.

FF A 27. Many of the chemical reactions at issue in this investigation involve solids. If you mix two solids together to create a chemical reaction, the mixing may not be very good. And the actual contact between the molecules in one solid and the molecules in another solid would be perhaps not very effective in achieving the close approach that is necessary to make the chemical reaction. Molecules have to come very close together, virtually touching one another as it were, before the reaction can proceed. Tutorial Tr. 33.

FF A 28. A reaction involving two solids would probably be very slow -- if it worked. So, chemists have to take the solids and dissolve them in a solvent, a liquid. In the liquid, the molecules of the solids are dispersed and are free to move about. Under those conditions, they can come together and create chemical reactions. Tutorial Tr. 33-34.

FF A 29. Solvents are powerful devices that have been discovered by experiment for achieving the close approach of the molecules in different reactants to enable them to undergo the chemical reaction. Solvents play a primary role in bringing the molecules which are dissolving them together so that chemical reaction can take place. Tutorial Tr. 34-35.

FF A 30. There are many, many thousands of different solvents available. Tutorial Tr. 34.

FF A 31. Solvents are not all the same; they have different abilities to

dissolve things. Tutorial Tr. 34.

FF A 32. There is a general rule that chemists have developed over the years that says, "like dissolves like." Tutorial Tr. 34.

FF A 33. Certain types of solvents, such as the molecule benzene, are frequently used. However, in the case of benzene, less so now because people have discovered that it's a carcinogen that was widely used. Tutorial Tr. 34-35.

FF A 34. Another solvent discussed in this investigation is the simple 3-carbon compound: acetone. And another solvent that is discussed in this investigation is a molecule called ethyl acetate. Tutorial Tr. 35.

FF A 35. Other solvents include ethyl alcohol and methyl alcohol. Tutorial Tr. 35.

FF A 36. One should not assume that solvents are not actually involved in the chemical reactions, because in some cases it is known that they are. They are not there just as a neutral medium to permit molecules to approach; in many cases they are involved. Tutorial Tr. 35.

FF A 37. In some cases, solvents actually participate in the chemical process itself. A classical example of that is the molecule of water. Tutorial Tr. 35

FF A 38. Water is a solvent It is not an organic compound, but it is known that it participates in chemical reactions. Particularly reactions of the acid base variety. Tutorial Tr 35-36.

FF A 39. By adding water to certain sorts of reactions, it has been found that water can actually act as a carrier of the proton from one acid to the base. So, it may participate in a hidden way in proton transfer reactions. Therefore, solvents are not totally neutral entities. They can

play a role in the chemical processes that take place. Tutorial Tr. 36.

FF A 40. There are many ways of categorizing or classifying solvents. Tutorial Tr. 36.

FF A 41. Some people use the term "donor solvent," for those solvents that can particularly solubleize, or dissolve positively charged species. Tutorial Tr. 36.

FF A 42. Some people use the term "aprotic solvents." Those solvents do not have readily accessible protons on them. Tutorial Tr. 36.

FF A 43. Protic solvents, such as alcohols, have readily accessible OHs that can participate in proton transfer reactions. Tutorial Tr. 36.

FF A 44. Solvents used successfully in a reaction must not be reactive towards the reagents in a way that is undesirable. So, if one uses a solvent that will consume the reagent that one was using to do a chemical reaction, it would be undesirable from the point of view of achieving the desired aim. Tutorial Tr. 37.

FF A 45. N-alkylation is like an alkylation reaction, except that instead one transfers a group we call Al, which is an alkyl group. Tutorial Tr. 37-38. The alkyl group is transferred from the donor of the alkyl group, to the base to give an anion plus the alkylated product. Tutorial Tr. 38.

FF A 46. An anion is a negatively charged species. It results from the loss of a proton from the neutral molecule. The proton is positive, so you are left with the anion. Tutorial Tr. 41.

FF A 47. In the alkylation at issue with the process of the '035 patent, the starting material is TZP. The alkylation occurs on a particular nitrogen atom. Tutorial Tr. 41.

FF A 48. In general, there are many ways of doing a reaction, such as

that of the '035 patent. Tutorial Tr. 42. FF A 1. The alkylating reagent in the '035 patent process is a compound that is called DMC hydrochloride. It is a salt. It is an ionic compound. It contains a positively charged species that will eventually become the alkylating agent; and it includes chloride in the salt structure. It is a white crystalline solid. Tutorial Tr. 43-44.

FF A 49. The DMC hydrochloride itself is not a reactive alkylating agent. The molecule is transformed into another molecule which is called DMC, by removing the elements of hydrogen chloride acid by use of a base. Tutorial Tr. 44.

FF A 50. DMC is a neutral molecule. It has lost a proton from the crystalline material to give a material which is a liquid. It is an oily material. Tutorial Tr. 44.

FF A 51. DMC is the alkylating agent. It is known from many studies that this type of compound gives rise to a new species which is positively charged, has chloride, and is called an aziridinium ion, abbreviated "Az". Tutorial Tr. 45. FF A 1. The aziridinium can, in fact, interact with the chloride and go back to where it came from. So, there is some evidence that these sort of forward-backward reactions occur. However, the important thing is that when one has this DMC material in the right environment, it can generate this aziridinium ion. Tutorial Tr. 45.

FF A 52. The aziridinium ion is intrinsically more reactive in alkylation reactions than the DMC. Tutorial Tr. 45.

FF A 53. Although the aziridinium ion is a reactive alkylating agent, other reactions can occur. However, some people will argue that maybe that is the alkylating reagent, rather than the aziridinium ion. Tutorial Tr. 46.

FF A 54. The aziridinium ion is positively charged; and the TZP is

negatively charged. That corresponds to a favorable orientation of charges, because opposite charges attract. Tutorial Tr. 46.

FF A 55. Potassium hydroxide and potassium carbonate bases are inorganic compounds. They are like sodium chloride in that they are ionic salts. They are white; some are crystalline materials; and they are very poorly soluble inorganic solvents. Tutorial Tr. 47.

FF A 56. When water dissolves potassium hydroxide and potassium hydroxide, it forms a solution in which we know there are the positive potassium ions and the hydroxide ions floating about in equal numbers. Tutorial Tr. 48.

FF A 57. Diltiazem is the N-alkylated TZP which has been acetylated. See Tutorial Tr. 50.

B. Dr. Taylor

FF A 58. One of the substrates in the Pachter article, on page 1, is acetanilide. Acetanilide has the so-called amide structure in it. The amide structure is also present in TZP, being the NH adjacent to a carbon double-bond oxygen. Tutorial Tr. 53-54.

FF A 59. In the acetanilide structure, the nitrogen is connected to a benzene ring (a feature common in a great deal of the prior art discussed in this investigation). Tutorial Tr. 54.

FF A 60. Functional groups have chemical reactivity; and the art of organic synthesis is really to carry out reactions on one functional group in the presence of other functional groups. Tutorial Tr. 54.

FF A 61. An n-aryl amide is an amide which has an aryl group which is, in the simplest case, a simple benzene ring attached to it, to the nitrogen. Tutorial Tr. 55.

FF A 62. Many of these structures that are discussed in this investigation have formal names which end in "one." That "one" means a certain C double-bond O functionality. So, in fact, correctly, TZP is not a benzothiazepine; it's a benzothiazepine-one derivative. But that is understood. Tutorial Tr. 57.

FF A 63. Sodium and potassium are grouped together in Group 1a of the Periodical Table of Elements. Tutorial Tr. 62. FF A 1. The purpose of the Periodic Table is to arrange elements in a periodic way relating to electronic structure, so that all of the compounds in Group 1a share an electronic similarity in that they all contain one electron in their outermost shell. They differ in size because of the number of shells of electrons in these atoms, but they all share a common chemical property in that they all form mono-cations. Tutorial Tr. 62-63.

FF A 64. Barium is found in Group 2a of the Periodic Table. Barium is a member of what is called the alkaline earth metal group, i.e., those metals which have two electrons in the outermost shell and when you make salts of them, you remove two electrons rather than one. Tutorial Tr. 63

FF A 65. The alkaline earth metals carry two positive charges rather than one, in contrast to potassium or sodium.
Tutorial Tr. 63.

FF A 66. It is often the case that the reactants that you wish to react with each other are not soluble in the same thing. Tutorial Tr. 68.

FF A 67. Potassium hydroxide is soluble in water. Barium hydroxide is soluble in water. Sodium hydroxide is soluble in water. Tutorial Tr. 68.

FF A 68. When you have all of the reactants dissolved in the same phase, that is called a homogenous reaction medium. Tutorial Tr. 68-69.

FF A 69. Abic uses the combination of solvents water and methylene chloride. Water and methylene chloride are not soluble in each other. Tutorial Tr. 69. That is, if you mix water and methylene chloride they separate, and you see a bottom layer of methylene chloride and a top layer of water. They do not dissolve in each other. The solubility of water in methylene chloride is very low, and the solubility of methylene chloride in water is very low. Tutorial Tr. 69.

FF A 70. TEBA is an acronym standing for triethylbenzyl ammonium chloride. Tutorial Tr. 71.

FF A 71. TEBA is one of among several types of phase transfer catalysts. Tutorial Tr. 70.

FF A 72. TEBA is what is called a quaternary ammonium salt. Tutorial Tr. 70.

FF A 73. A quaternary ammonium salt is a nitrogen atom which has four groups attached to it. The groups can be the same, they can be different. Tutorial Tr. 70.

FF A 74. TEBA is a classical phase transfer catalyst. It has a water soluble part, and it has a water insoluble part. Tutorial Tr. 72.

FF A 75. A catalyst is something which promotes the rate of a reaction without being consumed in the process of the reaction. Tutorial Tr. 74.

C. Dr. Taber

FF A 76. The base in the Profarmaco process is sodium carbonate. Tutorial Tr. 78.

FF A 77. Each of the solvents in claim 1 of the '035 patent have carbonyls. Tutorial Tr. 80.

FF A 78. The latin for potassium is kalium. Therefore, potassium is

abbreviated as "K". Tutorial Tr. 81.

FF A 79. In the structure of water, the oxygen has electron density on it that is negative. Therefore, it will orient itself around the positive potassium, and that stabilizes it. Tutorial Tr. 82.

FF A 80. Toluene is a not a carbonyl solvent. Tutorial Tr. 85.

FF A 81. Toluene has a central ring, a 6-membered all carbon and hydrogen benzene ring. Tutorial Tr. 85.

FF A 82. Toluene has carbons and, of course, hydrogens, but no oxygen. Toluene us called a hydro-carbon solvent. Tutorial Tr. 85.

FF A 83. Toluene has many of the properties similar to benzene without the toxicity. Tutorial Tr. 85.

FF A 84. Toluene is used as the organic solvent for the Profarmaco process. Tutorial Tr. 85.

FF A 85. Good donors are good at solvating positive ions. They have electrons available to share. Tutorial Tr. 86. By that definition, toluene is not considered a good donor solvent. Tutorial Tr. 85-86.

FF A 86. If one has an organic molecule with an even distribution of electrons, there is no charge, no partial charge anywhere. On the other hand, if one has something that attracts the electrons to one end, like an oxygen, for instance, they will be partially negative, leaving the other end partially positive. This is called a dipole or dipole moment. Tutorial Tr. 88-89.

FF A 87. If an ion is surrounded by a dipolar solvent, it will orient itself so that the negative end of the dipole is toward the positive ions. And similarly, it will orient itself so that the positive end of the dipole is toward the negative ion. Tutorial Tr. 89.

FF A 88. Methyl acetate, ethyl acetate, and acetone have a substantial

dipole moment. Tutorial Tr. 90. When toluene is compared to those solvents, hydrocarbon solvents such as toluene do not have much of a dipole moment. Id.

FF A 89. The dielectric constant refers to how insulating a solvent is. Tutorial Tr. 90.

FF A 90. Toluene and the hydro-carbon solvents in general are not soluble in water; water is not soluble in them; and they form two layers with water. Tutorial Tr. 92.

FF A 91. Ethyl acetate is appreciably water soluble.

FF A 92. Acetone is infinitely soluble in water. Tutorial Tr. 93.

FF A 93. The solvents listed in the '035 patent are hydrophilic, meaning they dissolve water, and also lipophilic. Lipophilic means they dissolve fat, and are fat-loving. Fat means, in this case, an organic molecule. Tutorial Tr. 93.

FF A 94. The solvents listed in the '035 patent are carbonyl containing. Toluene is not. Tutorial Tr. 94

FF A 95. Carbonyl solvents are both hydrophilic and lipophilic. Toluene is lipophilic, but is not hydrophilic. Toluene will dissolve the organic substrate in the alkylating agent, but it will not dissolve the inorganic bases that are used in these alkylations. Tutorial Tr. 95.

D. Dr. Lindholm

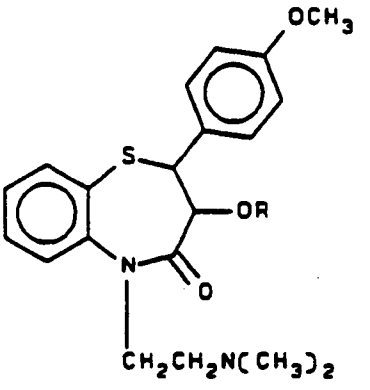
FF A 96. When one speaks about synthesis in terms of the pharmaceutical or the bulk pharmaceutical industry, one is speaking about batches in sizes ranging between 200 kilos to 1,000 kilos per batch. Tutorial Tr. 104-104.

FF A 97. In the pharmaceutical industry there are roughly 20 different solvents from which to choose. Tutorial Tr. 106.

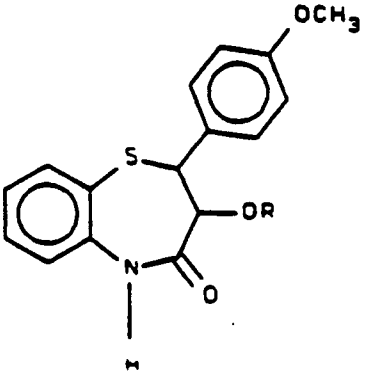
II. INTERPRETATION OF CLAIM 1 OF THE '035 PATENT

FF B 1. Claim 1 of the '035 patent reads as follows:

A method of preparing a benzothiazepine derivative of the formula:



wherein R is hydrogen or acetyl, or a pharmaceutically acceptable acid addition salt thereof, which comprises condensing a compound of the formula:



wherein R is the same as defined above, with 2-(dimethylamino)ethyl halide either in the presence of potassium hydroxide in acetone or in the presence of potassium carbonate in a solvent selected from acetone, lower alkyl acetate, a mixture of acetone and water and a mixture of lower alkyl acetate and water, and if required, further converting the product into a pharmaceutically acceptable acid addition said thereof.

CX 1.

FF B 2. The '035 patent is not a pioneer patent. Taylor Tr. 2594. No witness for complainants testified that it is.

FF B 3. On January 17, 1983, the PTO received a Statement of Art from Tanabe's counsel, dated January 6, 1983. CX 2.

FF B 4. The Statement of Art (January 1983) called the examiner's attention to U.S. Patent No. 3,562,257 and Chem. Eng. News, 44 (15), 48 (1966). Id.

FF B 5. Tanabe described the claimed invention, as follows:

> In contrast, Applicants' invention is the condensation of the acylated form of reference compound II (our II) without prior conversion to the alkali metal salt thereof but rather in the presence of potassium hydroxide in acetone or potassium carbonate in acetone, lower alkyl acetate, water-acetone, or water-lower alkyl acetate.

Id. at 2.

FF B 6. Tanabe distinguished the alleged invention of the '035 patent over the prior art, specifically the '257 patent, as follows:

> In view of the fact that the instant invention eliminates entirely the dangerous prior art step of conversion into the alkali metal salt and reduces the two step process to a single step, Applicants' invention is not anticipated by the prior art. Furthermore, it is clear that the reference process yields are in the range of 65 to 70% when converting compound II to compound I. Applicants' invention, on the other hand, gives yields which are no less than 87%. It is therefore clear that applicants' invention is patentable over the prior art.

Id. at 2-3 (emphasis added).

FF B 7. The '035 patent specification states in part, as follows:

> It is known that the benzothiazepine derivative (I) in which R is hydrogen is prepared by reacting 2-(4- methoyphenyl)-3-hydroxy-2,3-dihydro-1,5-benzo-thiazepine-4(5H)-one with a base such as sodium hydride, metallic sodium or sodium amide in a solvent such as dimethylsulfoxide, dioxane, toluene or xylene, and then reacting the resultant sodium salt with 2-(dimethylamino)ethyl halide (U.S. Pat. No. 3,562,257). Moreover, in this method, sodium hydride and dimeth-ylsulfoxide are known to be most suitable for use in carrying out said condensation reaction. However, the method of carrying out said condensation reaction by the use of sodium hydride and dimethylsulfoxide is still unsatisfactory in that said method is inevitably accompanied with side reactions due to methylsulfinylcarbonion (CH_3SOCH_2-) which is formed during the

reaction; and that sodium hydride is expensive and difficult to handle. Another disadvantage of the latter method is that, when sodium hydride is used in combination with dimethylsulfoxide, it is likely to explode. In fact, it has been reported that an explosion occurred when the alkylation of an aromatic heterocycle compound was carried out by using sodium hydride and dimethylsulfoxide (Chem. Eng. News, 44(15), 48(1966)).

An object of the present invention is to provide a novel and improved method of preparing the benzo-thiazepine derivative (I). Another object of the invention is to provide a method of preparing the benzothiazepine derivative (I) without the accompanying disadvantages mentioned above. A further object of the invention is to provide a method of preparing the ben-zothiazepine derivative (I) by using potassium hydroxide or potassium carbonate which is inexpensive and easy to handle. These and other objects of the present invention will be apparent to persons skilled in the art from the following description.

'035 Patent, col. 1, line 35 - col. 2, line 2 (emphasis added).

FF B 8. The '035 specification provides further:

As mentioned hereinbefore, in comparison with the known method disclosed in U.S. Pat. No. 3,562,257 (e.g., a method of preparing the benzothiazepine derivative (I) by the use of sodium hydride and dimethylsulf-oxide), the above-mentioned method of the present invention is quite advantageous and economical for preparing the benzothiazepine derivative (I) on an industrial scale because the benzothiazepine (I) can be prepared without undesirable side reactions by the use of such an inexpensive reagent as potassium hydroxide or potassium carbonate. Moreover, since the potassium hydroxide or potassium carbonate to be used in the present invention is quite stable and easy to handle, the method of the present invention can be carried out without explosive accidents as reported in Chem. Eng. News, 44, 48(1966).

Id. at col. 3, lines 21-36.

FF B 9. In the '035 patent it states that it is an improvement on the N-alkylation process disclosed by the '257 patent. The experts concur. CX 1 [RX 1194]; Kende Tr. 491; Taylor Tr. 2594.

FF B 10. The asserted improvement is said to lie in the use of five specific base-solvent combinations, said to be less expensive and less dangerous than those disclosed by the '257 patent and resulting in higher yields. CX 1 [RX 1194]; Taylor Tr. 2596.

FF B 11. The five base-solvent combinations disclosed and claimed in claim 1 of the '035 patent are:

Combination	Base	Solvent
1	Potassium hydroxide	Acetone
2	Potassium carbonate	Acetone
3	Potassium carbonate	Acetone and water
4	Potassium carbonate	Lower alkyl acetate
5	Potassium carbonate	Lower alkyl acetate and water

RX 1194; Taylor Tr. 2596-97; RPX 1063a.

FF B 12. Claims 2 through 12 of the '035 patent, i.e., the remaining claims of the '035 patent, are all dependent claims and refer only to the base/solvent combinations specified in claim 1. CX 1 [RX 1194].

FF B 13. The '035 patent does not disclose the use of any hydroxide base other than potassium hydroxide, and it does not disclose the use of any carbonate base other than potassium carbonate. CX 1 [RX 1194]; RX 1198; Taylor Tr. 2596, 2603.

FF B 14. Example 1 of the '035 patent reports a yield of 86.2%. CX 1.

FF B 15. Example 2 of the '035 patent reports a yield of 90.7%. CX 1.

FF B 16. Example 3 of the '035 patent reports a yield of 92.7%. CX 1.

FF B 17. Example 4 of the '035 patent reports a yield of 94.5%. CX 1.

FF B 18. Example 5 of the '035 patent reports a yield of 90.2%. CX 1.

FF B 19. Example 6 of the '035 patent reports a yield of 90%. CX 1.

FF B 20. Example 7 of the '035 patent reports a yield of 87.3%. CX 1.

FF B 21. Claim 1 of the '035 patent identifies only two specific bases for use in the claimed N-alkylation reaction: potassium hydroxide and potassium carbonate. CX 1.

FF B 22. A chemist of ordinary skill in the art would read claim 1 of the '035 patent to discover only potassium bases and not sodium bases. See

Taber, Tr. 2118.

FF B 23. Nowhere in the specification of the '035 patent is there any mention of/or reference to "alkali metal hydroxides" or "alkali metal carbonates." CX 1; Gokel, Tr. 815-17, 826.

FF B 24. Nowhere in the specification of the '035 patent is there any mention of/or reference to any specific alkali metal salts other than potassium salts. CX 1; Gokel, Tr. 815-17.

FF B 25. Each and every example of the '035 patent refers only to potassium bases. CX 1.

FF B 26. Neither sodium hydroxide nor sodium carbonate is mentioned or referred to anywhere in the '035 patent for use as a base in the claimed N-alkylation reaction. The only place in the '035 patent where sodium bases are discussed at all is in column 1, lines 38-47, and column 3, line 24, all in connection with the prior art '257 process. Gokel, Tr. 817-18.

FF B 27. The terms "alkali metal hydroxides" and "alkali metal carbonates" are and were well-known terms which would have included potassium bases, sodium bases, and certain other bases. Taber, Tr. 2115.

FF B 28. Sodium hydroxide and sodium carbonate are well-known bases. They are readily available and widely used in the chemical processing industry. Gokel, Tr. 819

FF B 29. If somebody mentioned to complainants' expert, Dr. Gokel, that they used potassium hydroxide or potassium carbonate in a chemical reaction, Dr. Gokel would automatically think of using sodium hydroxide or sodium carbonate in that reaction. Gokel, Tr. 819.

FF B 30. The cost of producing potassium carbonate is four to five times greater than the cost of producing sodium carbonate. Thus, sodium carbonate

is almost always used for applications in which the two carbonates are equivalent chemically. Gokel, Tr. 820; RX 3953. Sodium hydroxide also is "substantially less expensive than potassium hydroxide." Taylor, Tr. 2626.

FF B 31. Nonetheless, Tanabe restricted the '035 patent to two potassium bases -- potassium hydroxide and potassium carbonate -- and excluded the sodium bases. RX 1194; Taylor Tr. 2596, 2603-04; Taber Tr. 2117-18.

FF B 32. When complainants' expert, Dr. Gokel, was asked whether he would agree that it is unlikely that the Tanabe scientists had inadvertently forgotten to mention sodium hydroxide or sodium carbonate when describing their invention in the '035 patent, Dr. Gokel replied: "I would certainly not have forgotten. Whether they would -- I don't know -- I would not have forgotten." Furthermore, the person of ordinary skill in the art "would be generally knowledgeable about bases" to use in a chemical reaction such as an N-alkylation reaction. Gokel, Tr. 822-23.

FF B 33. Had Tanabe considered hydroxide or carbonate bases other than the potassium bases specifically identified in claim 1 of the '035 patent to have been part of its invention, Tanabe could have used the phrases "alkali metal hydroxides" and "alkali metal carbonates." For example, other chemical process patents obtained by Tanabe during the relevant time frame used the phrase "alkali metal" and "alkali metal hydroxide." U.S. Patent No. 4,416,819 (the "'819 patent") (RX 3952), U.S. Patent No. 4,443,615 (the "'615 patent") (RX 3949), U.S. Patent No. 4,438,044 (the "'044 patent") (RX 3950) and U.S. Patent No. 5,260,438 (the "'438 patent") (RX 3951). Taber, Tr. 2115-2119.

FF B 34. The '819, '615 and '044 patents were prosecuted by the law firm of Bierman and Bierman, the same firm that prosecuted the '035 patent. RX 3952; RX 3949; RX 3950.

FF B 35. The '035 patent does not disclose the use of any organic solvent other than acetone and lower alkyl acetates for use in the N-alkylation process. RX 1198, RX 1194; Taber Tr. 2601; Gokel Tr. 767-68.

FF B 36. Although the '035 patent did disclose a subclass of lower alkyl acetates, it did not disclose a class or subclass of lower alkyl ketones. Taylor Tr. 2615.

FF B 37. Rather, the disclosure of ketones was limited to a single ketone -- acetone. Taylor Tr. 2615; CX 1.

FF B 38. Tanabe did not disclose the use of organic solvents generally, much less the use of "aprotic" solvents. RX 1198; RX 1194; Liotta Tr. 1732-33; Gokel Tr. 773.

FF B 39. The '035 patent did disclose in its examples the use of such solvents as ethanol, toluene, methanol, and chloroform in the work-up of the product of the alkylation, but did not teach that those solvents are useful as solvents for the N-alkylation reaction. CX 1 [RX 1194].

FF B 40. Tanabe knew how to disclose solvents generally when it wished to do so, having done so in its '257 patent, which disclosed that the N-alkylation of that patent is carried out in "a solvent (e.g. dioxane, toluene, xylene, dimethylsulfoxide)." RX 1140.

FF B 41. The disclosure of the '257 embraces a range of solvents from toluene to DMSO. Taylor Tr. 2595.

FF B 42. Tanabe also disclosed broad ranges of solvents in its other patents. RX 4002; RX 4003; RX 3952-2; Taber Tr. 2119-20.

FF B 43. In defining bases for use in the N-alkylation of TZP with DMC, the '257 patent includes the phrase "alkali metal" which it defines as: "alkali metal (e.g., sodium, potassium, etc.)." RX 3116.

FF B 44. The '035 patent does not mention that any bases resembling a "superbase," i.e., with a pK of greater than 18, is excluded. Kende, Tr. 1395-1396.

FF B 45. Claim 1 of the '035 patent covers an N-alkylation reaction employing as solvents acetone, a mixture of acetone and water, lower alkyl acetate, or a mixture of lower alkyl acetate and water. CX 1.

FF B 46. When potassium hydroxide is used as the base in the N-alkylation process of claim 1 of the '035 patent, it is only claimed in combination with acetone, and the acetone is not indicated as being mixed with or in any way associated with water. CX 1.

FF B 47. When potassium carbonate is used as a base in the N-alkylation process of claim 1 of the '035 patent, water is indicated as being optionally mixed with either acetone or lower alkyl acetate as solvents. CX 1; Kende, Tr. 1428.

FF B 48. Water is disclosed to be an optional component in one of the two embodiments (the potassium carbonate embodiment) of the '035 patent. It is not taught as an essential component of either embodiment. See Taylor Tr. 2601-02; RX 1194; RX 1198.

FF B 49. The '035 patent teaches that potassium hydroxide can be used only with acetone, and that it cannot be used with mixtures of acetone and water. RX 1194; Taylor Tr. 2601-02.

FF B 50. Indeed, the '035 patent teaches that dehydrating agents were to be used with the KOH-acetone base-solvent combination. In Example 1, the only example in the '035 patent illustrating use of this combination, the dehydrating agent sodium sulfate is used in large amounts. RX 1194; Gokel Tr. 1925.

FF B 51. The '035 patent teaches that when potassium hydroxide is the base, if any water is initially present in the acetone solvent, or is formed in the reaction, it should be removed. Taylor Tr. 2601-02; RX 1194.

FF B 52. The specification of the '035 patent refers only to the following solvents: acetone, ethyl acetate, methyl acetate, acetone and added water and ethyl acetate and added water as possible solvents. CX 1; Kende, Tr. 502, 509.

FF B 53. Complainants' expert on claim interpretation, Dr. Kende, has testified that the class of solvents expressly disclosed in the '035 patent is "organic solvents containing a carbonyl group of low molecular weight, more or less miscible with water." Kende, Tr. 1258-59, 1454-55; Kende Dep. Tr. 272.

FF B 54. Toluene does not contain a carbonyl group. Taber, Tr. 2059, 2145.

FF B 55. Toluene is not miscible with water. Taber, Tr. 2068.

FF B 56. Nowhere in the '035 patent is there any specific mention of any ketones other than acetone as a solvent for the claimed N-alkylation process. Gokel, Tr. 768.

FF B 57. Lower alkyl acetates are esters. Gokel Tr. 768.

FF B 58. The '035 patent does not refer to any esters other than lower alkyl acetates. Gokel Tr. 768.

FF B 59. Nowhere in the '035 patent is there any mention of any esters, other than acetate esters, for use as a solvent in the claimed N-alkylation reaction. Gokel, Tr. 768.

FF B 60. Dioxane, a solvent that organic chemists use in organic reactions, is mentioned in the '035 patent only in connection with its use as a prior art solvent in the '257 patent. The Tanabe inventors "certainly knew

about dioxane" for use as a solvent in an N-alkylation reaction. Gokel, Tr. 770-771.

FF B 61. Aromatic hydrocarbon solvents such as toluene, xylene and chlorobenzene are commonly used as organic solvents in organic reactions. Toluene and xylene are mentioned in the '035 patent, but only in column 1 in connection with the solvents that Tanabe lists as having been used in the prior art '257 process. Nowhere in the '035 patent are these solvents specifically mentioned for use in the claimed N-alkylation reaction. Gokel, Tr. 771-772.

FF B 62. Not only were the Tanabe inventors aware of the use of aromatic hydrocarbon solvents for carrying out N-alkylation reactions (based on Tanabe's previous work disclosed in the '257 patent), but just about any competent organic chemist would have been aware of aromatic hydrocarbon solvents. Gokel, Tr. 772.

FF B 63. Nowhere in the '035 patent is there any mention of the term "aprotic" organic solvent. CX 1; Gokel, Tr. 772-773.

FF B 64. Tanabe could have used general, descriptive language if it had intended to include solvents other than acetone, acetone and water, lower alkyl acetate or a mixture of lower alkyl acetate and water. For example, Tanabe used such general language in other chemical patents prosecuted in the same time period as the '035 patent, by the same agents, Bierman and Bierman, who prosecuted the '035 patent. U.S. Patent No. 4,228,168 (RX 4003), U.S. Patent No. 4,367,230 (RX 4002) and U.S. Patent No. 4,416,819 (RX 3952). Gokel, Tr. 776-78. Taber, Tr. 2119-20.

FF B 65. Complainant's expert, Dr. Gokel, "certainly [would] agree that people of [the Tanabe inventors'] competence and skill in the art and so on

would certainly have knowledge about" how to describe solvents more broadly than the use of acetone and lower alkyl acetates. Gokel, Tr. 774.

FF B 66. At the time the '035 application was written and prosecuted, Tanabe was aware of toluene as a solvent with was known in the art for use in the N-alkylation of benzothiazepinones, as reflected by the fact that the '035 patent teaches that toluene is a prior art solvent for the claimed N-alkylation reaction. CX 1. Gokel, Tr. 771-72.

FF B 67. Toluene does not appear in any of the examples of the '035 patent. CX 1.

FF B 68. A chemist of ordinary skill in the art would not read into claim 1 of the '035 patent toluene as a solvent for the claimed N-alkylation reaction. Instead, a chemist of ordinary skill in the art in 1981 reading the '035 patent would have concluded that toluene was excluded from the claims, specifically because there is nothing in claim 1 that would suggest that toluene would work in the claimed N-alkylation reaction. Taber, Tr. 2120-21.

FF B 69. Nothing in the '035 patent explicitly teaches that water is involved in the way in which the claimed N-alkylation process works. CX 1.

FF B 70. Nowhere in the '035 patent is there any explicit teaching that water is critical to the success of the claimed N-alkylation reaction. Kende, Tr. 1428; Taylor, Tr. 2601. Thus, a chemist of ordinary skill in the art reading the claims and examples of the '035 patent would not conclude that water is necessary for the claimed N-alkylation process. Taber, Tr. 2149-50.

FF B 71. Because claim 1 of the '035 patent does not require that water be added to or produced during the claimed N-alkylation process, the intention of the '035 inventors was that water is not necessary to carry out the claimed N-alkylation reaction. CX 1; Taber, Tr. 2096-97, 2099, 2117-18.

FF B 72. The only specific mention of the use of water in the '035 patent relates to optionally "added water"; that is, water that is physically added by the operator of the process. CX 1; Taylor, Tr. 2602; Kende, Tr. 1427.

FF B 73. The reference in claim 1 of the '035 patent to "a mixture of acetone and water and a mixture of lower alkyl acetate in water," relates solely to physically added water, as taught in column 2, line 63, to column 3, line 4, as follows:

> Concomitantly, when the mixed solvent (i.e., a mixture of acetone and water or a mixture of lower alkyl acetate in water) is used as the solvent, it is preferred to carry out the reaction by refluxing a mixture of the compound (II), the compound (III), potassium carbonate and acetone or lower alkyl acetate, adding water to the mixture and then further refluxing the aqueous mixture. In this case, a suitable amount of water to be added is 0.01 to 0.1 ml per ml of acetone or lower alkyl acetate.

CX 1 (emphasis added); Gokel, Tr. 602-604.

FF B 74. Complainants' expert, Dr. Kende, agrees that the only place in claim 1 where water is specifically mentioned is the language "a mixture of acetone in water and a mixture of lower alkyl acetate in water." Kende, Tr. 3395.

FF B 75. Nowhere in the '035 patent is the term "surface solvent phase" described. CX 1; Gokel, Tr. 1066.

FF B 76. Experiments performed by Tanabe scientists in 1981 demonstrated that using potassium carbonate as the base in the '035 process without added water does not work. Taber, Tr. 2099, 2148; RX 3362; RX 3494; Taylor, Tr. 2676-77.

FF B 77. When Examples 4 and 5 of the '035 patent, which specify no added water, were run with powdered potassium carbonate and no added water, the N-alkylation reaction did not proceed. RPX 1051A (Experiments 8 and 9

which correspond to Examples 4 and 5 of the '035 patent); Taylor, Tr. 2674-2676.

FF B 78. One explanation offered by Tanabe for why Tanabe reported yields in Examples 4 and 5 of the '035 patent, wherein potassium carbonate and acetone (without added water) were used in Example 4, and potassium carbonate and ethyl acetate (without added water) were used in Example 5, is that the acetone and ethyl acetate contained water. However, nowhere in the '035 patent is the purity (e.g., water content) of either the acetone or ethyl acetate used in Examples 4 and 5 mentioned. Taber, Tr. 2149; Taylor, Tr. 2786-89. Another explanation is that Examples 4 and 5 are incorrect, since they are not repeatable using the directions of the '035 patent. Taylor, Tr. 2675-76, 2680-81.

FF B 79. The combinations of potassium carbonate and acetone (without added water) or potassium carbonate and lower alkyl acetate (without added water) will not generate water during the claimed N-alkylation process because the reaction temperatures at which the claimed process is carried out are too low to cause the decomposition of potassium bicarbonate to form water, which would be evidenced by the evolution of carbon dioxide. Taber, Tr. 2097-98.

FF B 80. An October 1991, "Process Development Study for the Manufacture of Diltiazem Hydrochloride" by the Chemistry Technology Division of Tanabe reported that when the N-alkylation of TZP was carried out using C

C as the base and C as the solvent:

C
C
C
C
C
C

C

RX 4020 (emphasis added).

The reaction did not proceed at C with C water because the water concentration was too low. The reaction also did not proceed at C mL with C water because the amount of water was more than would dissolve in the ethyl acetate. At C with C water, enough water was in solution so that the reaction proceeded. Taber, Tr. 2180-81.

FF B 81. The alkylating agent in claim 1 of the '035 patent "2-dimethylaminoethyl halide" would include both dimethylaminoethylchloride (DMC) and dimethylaminoethylbromide (DMB), as well as other possible dimethylaminoethyl halides, including the fluoride and the iodide. Gokel, Tr. 848.

FF B 82. The objective of the Tanabe Project Team comprised of the '035 inventors was to develop an improved process for the synthesis or production of diltiazem. RX 3737C; RX 3742C.

FF B 83. In conducting the experimental work leading up to the '035 patent, the Tanabe inventors tested toluene as a solvent for the N-alkylation of TZP. Specifically, as reported in a October 1981 report entitled "Technology Department Report for the First 20 Days of October," (approximately two months prior to the December 1981 date of the Japanese priority patent application upon which the '035 patent is based), the Tanabe scientists investigated a reaction using C as the base and C as the solvent. First, C ml of water was added to the reaction at C C °C for C hours. The Tanabe scientists noted from the results that numerous foreign spots were observed on the thin layer chromatogram. The Tanabe scientists further reported that the experiment was discontinued. Next, the Tanabe scientists repeated the reaction using C ml of water instead

of C ml, and after C hours of refluxing, they concluded that the reaction did not take place. RX 3494-C; Gokel, Tr. 779-784.

FF B 84. When these experiments by Tanabe scientists were pointed out at the hearing to Dr. Gokel, complainants' expert on the Profarmaco process, he expressed surprise, remarking, "[y]es, Isn't that odd?...Isn't that odd?" Gokel, Tr. 782.

FF B 85. Dr. Gaino, one of the co-inventors named in the '035 patent, reported in his notebook that N-alkylating TZP using C as the base and C as the solvent failed to work. Taber, Tr. 2138-39; RX 3368C.

FF B 86. Dr. Gaino, one of the Tanabe inventors of the '035 process, attempted in June 1981 (about 6 months prior to the December 1981 date of the Japanese priority patent application upon which the '035 patent was based) to N-alkylate TZP with DMC.HCl using C as the base. Specifically, Dr. Gaino used C in place of C in combination with the solvent C . Dr. Gaino reported that the reaction using C C did not take place. RX 3362-C; Gokel, Tr. 826-28; Taber, Tr. 2123, 2131-35, 2139.

FF B 87. In a June 1981 laboratory report authored by three of the Tanabe scientists, Iijima, Nakao, and Gaino, N-alkylation of TZP was carried out using C as the base. The data generated from this reaction was identified in entry #5 in a table on T001707 of RX 3361-C. On the next page of the document, T001708, the Tanabe scientists reported "when C C is used as base there was no reaction noted (#5)." RX 3361-C; Gokel, Tr. 828-33; Taber, Tr. 2123, 2131-35, 2139.

FF B 88. Tanabe tested several base/solvent combinations other than

those listed in the '035 patent, prior to filing the application for the '035 patent and its earlier Japanese counterpart. Tanabe did not claim any combinations used in experiments in which yields were not obtained, or in which the yields obtained were not very high. See Taylor Tr. 2628-2634; Gokel Tr. 828; RPX 1061; RX 1272.

FF B 89. After the issuance of the '035 patent, the European, Finnish, and Israeli Patent Offices, all citing U.S. Patent No. 3,075,967 to Krapcho, initially rejected Tanabe's respective applications corresponding to the '035 patent. RX 1097; RX 1099; RX 1101; RX 1202.

FF B 90. The European examiner reasoned as follows:

> The problem is solved by replacing the bases of the prior art (A) [the '257 patent] (alkali metal, alkali metal hydride or an alkali metal amide) by potassium hydroxide or potassium carbonate and the solvents of the prior art (A) (dioxane, toluene, xylene and dimethylsulfoxide) by acetone, alkyl acetate, a mixture of acetone and water and a mixture [of] alkyl acetate and water. Firstly, it cannot be seen, at present, what kind of improvement is obtained by such a modification. Secondly, the solution to the problem which avoids the use of sodium hydride and dimethylsulfoxide is obvious to the man skilled in the art, since the replacement of certain unsatisfactory bases and solvents by very common bases (for instance the base alkali metal hydroxide is used in document (B) [the Krapcho '967 patent] for a similar reaction) belongs to the routine work of a man skilled in the art. Thus in the absence of any evidence of a surprising effect, the process lacks an inventive step (Articles 52(1) and 56). Therefore, at present, the Claims 1 to 7 are not considered to be patentable.

EPO Communication Pursuant to Article 96(2) and Rule 51(2) (RX 1096).

FF B 91. In response to these rejections by the three foreign patent offices, Tanabe argued that the invention was patentable over the alkali metal hydroxide base of the '967 patent because Tanabe's five specific base-solvent combinations gave unexpectedly better results than other combinations of bases and solvents, including combinations which contained either the base, or the solvent, of the '035 combinations, but not both. RX 1097; RX 1099; RX 1101;

RX 1202, Taylor Tr. 2634-36; RPX-1002.

FF B 92. In support of that argument, Tanabe submitted a Comparative Test Report to show the European and other examiners that the five specific base-solvent combinations were better than other base-solvent combinations, even combinations which included one of the '035 bases or one of the '035 solvents. RX 1097; RX 1052; Taylor Tr. 2633-36.

FF B 93. Tanabe presented data in the Comparative Test Report showing that the potassium hydroxide-acetone combination was superior to combinations of potassium hydroxide with other solvents such as dioxane or toluene. Taylor Tr. 2634-35; RPX 1002.

FF B 94. Tanabe also presented data showing that the potassium hydroxide-acetone combination was superior to combinations of acetone with another alkali metal base, sodium hydroxide. Taylor Tr. 2635-36; RPX 1146.

FF B 95. Tanabe states in the Comparative Test Report as follows:

> Contrary to the facts mentioned hereinbefore, the present invention has been established based on findings that the desired product can be obtained in a high yield by the use of specific base-solvent combinations without accompanying [sic] the problems caused by the use of sodium hydride in combination with dimethylsulfoxide.

RX 1097.

FF B 96. Based on the experimental data reflected in the Comparative Test Report, Tanabe argued that its invention, as limited to the five specific base-solvent combinations, was not obvious as follows:

> Judging from the facts (i) that [Krapcho] teaches neither the use of potassium carbonate as the base nor the use of specific base-solvent combinations to be employed in the method of the present invention; (ii) that, when the condensation reaction was carried out by the use of sodium hydroxide or sodium carbonate as the base, the yield of the product was less than 10%; and (iii) that, even if potassium hydroxide or potassium carbonate was used as the base, the yield of the product was less than 30% in the case where dioxane, toluene or methanol was used, it is believed that the above mentioned advantages of the present invention have never been taught

> or suggested by [Krapcho]. Thus the specific base-solvent combinations of the present invention is not obvious.

RX 1097 (emphasis added).

FF B 97. Tanabe made the identical arguments and submitted the same Comparative Test Report in response to rejections by the Israeli and the Finnish patent offices. RX 1099 and RX 1101.

FF B 98. Patents were granted to Tanabe from the EPO, Israeli Patent Office and the Finnish Patent Office only after Tanabe provided experimental evidence that the invention was limited to the five specific base-solvent combinations actually disclosed and claimed. RX 1097, RX 1098, RX 1101.

FF B 99. Complainants take the position that Fermion's expert, Dr. Magnus, testified that the scope of the '035 patent includes a "wide range of bases," including hydroxide and carbonate bases such as sodium carbonate and barium hydroxide. Complainants take the position that Dr. Magnus testified that toluene and methyl chloride are within the scope of the '035 patent. Complainants' Post-Trial Brief at 9.

FF B 100. Dr. Magnus was asked what the scope of the '035 patent is "in the chemical sense." Dr. Magnus did not testify, and was not competent to testify, about the scope of the '035 patent in a legal sense. Dr. Magnus's testimony was based on knowledge gained through Dr. Baldwin's tests conducted for this litigation, and not from information available to one of ordinary skill in the art who read the '035 patent. Magnus Tr. 3226-3227.

FF B 101. Based on what Dr. Magnus currently knows about the chemistry involved in the '035 patent, it appears to him that the author of the patent unnecessarily restricted himself in drafting it. Indeed, he found the restrictive nature of the patent to be surprising and perplexing. There is no evidence that Dr. Magnus understood the reason why claim 1 of the '035 was

drafted in a restricted form. Magnus Tr. 3325-3228.

FF B 102. Dr. Magnus testified in pertinent part as follows:

THE WITNESS: Yes, I would like to read from my deposition in the parts that preceded the statement you made and parts after. It starts with -- this would be page 503 line 8. That's myself.

"Answer: My own first reading of that patent," this is presumably '035, "was I was surprised as to why they had been narrow, because you do have the opportunity to -- I believe there is some phrase used for expanding the sets of conditions available.

"Can I ask you what this phrase? It's suddenly slipped my mind."

"MR. ZOLTICK [counsel for respondent Fermion]: No."
"Well, whatever" -- he has got phrase, I assume it must be phase.

MR. SIPIO [counsel for complainants Tanabe and MMD]: I believe it's phrase.

THE WITNESS: "Well, whatever the phrase is, do you have the opportunity to encompass in a process things. Say, for example, if you actually haven't run that experiment but you're allowed to say, well, probably agree we should cover 2-butanone, this, that and the other," boy, I wasn't speaking very well, "and so you can give a range of ketones. You can't" -- it should be you can "overdo this, or at least if you want to overdo it, you've got to then provide some examples where, yes, it does work in some of these things. You're allowed that scope. It seemed that was lacking in this patent."

"Question:" yourself that is, "So would you feel that a chemist of ordinary skill in the art should be allowed to get a wider scope than what's literally claimed?"
Mr. Zoltick. Go straight on to my answer.

"I can answer your question. My own view on this they had their chance to define that scope and didn't."

"Question: Well, let's talk about scope in the chemical sense. What do you think the scope of the bases of the '035 patent comprise?"

"Answer: I would say there's a wide range of bases, which is evident from all of the information that we have accomplish that reaction."

At that point I'm referring to the wide range of bases that Professor Baldwin used.

Correspondingly, "Would barium hydroxide be within the scope of that chemical patent?"

"Answer: Yes."

"Would sodium carbonate" --

JUDGE HARRIS: Where is the reference to Dr. Baldwin's experiments?

THE WITNESS: There isn't.

JUDGE HARRIS: In the deposition where is the reference?

THE WITNESS: At that point there isn't one.

JUDGE HARRIS: So that's your explanation.

THE WITNESS: Can I just read it? I'll try to be quick as possible.

JUDGE HARRIS: Yes.

THE WITNESS: "Would sodium carbonate be within the scope of that chemical patent?"

"Yes."

"Would toluene be within the scope of solvents --"

"Yes."

Question: -- that you would use? And would methylene chloride be within the scope of solvents that you can use?"

Answer: I would say all of that is true. That's what perplexes me about the whole thing, is why didn't they say this. They had the opportunity when they wrote the document. I have written patents, and I'm not an expert on writing patents, but I give myself a few solvents."

"So you believe that the author of the patent unnecessarily restricted himself or herself?"

"Answer: All I can say is it appears that that is the case; although --" I think that's probably enough.

JUDGE HARRIS: All right. So now, what is the pending question?

MR. SIPIO: Well, I think he got most of it.

(Laughter.)

MR. SIPIO: I will try to ask him.

JUDGE HARRIS: I guess you asked did he say -- he gave testimony, I forgot exactly what it was, that it was very narrow, only two bases.

You're trying to impeach him with this. So what is your response, Dr. Magnus? Have you read all of that? How would you summarize your response to his claim that you said something different in the deposition?

A My response is knowing, particularly from the Baldwin experiments, that in fact you have a lot of bases that you can use and get various yields of product, and that I think is undeniable. In the patent itself they didn't give themselves any scope and normally they do, so I was -- I've stated before, somewhat surprised. I don't think that you can now sort of go forward in time and say in fact we meant all these other things now we've run these experiments.

Magnus Tr. 3224-3228.

FF B 103. The '035 patent specification provides in part as follows:

> The benzothiazepine derivative (I) in which R is aetyl [sic], especially cis-(+)-2-(4-methoxyphenyl)-3-acetoxy-5-[2-(dimethylamino)ethyl]-2,3-dihydro-1,5-benzothiazepine-4(5H)-one, is useful as a coronary vasodilator. One the other hand, the benzothazepine derivative (I) in which R is hydrogen, especially cis-(+)-2-(4-methoxyphenyl)-3-hydroxy-5-[2-(dimethylamino)ethyl]-2,3-dihydro-1,5-benzothiazepine-4(5H)-one, is useful as an intermediate of the above-mentioned coronary vasodilator.

CX 1 (emphasis added).

FF B 104. Formula II of claim 1 defines two starting materials, in which R may be hydrogen or acetyl. RX 1194.

FF B 105. Formula I of claim 1 defines two products of the process, in which R may by hydrogen or acetyl. RX 1194.

FF B 106. When R in the starting material (formula II) is acetyl, then R in the product (formula I) is acetyl, and when R in the starting material is hydrogen, then R in the product is hydrogen. RX 1194.

FF B 107. In the C

C CPX 20; Nakao Tr. 363-365; Complainants' Rebuttal to Abic's Proposed Findings of Fact at 142.

FF B 108. There is no explicit language anywhere in the '035 patent disclosing acetylation of the N-alkylated product when R in the starting material is hydrogen. RX 1194; Kende Tr. 490, 518; Taylor Tr. 2617-2619.

FF B 109. No acetylation step is referred to or discussed in any of the seven examples of the '035 patent. Kende Tr. 498, 561; CX 1.

FF B 110. The only explicit reference to acetylation in the '035 patent is a preparation example to convert the starting material where R is hydrogen (TZP) to the starting material where R is acetyl (TZP-OAc). Kende Tr. at 560-562; RX 1194.

FF B 111. Complainants believe that the acetylation step is implicitly contained in claim 1 and is "optional" in that one could infringe the patent without performing the acetylation. Kende Tr. 541-542; Complainants' Rebuttal to Staff Findings of Fact at 16.

FF B 112. Tanabe knew how to specify steps in addition to the alkylation step when it wanted them in a claim. RX 1194; RX 1140; RX 1252.

FF B 113. Tanabe expressly included formation of an acid addition salt as an optional step in claim 1 of the '035 patent. RX 1194.

FF B 114. The references to the '257 patent in the '035 patent are by way of background and do not specifically refer to acetylation. CX 1.

FF B 115. Similar to claim 1 of the '035 patent, Tanabe's application for the '257 patent contained a claim (claim 89) for the N-alkylation of TZP. RX 1252.

FF B 116. The '257 application also had claim 90 which expressly recited an acetylation step to follow the alkylation step of claim 89. RX 1252; Taylor Tr. 2618-2619.

FF B 117. The '257 patent contains a detailed explanation of acetylation in the specification. RX 1140.

FF B 118. Tanabe's British patent that corresponds to the '257 patent contains process claims, including one that expressly covers acetylation of N-alkylated TZP. RX 1700; Haber Tr. 2432-2434.

III. INFRINGEMENT

A. The Profarmaco Process Does Not Infringe Claim 1 of the '035 Patent

1. The Development of the Profarmaco Process

FF CP 1. In approximately late 1982, Profarmaco began work to synthesize diltiazem. Piselli, Tr. 1966.

FF CP 2. Using the German counterpart to the '257 patent, one of the Profarmaco scientists, Dr. Piselli, ran several experiments involving the N-alkylation step. Piselli, Tr. 1967-1969, 1998.

FF CP 3. In these, he used sodium hydride and anhydrous ("DMF") to become more familiar with the N-alkylation of TZP. Piselli, Tr. 1967-1969, 1998-99.

FF CP 4. Knowing that sodium hydride is unacceptable for commercial scale synthesis, Dr. Piselli almost immediately tried potassium carbonate and DMF. Piselli, Tr. 1967-69.

FF CP 5. The potassium carbonate/DMF combination -- which was the first one that Dr. Piselli tried -- was selected based on a 1978 article by Professor Makosza, an organic chemist known as the "inventor of phase transfer," which specifically disclosed the use of potassium carbonate and DMF in similar reactions. Piselli, Tr. 1967-69; RX 3025.

FF CP 6. The Makosza article described the possibility of replacing the reagents described in the '257 patent with potassium carbonate and DMF. Piselli, Tr. 1967; RX 3025.

FF CP 7. The article specifically described the advantages of potassium carbonate/DMF over sodium hydride, including the eliminations of potentially dangerous reactions caused by anhydrous organic solvents. Piselli, Tr. 1968; RX 3025.

FF CP 8. Dr. Piselli had previously used such a system at Profarmaco and he therefore followed Makosza's suggestions and tried potassium carbonate/DMF in his first experiments. Piselli, Tr. 1969.

FF CP 9. This potassium carbonate/DMF process -- the first one that Dr. Piselli tried -- was successful. Piselli, Tr. 1969.

FF CP 10. Within two months, Dr. Piselli had developed an industrial process using potassium carbonate/DMF. Piselli, Tr. 1969.

FF CP 11. Profarmaco used this process for producing bulk diltiazem from approximately mid-1983 to July 15, 1986. Piselli, Tr. 1970; RPX 4026.

FF CP 12. In order to increase the consistency of the yield, Profarmaco experimented with the addition of water to the reaction and found that C C % by volume of water caused more consistent yields. During the summer of 1986, Profarmaco therefore modified its process to include the addition of C % water to its potassium carbonate/DMF process. Piselli, Tr. 1969-1970, 2001-2002; RPX 4026.

FF CP 13. Shortly after December 30, 1986, Profarmaco first learned from a French pharmaceutical firm, Sanofi, of the Tanabe European Patent Application corresponding to the '035 patent. Russolo, Tr. 1924; Piselli, Tr. 2001; RX 3930C.

FF CP 14. This was the first time anyone at Profarmaco became aware of the existence of the '035 patent or any of its counterparts. Russolo, Tr. 1924; Piselli, Tr. 1970, 2001.

FF CP 15. Profarmaco reviewed this patent application and after such review concluded that its potassium carbonate/DMF process did not infringe. Russolo, Tr. 1934.

FF CP 16. Profarmaco therefore continued using this process for five additional years. Russolo, Tr. 1934.

FF CP 17. In April 1989, after expiration of the '257 patent and with the end of MMD's Waxman-Hatch exclusivity on the horizon, Gyma, Profarmaco's exclusive agent in the United States, wrote to MMD requesting disclosure of any process patents which MMD contended might cover processes for the

manufacture of diltiazem. RX 3947C at 214-215; Russolo, Tr. 1924-25.

FF CP 18. MMD responded shortly thereafter by identifying four patents, including the '035 patent. RX 3947C at 216; Russolo, Tr. 1924-25.

FF CP 19. Gyma forwarded MMD's process patent disclosure letter to Profarmaco for review. Russolo, Tr. 1924-25.

FF CP 20. Profarmaco, after reviewing the '035 patent, continued to use its potassium carbonate/DMF process. Russolo, Tr. 1934.

Receipt by Profarmaco of the EPO Comparative Test Report

FF CP 21. On June 13, 1991, Profarmaco received from its Italian patent attorneys (in connection with an inquiry from Profarmaco on a different matter) Tanabe's October 1, 1984 submission to the European Patent Office, including the Comparative Test Report. Russolo, Tr. 1925-27; RX 4032-C.

FF CP 22. Dr. Russolo, Profarmaco's Managing Director and General Manager, testified that, Profarmaco is a conservative company, and immediately decided to ascertain whether it could develop a process using a base not specified in the '035 patent claims and, particularly, bases and solvents that Tanabe had expressly represented to the EPO not to be the subject of its invention. Russolo, Tr. 1916-1917, 1925-1927.

FF CP 23. On June 27, 1991, two weeks after receipt of the Comparative Test Report, Profarmaco held an R&D meeting attended by, among others, Drs. Russolo and Piselli. Russolo, Tr. 1927-29; Piselli, Tr. 1970-71; RX 3928-C.

FF CP 24. At that meeting, Dr. Piselli was directed to try to develop an N-alkylation process using sodium carbonate as the base. Russolo, Tr. 1927-29; Piselli, Tr. 1970-71.

FF CP 25. Specifically, the meeting minutes state: "try the attachment of the chlorobase [i.e., 2-dimethylaminoethyl-chloride ("DMC")] with sodium

carbonate/DMF with different percentages of water." RX 3928-C; Russolo, Tr. 1928-29; Piselli, Tr. 1970-71.

FF CP 26. Sodium carbonate was chosen as a target base because Tanabe had identified the base in the Comparative Test Report as being outside the scope of its invention. Russolo, Tr. 1928-29.

FF CP 27. Profarmaco therefore viewed the use of sodium carbonate as a "zero-risk situation by using what inventors were saying not to be part of the invention." Russolo, Tr. 1926-1927.

FF CP 28. DMF was identified because that was the solvent that Profarmaco was then using in its current potassium carbonate/DMF process which was "a very good process." Russolo, Tr. 1928-29; Piselli, Tr. 1973.

FF CP 29. Four days after this R&D meeting, on July 1, 1991, Dr. Piselli conducted the first experiment using sodium carbonate in the period following receipt of the Comparative Test Report. Piselli, Tr. 1972; RX 3926C; RX 3932C.

FF CP 30. Dr. Piselli used sodium carbonate and DMF with C percent water. RX 3926 at Prof 436; Russolo, Tr. 1929-30; Piselli, Tr. 1972.

FF CP 31. During approximately the next eight months, Profarmaco was able to develop a new process for N-alkylating TZP using sodium carbonate as the base. Piselli, Tr. 1971-1972; RX 3926C; RX 3932C.

FF CP 32. In developing this process, Profarmaco conducted approximately 100 experiments. Piselli, Tr. 1972; RX 3932C.

FF CP 33. Profarmaco experimented by including and not including a phase transfer catalyst, by conducting the reaction at various temperatures, by varying times, by using various solvents, and by adding or removing water. Piselli, Tr. 1973-74; RX 3932-C.

FF CP 34. Experimental evidence provided by complainants in this investigation shows that water removal is not critical in order to get a low yield from the Profarmaco process. Taber Tr. 2094-95.

FF CP 35. Profarmaco discovered during the course of these experiments that only by removing water (through azeotropic distillation) could Profarmaco achieve an industrially valid high-yield process. Piselli, Tr. 1975.

FF CP 36. Dr. Piselli characterized the removal of water as very important and essential. Piselli, Tr. 1975.

FF CP 37. If water is not removed from the current Profarmaco process, the reaction is "never complete" and there are by-products and impurities. Piselli, Tr. at 1975.

FF CP 38. Profarmaco also discovered that if the temperature of the reaction is less than C °C, then the N-alkylation reaction cannot be completed. Piselli, Tr. at 1976.

FF CP 39. During the next eight months, Profarmaco scientists conducted approximately 100 experiments with different base/solvent combinations, and by February 1992, determined to use sodium carbonate and toluene, a base and a solvent, both of which were expressly identified by Tanabe in the Comparative Test Report as not included within its invention. Russolo, Tr. 1930; RX 3928C at 312, 315.

FF CP 40. On March 6, 1992, the sodium carbonate and toluene process went to the Pilot Plant. RX 3016C at Prof 166.

FF CP 41. By June 4, 1992, that process had been prepared for production and was ready for use. Piselli, Tr. 1978; RX 3928C at 316.

The Profarmaco Sodium Carbonate/Toluene Process

FF CP 42. Profarmaco conducts its process for manufacturing bulk

diltiazem in a C reactor vessel with a volume of C cubic meters. Piselli, Tr. 1979-80.

FF CP 43. The reactor vessel contains a distillation column, C

C

C

C

C , and a variety of other equipment. The distillation device which allows for azeotropically distilled vapors to be cooled, condensed, and then either removed from the system, or returned to the reactor vessel is known as a Markusson trap. Piselli, Tr. 1978-1980; RX 3996.

FF CP 44. In the step immediately preceding N-alkylation, Profarmaco carries out the C . Profarmaco first charges C . Profarmaco then C C . Following this step, Profarmaco allows the contents of the reactor vessel C , which results in the formation of two phases: a lower aqueous phase and an upper phase containing C . The Profarmaco operator, following the separation, C C . Following this procedure, the operator causes C C , thus removing any last traces or droplets of water which may have adhered to the sides of the reactor vessel. Any water that is gathered as a result of C is then discharged by the operator C C . Piselli, Tr. 1979-1980; RX 3996(a).

FF CP 45. The next step is the N-alkylation. That process is carried

out in the same reactor vessel. The reactor vessel already contains DMC free base in a toluene solution. To that solution Profarmaco adds sodium carbonate which, by its specification, may not contain more than C% water by weight. It also adds TZP, which is prepared at Profarmaco, and which is heated by Profarmaco to remove all water. Piselli, Tr. 1980-82, 1986; RX 3996(b).

FF CP 46. Once the TZP and sodium carbonate have been added to the toluene solution containing DMC base, the operator heats the reactor vessel as quickly as possible using the maximum amount of steam flowing through the jackets surrounding the reactor vessel. At C °, the operator reduces the steam flow so that the inside temperature will reach about C°C without the reactor's contents overflowing. Through thermal inertia, the reaction mixture increases in temperature to approximately C ° and the reaction mixture is then heated to C °. It takes C for the reaction mixture to reach C°; C for the reaction mixture to reach C °; and the reaction mixture is then heated at a C ° for C hours. Piselli, Tr. 1982-83; RX 3996(b).

FF CP 47. At the C ° range, the water/toluene solution begins to distill azeotropically. Profarmaco begins to see carbon dioxide evolution at approximately C° and begins to see water collecting in the Markusson trap also at approximately C°. Because water is heavier than toluene, the water collects in the Markusson trap while the toluene returns to the reaction vessel. Piselli, Tr. 1983-84.

FF CP 48. Profarmaco observed in the R&D laboratory a relationship between carbon dioxide evolution and N-alkylation. Profarmaco has observed that the N-alkylation reaction takes place while carbon dioxide evolution is occurring. Piselli, Tr. 1984-85.

FF CP 49. Profarmaco takes five separate steps to prevent water from

entering the reactor vessel and to remove water created during N-alkylation step. RX 4024-C; RX 3996(a); RX 3996(b); Piselli, Tr. 1985-87, 1977-81. Specifically:

1. during the C step, which immediately precedes N-alkylation, the Profarmaco operator C C and to settle into two phases, the lower of which is water. That aqueous phase is then discharged C C . RPX 4024-C; RX 3996(a); Piselli, Tr. 1980.

2. The operator then causes C C C ." These last traces of water are then discharged C to make sure that there is no water in the reactor. RPX 4024(c); RX 3996(a); Piselli, Tr. 1980.

3. During the N-alkylation step, Profarmaco adds to the reactor vessel (which already contains a toluene solution containing C) TZP which Profarmaco has dried by heating. Piselli, Tr. 1981-82; RX 4024-C; RX 3996(a).

4. C C C . Piselli, Tr. 1981-82; RPX 4024-C; RPX 3996(a).

5. C C C Piselli, Tr. 1985-86, 1978-79; RX P4024-C.

2. Differences Between the Profarmaco Process and the '035 Process

FF CP 50. The differences between the Profarmaco process currently employed to manufacture bulk diltiazem in the N-alkylation step and the processes claimed in the '035 patent (and in the Examples contained in the patent) include the following:

a) Profarmaco uses sodium carbonate as a base; the '035 patent specifies potassium carbonate and potassium hydroxide;

b) Profarmaco uses toluene as a solvent; the '035 patent uses acetone and lower alkyl acetates, or mixtures of those solvents and water;

c) according to complainants' theory of the case, the '035 patent process operates in the presence of water, and calls for the optional addition of water; Profarmaco's process requires that water be removed constantly throughout the N-alkylation reaction and no water is specifically added.

d) Profarmaco's process is conducted at a temperature of approximately C °; the '035 processes are conducted at a maximum of 77°. CX 1 ('035 patent, col. 2, line 62).

e) in the Profarmaco process, Profarmaco arrives at a solution in toluene of the intermediate; Profarmaco is therefore ready to conduct the subsequent acetylation reaction in the same reactor vessel using the same reactants. By contrast, in the '035 process the intermediate is isolated.

See Piselli, Tr. 1986-87.

a. Solvents

FF CP 51. In comparing the solvent system of toluene to either acetone or ethyl acetate, "there are certainly differences that one can point to in the properties of these solvents." Gokel, Tr. 698.

FF CP 52. According to complainant's expert Dr. Gokel, "the key difference" of the Profarmaco process from the '035 process is the use of toluene as the solvent. Gokel, Tr. 764.

FF CP 53. The information reported in Dr. Gokel's report entitled "Fermion and Profarmaco Versions of Tanabe Diltiazem Synthesis" reflects what Dr. Gokel "constructed to aid [his] thinking at an early stage" in the present litigation. In determining the equivalence between the Fermion and Profarmaco processes with the '035 process, Dr. Gokel considered many parameters relating to the solvents used for the N-alkylation reaction. One of the parameters that Dr. Gokel considered and thought might influence his opinion was solvent polarity parameters, while another was a comparison of the water miscibilities of the different solvents. Dr. Gokel also listed and considered dipole moments and dielectric constants for the different solvents. Dr. Gokel

summarized all of the different values in a solvent table on pages 13-15 of his report. CX 606; Gokel, Tr. 810-15.

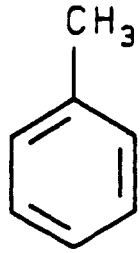
FF CP 54. When looking at the solvent tables included in Dr. Gokel's report entitled "Fermion and Profarmaco Versions of Tanabe Diltiazem Synthesis," Dr. Gokel compared the relevant values of one solvent with a second solvent, as determined by the same methodology, same tester, same equipment, etc. for the different solvents. CX 606; Gokel, Tr. 814-15.

Toluene is Substantially Different in Structure From the '035 Carbonyl Solvents

FF CP 55. The predominant structural feature of each of the solvents claimed in the '035 patent is the presence of a carbonyl group, which is shown enclosed by the dotted lines in the following formulas:

RRX 3983; Taber, Tr. 2058-59.

FF CP 56. Toluene is an aromatic hydrocarbon whose structure is illustrated by the formula:



RPX 3987.

FF CP 57. Toluene contains neither a carbonyl group nor any structure analogous to a carbonyl. Toluene is not a ketone (like acetone) or an ester (like an alkyl acetate). Taber, Tr. 2145; Gokel, Tr. 702.

FF CP 58. The oxygen atoms in the carbonyls of the solvents claimed in the '035 patent have two unbonded pairs of electrons which can be donated to positively charged species ("cations"), such as potassium ions (K^+), as depicted below:

RX 3983; Taber, Tr. 2059.

FF CP 59. The second oxygen atom in an alkyl acetate also possesses two pairs of unbonded electrons that can be donated. RX 3983; Taber, Tr. 2059.

The '035 Carbonyl Solvents Are Good Donor Solvents Whereas Toluene Is Not

FF CP 60. A donor solvent is a solvent which can donate electron density to stabilize an electron deficient species such as a cation. A donor solvent provides stabilization to an electron deficient species, such as a sodium or potassium cation, which are both electron deficient. Gokel, Tr. 702.

FF CP 61. The '035 carbonyl solvents are good donor solvents. RPX 3984;

Taber, Tr. 2060; Taylor, Tr. 2606.

FF CP 62. Toluene is a very poor donor solvent. RPX 3984; Taber, Tr. 2060, 2145.

FF CP 63. A donor solvent is "a material that has a polar functional group that can solvate a Lewis acid entity." A Lewis acid entity would include a potassium ion. Gokel, Tr. 802.

FF CP 64. Acetone and lower alkyl acetates are stronger donors than toluene. Gokel. Tr. 806.

FF CP 65. Because '035 carbonyl solvents can donate electrons, particularly when they contain water, they are able to solvate (or solubilize) and thus stabilize cations of inorganic bases, such as the potassium bases of the '035 patent. Taber, Tr. 2058, 2059.

FF CP 66. Potassium bases are more soluble in carbonyl solvents than are sodium bases. RX 4038C; Taber, Tr. 2147; Kende, Tr. 1455.

FF CP 67. Because of its poor donorability, toluene cannot effectively solvate (or solubilize) and thus stabilize cations of inorganic bases, such as potassium ions or sodium ions. RX 4034; Taber, Tr. 2061-2065.

FF CP 68. Sodium carbonate is not soluble in toluene. Taber, Tr. 2093.

The '035 Carbonyl Solvents Possess Medium Polarity Whereas Toluene Is Nonpolar

FF CP 69. The '035 carbonyl solvents, methyl acetate, acetone and ethyl acetate range in donor number from 16.4 to 17.1. RPX 3984; Taber, Tr. 2060.

FF CP 70. The donor number for toluene is 0.1. RPX 3984; Taber, Tr. 2060.

FF CP 71. The '035 carbonyl solvents are more than 160 times better donors than is toluene. RPX 3984

FF CP 72. The '035 carbonyl solvents, methyl acetate, ethyl acetate and

acetone, are of medium polarity, having dipole moments ranging between 5.7 and 9.0 and dielectric constants ranging from 6.0 to 20.56. RPX 3985

FF CP 73. Toluene is a non-polar solvent, having a dipole moment of 1.0 and dielectric constant of 2.38. RPX 3985; Taber, Tr. 2145; Gokel, Tr. 810.

FF CP 74. Because water is soluble in the '035 carbonyl solvents, it increases the dielectric constant of the '035 carbonyl solvents. Taber, Tr. 2067.

FF CP 75. Ionic species are solvated and stabilized better by polar solvents than by non-polar solvents. Gokel, Tr. 810.

FF CP 76. Toluene, being a non-polar solvent, lacks the ability to dissolve inorganic bases. Taber, Tr. 2064-65.

The '035 Carbonyl Solvents and Water Are Substantially Soluble Within Each Other Whereas Toluene and Water Are Not

FF CP 77. The '035 carbonyl solvents are substantially soluble in water, and water is substantially soluble in those solvents. RPX 3986; Taber, Tr. 2068.

FF CP 78. Acetone is infinitely soluble in water, and water is infinitely soluble in acetone. RPX 3986

FF CP 79. Methyl acetate is very soluble in water (approximately 23%), and water is very soluble in methyl acetate. RPX 3986

FF CP 80. Ethyl acetate is soluble in water at 2.94%, and water is soluble in ethyl acetate at 8.08%. RPX 3986

FF CP 81. Toluene is soluble in water at 0.052% and water is soluble in toluene at 0.033%. RPX 3986

FF CP 82. The solubility of water in the "wet toluene" used in the Profarmaco process is .03%. Taber, Tr. 2068.

FF CP 83. It is "well-known" that water is immiscible in toluene.

Taylor, Tr. 2607.

FF CP 84. The least soluble of the '035 carbonyl solvents (ethyl acetate) is more than 50 times more soluble in water than toluene, and water is more than 200 times more soluble in ethyl acetate than in toluene. RPX 3986.

Water Can Solvate Inorganic Bases

FF CP 85. The solubility of water in the '035 carbonyl solvents, and vice versa, contributes to the ability of the '035 carbonyl solvents to solvate (or solubilize) the potassium bases disclosed in the '035 patent. Taber, Tr. 2145-46.

FF CP 86. One of ordinary skill in the art in 1981 would have known that the solubility of potassium salts in acetone would be enhanced by the addition of water. Taylor, Tr. 2606.

FF CP 87. Water stabilizes and thus makes more soluble negatively charged hydroxide and carbonate ions ("anions") in a reaction solution. RPX 3994; Taber, Tr. 2057-58.

The '035 Carbonyl Solvents Are Both Hydrophilic and Lipophilic Whereas Toluene Is Only Lipophilic

FF CP 88. The '035 carbonyl solvents possess both hydrophilic (water-loving) and lipophilic (oil-loving) properties. RPX 3993; Taber, Tr. 2058; 2068-69.

FF CP 89. Because the '035 carbonyl solvents have both hydrophilic and lipophilic properties, they are able to bring together in solution TZP, the inorganic base, and DMC (in the form of aziridinium). Taber, Tr. 2146.

FF CP 90. Because the '035 carbonyl solvents have both hydrophilic and lipophilic properties, the TZP, inorganic base, and DMC all dissolve in the organic-aqueous phase surrounding the inorganic base particles. Taber, Tr.

2083, 2146.

FF CP 91. Toluene has strongly lipophilic properties with little or no hydrophilic properties. RX 3993; Taber, Tr. 2069, 2077, 2146.

FF CP 92. Because toluene has very little hydrophilic properties, most water included in the Profarmaco process is associated with the surface of the sodium carbonate base particle. Taber, Tr. 2146.

b. Bases

Sodium and Potassium Bases Are Not Interchangeable in the '035 Process, but Are Interchangeable in Profarmaco's Process

FF CP 93. Sodium carbonate is not equivalent to the potassium bases claimed in claim 1 of the '035 patent. Taber, Tr. 2150.

FF CP 94. The carbonyl containing solvents of the '035 patent are known to be able to solvate at least to some degree potassium. This same phenomenon is not known, however, with sodium, at least not to the same degree. Thus, especially given the teachings of the '035 patent, a person skilled in the art at the time of the alleged '035 invention would have believed that the specific carbonyl containing solvents of the '035 patent were linked with and were capable of providing some solubility only to potassium hydroxide and potassium carbonate. Taylor, Tr. 2604-05.

FF CP 95. Potassium salts are generally more soluble in solvating organic solvents than are sodium salts. Gokel, Tr. 844; Taylor, Tr. 2604-05.

FF CP 96. The sodium cation is more charge dense than the potassium cation. Gokel, Tr. 844.

FF CP 97. Whereas sodium carbonate does not work in the same way as the potassium bases in the '035 patent, sodium carbonate would work in the same way as potassium carbonate in the Profarmaco process. This is because sodium and potassium bases are often interchangeable when dealing with reaction

solutions containing pure water, as in the aqueous phase surrounding the inorganic base particle in the Profarmaco process. Taber, Tr. 2146-47.

FF CP 98. Potassium salts and sodium salts are interchangeable in aqueous systems. Taber, Tr. 2117-18.

c. Reaction Mechanisms

The Profarmaco and '035 Processes Operate with Substantially Different Reaction Mechanisms

FF CP 99. The Profarmaco process proceeds with a different mechanism than does the '035 process. Taber, Tr. 2111-12.

FF CP 100. The '035 process is one in which the inorganic base particles (potassium base particles) are surrounded by a solvent-water mixture, wherein the concentration of water is greatest at the surface of the particle and decreases with distance from the particle. Some water is dissolved in the bulk organic phase. Taber, Tr. 2069-71; Gokel, Tr. 705.

FF CP 101. Complainants' expert, Dr. Gokel, has carried out no experiments and is unaware of any experiments carried out by others, comparing a surface solvent phase formed in the '035 process with a surface solvent phase formed in any of the Respondents' processes. Gokel, Tr. 1053.

FF CP 102. Dr. Baldwin would expect to find more dissolved base in the solvent system of the '035 process than he would in the toluene phase of the Profarmaco process. RX 3048C.

FF CP 103. The pH of the carbonate buffer contained in the aqueous phase of the Profarmaco process is the same, whether sodium carbonate or potassium carbonate is used as the base. Because a dramatic difference is obtained in the '035 process when using a sodium base instead of a potassium base, this indicates that the '035 reaction system is a mixed solvent system, comprising water, organic solvents and potassium base. This mixed solvent system is

further evidenced by the knowledge that potassium bases are more soluble than sodium bases in the '035 carbonyl solvents, due to the ability of the carbonyl solvents to solvate potassium ions more efficiently than sodium ions. Taber, Tr. 2147.

FF CP 104. The ratio of water to organic solvent in the '035 process is a gradient or continuum extending outward from the solid base particles of the '035 patent. Taber, Tr. 2069-71. In the '035 system, there exists a "phase boundary" between the ethyl acetate and water phases "which is on the ethyl acetate side more like ethyl acetate; on the water side, more like water. And in the middle there is a progression from one to the other. Gokel, Tr. 705.

FF CP 105. Complainants' expert Dr. Gokel "would certainly expect" that the difference between toluene and ethyl acetate would alter the phase boundary present in the respective systems. Gokel, Tr. 707.

FF CP 106. The TZP in the '035 process is deprotonated by carbonate or hydroxide ions and the resulting amide anion reacts with the aziridinium ion to yield the alkylated product. Taber, Tr. 2074-75.

FF CP 107. No direct experimental evidence exists that the claimed N-alkylation process of the '035 patent using potassium carbonate as a base is hydroxide-mediated. Gokel, Tr. 1028. If anything, there are indications that it is not hydroxide-mediated. Taylor, Tr. 2674.

FF CP 108. The particular base-solvent combinations of the '035 patent result in the reactants coming together in solution and thus allow the reaction to proceed at relatively low temperatures with good yields. Kende, Tr. 1194.

FF CP 109. Complainants' expert, Dr. Gokel, was unsure whether the actual alkylating agent in either the Profarmaco or the '035 processes is the

aziridinium ion. Specifically, the only thing Dr. Gokel knows is that in both reactions some aziridinium ion is formed, but he does not know whether the aziridinium ion is the actual alkylating agent or not. Although he "think[s], it is reasonable that it could be, . . . [he] can't rule out the other possibility." That the alkylation of TZP occurs predominantly through the aziridinium ion would be a "guess" to Dr. Gokel. Gokel, Tr. 849-51.

FF CP 110. Dr. Gokel also agreed that the aziridinium ion would be likely involved in the '257 process, in addition to its likely involvement in both the '035 and Profarmaco processes. Gokel, Tr. 850-51.

FF CP 111. Dr. Baldwin's labeling experiments in JEB1-JEB4 do not prove that the aziridinium ion is the alkylating species. RX 3963; RX 4038C.

FF CP 112. Profarmaco's expert testified that in the Profarmaco reaction, the aziridinium ion acts as a phase transfer agent between the thin water layer surrounding the inorganic base particle and the bulk toluene phase. Taber, Tr. 2081, 2109-12; RPX 4000, 4001.

Substantially Lower Amounts of Water Are Present in the Profarmaco Process

FF CP 113. In the Profarmaco process, the amounts of water present are much smaller than the amounts of water present in the '035 process. Specifically, in Example 3 of the '035 patent, the amount of water associated with potassium carbonate is about 1.1 moles of water per mole of potassium carbonate. RX 1688 (Liotta Dep. Tr. 977-78). In contrast, in the Profarmaco process wherein the water concentration of the water-extracted toluene is C %, the molar ratio of water to sodium carbonate is about C % or C times less than in the '035 process. RX 1688.

FF CP 114. The small amount of dissolved water in the toluene of the Profarmaco process exists in aggregates of molecules. Taber, Tr. 2077; RPX

4000.

FF CP 115. The minuscule amounts of water in the toluene associate with the surface of the sodium carbonate base in the Profarmaco process, whereas in the process of the '035 patent significant amounts of water are dissolved in the carbonyl solvent and the water participates in the solvation and dissolution of the inorganic potassium base. RPX 4000; Taber, Tr. 2069-71, 2076-78.

FF CP 116. No mention is made of azeotropic removal of water in any of the examples of the '035 patent. Instead, the '035 patent teaches in the examples that the reaction is carried out under reflux conditions, meaning that the vapors of solvent released from the reaction mixture during boiling are condensed to a liquid in a reflux condenser and returned to the reaction vessel. Gokel, Tr. 904-06.

The Profarmaco Process Is More Like the '257 Process Than the '035 Process

FF CP 117. The Profarmaco process is much more like the '257 process than the '035 process because where reversible deprotonation of the TZP starting material occurs in the '035 process, the TZP starting material in the Profarmaco process is directly alkylated after deprotonation occurs. Thus, no equilibrium (or reversibility) exists in the Profarmaco process between the TZP starting material and its anion. Taber, Tr. 2112-14; RPX 4001.

More Energy Is Required to Carry Out Profarmaco Process

FF CP 118. A higher amount of energy is required for the reaction occurring in the Profarmaco process than for the reaction occurring in the process of the '035 patent, as reflected by the higher reaction temperatures required for obtaining good yields in the Profarmaco process. Taber, Tr. 2109.

FF CP 119. The Profarmaco process is carried out at a temperature of C °C versus 77°C or less in the '035 process. CX 1; Piselli, Tr. 1987.

Evolution of Carbon Dioxide Occurs in the Profarmaco Process, But Not in the '035 Process

FF CP 120. Because of the higher reaction temperatures necessary to carry out the Profarmaco process, carbon dioxide is evolved during the Profarmaco process, thereby also producing sodium hydroxide. Taber, Tr. 2088.

FF CP 121. Nothing in the '035 patent indicates that carbon dioxide is evolved during the '035 process. Taber, Tr. 2088; Gokel, Tr. 1043-1044.

FF CP 122. The fact that the evolution of carbon dioxide in the Profarmaco process coincides with the production of product indicates that the hydroxide ion formation, which occurs simultaneously with carbon dioxide evolution, is important to the Profarmaco process. Taber, Tr. 2089.

Different pH Levels Exist in Profarmaco and '035 Processes

FF CP 123. While the pH in the '035 process drops from an initial pH of 11.5 to 8.5, the pH in the Profarmaco process is maintained at a minimum level of 11.5. Taber, Tr. 2088-89.

FF CP 124. One pH interval level represents a difference in hydroxide ion concentration of a factor of 10. Thus, there is 1000 times more hydroxide ion present in the Profarmaco process than in the '035 process. Taber, Tr. 2089.

FF CP 125. The Profarmaco process operates at a much higher pH level than the process of the '035 patent, due to the higher hydroxide ion concentration and significantly lower amount of water present in the Profarmaco process. Taber, Tr. 2089-90.

d. Experimental Evidence Demonstrates That the Profarmaco Process Works in A Substantially Different Way Than the '035 Process

FF CP 126. At least four different sets of experiments have been made of record in the present investigation demonstrating that when the solvent toluene is substituted for the '035 carbonyl solvents in the '035 process the reaction proceeds very differently: (1) the experiments underlying the EPO Comparative Test Report submitted by Tanabe during the prosecution of the European application corresponding to the '035 patent; (2) experiments conducted by Tanabe scientists in the early 1980's; (3) experiments conducted by complainants' expert Dr. Baldwin; and (4) experiments conducted by Profarmaco. RX 3929, 3494, 3963, 3936; Taber, Tr. 2120-23, 2131-2145.

FF CP 127. At least four different sets of experimental data demonstrate that sodium carbonate reacts quite differently than potassium carbonate in the '035 process: (1) the EPO Comparative Test Report submitted by Tanabe during the prosecution of the European application corresponding to the '035 patent; (2) research reports by the '035 inventors; (3) experimental tests by complainants' expert Dr. Baldwin; and (4) experiments conducted by Profarmaco. RX 3929, 3361, 3963, 3936; Taber, Tr. 2119-23, 2131-2145.

Comparative Test Report

FF CP 128. In Experiment No. 1 of Table 1, a yield of 86.2% was reported when using potassium hydroxide and acetone at a reaction temperature of 50°C for a reaction period of 7 hours. RX 3929C. The reaction temperature of 50-60°C was within the range described in the '035 patent specification. RX 3048C.

FF CP 129. In Experiment No. 2 of Table 1, a yield of 94.5% was reported when using potassium carbonate and acetone under reflux conditions for a reaction period of 9 hours. RX 3929C.

FF CP 130. In Experiment No. 3 of Table 1, a yield of 90.2% was reported

when using potassium carbonate and ethyl acetate under reflux conditions for a reaction period of 23 hours. RX 3929C.

FF CP 131. In Experiment No. 4 of Table 1, a yield of 90.7% was reported when using potassium carbonate and acetone/water under reflux conditions for a reaction period of 3 hours. RX 3929C.

FF CP 132. In Experiment No. 5 of Table 1, a yield of 92.7% was reported when using potassium carbonate and ethyl acetate/water under reflux conditions for a reaction period of 6 hours. RX 3929C.

FF CP 133. In Experiment No. 6 of Table 1, a yield of 87.3% was obtained when using potassium carbonate and methyl acetate/water under reflux conditions for a reaction period of 30 hours. RX 3929C.

FF CP 134. The base and solvent systems, reaction temperatures, reaction times and yields obtained in Experiment Nos. 1-6 in Table 1 of the EPO Comparative Test Report correspond with the bases and solvents, reaction conditions and yields obtained in Examples 1, 4, 5, 2, 3 and 7, respectively, of the '035 patent. CX 1; RX 3929-C.

FF CP 135. In Experiment No. 8 of Table 1, the yield of product was reported as "no reaction" when potassium hydroxide and toluene were used at a reaction temperature of 50-60°C for a reaction period of 7 hours. RX 3929C. The reaction temperature of 50-60°C was within the range described in the '035 patent. RX 3048C.

FF CP 136. In Experiment No. 11 of Table 1, a yield of 10% was reported when using sodium hydroxide and acetone under reflux conditions for a reaction period of 15 to 20 hours. RX 3929C.

FF CP 137. In Experiment No. 12 of Table 1, the yield of product was reported as "no reaction" when sodium carbonate and acetone were used under

reflux conditions for a reaction period of 15 to 20 hours. RX 3929C.

FF CP 138. Where "no reaction" is reported in Experiments 8 and 12 of the Comparative Test Report, Tanabe did not necessarily mean zero yield but rather meant a poor yield. Taber, Tr. 2281.

FF CP 139. Complainants' expert, Dr. Gokel, provided as an explanation for why a 86.2% yield was obtained in Experiment No. 1 (KOH/Acetone) of Table 1, whereas only a 10% yield was obtained in Experiment No. 11 (NaOH/Acetone) of Table 1, was that "[i]t can be explained by the fact this is sodium hydroxide and that's potassium hydroxide . . . ." Another possible explanation for why different yields were obtained in Experiments Nos. 1 and 11 is that in a theoretical sense there exists a difference in the solubilities of potassium hydroxide and sodium hydroxide, which thus could account for the differences in the reaction yields obtained. Dr. Gokel recognized this to be a "well-known phenomenon." Gokel, Tr. 845-47.

Experiments Performed by Tanabe Scientists

Toluene Did Not Work in '035 Process

FF CP 140. In a Tanabe technology department report, dated October 1981 (approximately two months prior to the December 1981 date of the Japanese priority patent application upon which the '035 patent is based), Tanabe scientists reported that the N-alkylation of TZP at a reaction temperature of C °C using C as the base and C as the solvent did not work. Tanabe repeated the reaction several times, varying the reaction temperature and amount of water added, but were unable to obtain an appreciable product. Taber Tr. 2136-37; Gokel, Tr. 779-84; RX 3494.

FF CP 141. Dr. Gaino, one of the co-inventors named on the face of the '035 patent, reported in his notebook that N-alkylating TZP using C

C as the base and C as the solvent failed to work. Taber, Tr. 2138-39; RX 3368C.

FF CP 142. The Tanabe research reports reflect the Tanabe scientists' finding that toluene is not a useful solvent for the '035 process. Taber, Tr. 2139.

Sodium Carbonate Did Not Work in the '035 Process

FF CP 143. Tanabe performed experiments about three months prior to the December 1981 date of the Japanese priority patent application upon which the '035 patent is based wherein C and C were substituted for C as the base for N-alkylating TZP in C . When using either C or C , Tanabe scientists were unable to make the N-alkylation reaction work. The experiment using sodium carbonate and acetone corresponded with Experiment No. 12 in Table 1 of the European Comparative Test Report using sodium carbonate and acetone wherein "no reaction" is reported. Thus, Experiment 12 may be based on this test. RX 3362C, RX 3361C; Taber, Tr. 2123, 2131-35.

FF CP 144. Tanabe Research Reports reflect the finding of Tanabe scientists that sodium carbonate is not useful as a base in the '035 process. Taber, Tr. 2139.

Experiments Performed by Complainants' Expert, Dr. Baldwin, During the Investigation

FF CP 145. Experiments carried out by Complainant's expert Dr. Baldwin demonstrate that toluene does not work as a solvent in the '035 process. Taber, Tr. 2143-44; RX 3963, RPX 3991C.

FF CP 146. Experiments carried out by Complainant's expert Dr. Baldwin demonstrate that sodium carbonate does not work efficiently as a base in the '035 process, as that process is taught in the patent's examples. Taber, Tr.

2143-2144; RX 3963, RPX 3991C.

FF CP 147. In Experiment JEB15, which was designed to simulate a process of the '035 patent in which toluene was interchanged for a solvent of the '035 patent, a yield of 24% was obtained when N-alkylating TZP with potassium hydroxide as the base and toluene as the solvent at a reaction temperature of 111°C. RX 3963; RX 3048C.

FF CP 148. In Experiment JEB16, which was designed to simulate a process of the '035 patent in which toluene was interchanged for a solvent of the '035 patent, a yield of 56% was obtained when N-alkylating TZP with potassium carbonate as the base and toluene as the solvent at a reaction temperature of 111°C. RX 3963; RX 3048C.

FF CP 149. In Experiment JEB17, the yield of product obtained dropped from 90.7% to 35% when sodium carbonate was substituted for potassium carbonate under some reaction conditions of Example 2 of the '035 patent. RX 3963; RPX 3991C.

FF CP 150. In Experiment JEB18, the yield of product obtained dropped from 92.7% to 65% when sodium carbonate was substituted for potassium carbonate under some reaction conditions of Example 3 of the '035 patent. RX 3963; RPX 3991C.

FF CP 151. In Experiment JEB19, the yield of product obtained dropped from 90.7% to 10% when sodium carbonate was substituted for potassium carbonate under some reaction conditions of Example 2 of the '035 patent. RX 3963; RPX 3991C.

FF CP 152. In Experiment JEB20, a yield of 97% was obtained when sodium carbonate was substituted for potassium carbonate under some reaction conditions of Example 3 of the '035 patent, but only after heating the

reaction mixture at reflux temperature for 23 hours (almost 4 times the reaction time in Example 3). RX 3963; RPX 3991C.

FF CP 153. Experiment No. 12 in Table 1 of the Comparative Test Report, in which "no reaction" was reported for an N-alkylation reaction using sodium carbonate and acetone, is consistent with the 10% yield that the complainants' expert Dr. Baldwin obtained in JEB 19, wherein sodium carbonate and acetone also were used. Taber, Tr. 2281.

FF CP 154. Experiment No. 8 in Table 1 of the Comparative Test Report, in which "no reaction" was reported for an N-alkylation reaction using potassium hydroxide and toluene, is consistent with the 24% yield that the complainants' expert Dr. Baldwin obtained in JEB 15, wherein potassium hydroxide and toluene also were used. Taber, Tr. 2281.

FF CP 155. Dr. Baldwin's experiments also demonstrated the importance of water removal during the Profarmaco process. RPX 3992; RX 3963.

FF CP 156. In Experiment JEB2 (which sought to mimic the Profarmaco process), Dr. Baldwin's assistants failed to follow his instruction that steps be taken to remove water during the reaction. RX 4038C; Gokel, Tr. 866-67.

FF CP 157. Without taking steps to remove water in JEB2, a yield of only 32% was obtained. RX 3963.

FF CP 158. When Dr. Baldwin repeated Experiments JEB2 with azeotropic water removal, the yield increased from 32% to 98%. RX 3963.

FF CP 159. Complainants' expert, Dr. Gokel, agreed that "an effort was made to remove water" during Dr. Baldwin's repeat of JEB2, including transferring the reaction mixture to a clean Wheaton vile after the neutralization step, as well as using a heat gun to heat the distillation head to ensure that any water adhering to its walls was driven over into the

condenser. In addition, a clean condenser was attached to the reaction system prior to completing the reaction. The effort made to remove water in the repeat of Experiment JEB2 was consistent with Profarmaco's effort to remove water during its process by azeotropic distillation. Gokel, Tr. 867-69.

FF CP 160. No attempt also was made to remove water azeotropically during Experiments JEB 15 and JEB 16. Gokel, Tr. 801; RX 3048C.

FF CP 161. Complainants' expert, Dr. Gokel, had no idea whether Dr. Baldwin's Experiment Nos. JEB1-JEB20 had been optimized; in other words, they may have been or they may not have been. Gokel, Tr. 616-617.

FF CP 162. If Dr. Baldwin's experiments were not already optimized, they could have been optimized if complainants' counsel chose to have it done. Gokel, Tr. 1113-15.

Experiments Performed by Profarmaco During Investigation

FF CP 163. During the course of this investigation, Dr. Piselli of Profarmaco conducted certain experiments. Those experiments are summarized at page 703 of RX 3936. Trial Tr. at 1987-88.

FF CP 164. In Experiments 1-3, Dr. Piselli repeated Example 3 of the '035 process. These experiments were run in triplicate. Piselli, Tr. 1988; RX 3936.

FF CP 165. The yields obtained by Dr. Piselli in these three repetitions of Example 3 of the '035 patent were virtually identical to the yield indicated in the '035 patent itself. Similarly, the product produced, based on TLC analysis and melting point range, appears to be identical to that indicated in Example 3 of the '035 patent. Piselli, Tr. 1988; RX 3936; CX 1.

FF CP 166. In Experiments 4-6, Dr. Piselli used Example 3 of the '035 patent as a starting point for three experiments, in which he substituted

sodium carbonate for potassium carbonate. Dr. Piselli ascertained that after a period of time that was slightly longer than that specified in Example 3 of the '035 patent, each of the three experiments provided a low yield. Piselli, Tr. 1989-1990; RX 3936.

FF CP 167. In Experiment 4, Dr. Piselli therefore extended the reaction time to 15 hours, and in Experiment 6 extended the reaction time to 30 hours and changed a number of other factors. In each instance, the yield remained low. Piselli, Tr. 1989; RX 3936.

FF CP 168. Also, in Experiments 5 and 6, the purity of the product obtained was poor, as characterized by a "NEG" indication in the "Purity by TLC" column. RX 3936 at 703.

FF CP 169. Similarly, the melting points of the product obtained in Experiments 5 and 6 were significantly lower than the melting range for the product obtained by a simple replication of the Example 3 of the '035 patent. Piselli, Tr. 1988-1990; RX 3936 at 703.

FF CP 170. With respect to Experiments 4-6, Dr. Piselli testified that the yields reflected in those experiments "is not a process. It's something that should be abandoned." Piselli, Tr. 1990.

FF CP 171. In Experiments 7 and 8, Dr. Piselli replicated Example 4 of the '035 patent. Piselli, Tr. 1990; RX 3936.

FF CP 172. The yields and quality obtained in Experiments 7 and 8 compare favorably with the yields and quality reflected in Example 4 of the '035 patent. Piselli, Tr. 1990-1991; RX 3996 at 703.

FF CP 173. In Experiments 10 and 11, Dr. Piselli replicated Example 4 of the '035 patent, except that he substituted sodium carbonate for potassium carbonate. Piselli, Tr. 1991; RX 3936.

FF CP 174. Experiments 10 and 11 produced a low yield and a poor quality product, as reflected by the "neg" comment in the purity by TLC column. These results were not improved by continuing the reaction for 18 hours. Piselli, Tr. 1991; RX 3936 at 703.

FF CP 175. Experiments 4-6 and 10-11 demonstrate that sodium carbonate is not a useful base in the '035 process. Taber, Tr. 2142.

FF CP 176. In Experiment 15, Dr. Piselli replicated Example 3 of the '035 patent except that he substituted toluene as the solvent in the place of ethyl acetate. Dr. Piselli used the reflux temperature of ethyl acetate, as used in the patent example. The yield was extremely low and the product was not pure. Piselli, Tr. 1991-1992, 2031; RX 3936 at 703.

FF CP 177. In Experiment 16, Dr. Piselli replicated Example 3 of the '035 patent except that he substituted toluene for acetone. There was no yield in this reaction at all. Dr. Piselli used the boiling temperature of acetone. Piselli, Tr. 1992, 2031; RX 3936 at 703.

Optimization Defined

FF CP 178. Optimization is not the same thing as experimentation. A process is optimized only after it has been found to be a "consistent" process, specifically a process from which "a well-defined product with a well-defined yield" is obtained. It is only at this point in time that "technological optimization" (i.e., trying "small variations in the operating parameters") of a process is conducted. For example, if an experiment using the same reactants and reaction conditions was repeated ten times, any variation in yield would be minimal. Piselli, Tr. 2017-18, 2021.

FF CP 179. Dr. Piselli testified that one could not "optimize" the Profarmaco experiments: "Optimization is one thing, the process is another.

You optimize a process that has a certain consistency and is valid, but if the process doesn't exist, you don't optimize it." Piselli, Tr. 1990.

e. The Profarmaco Process Also Performs A Substantially Different Function and Achieves A Substantially Different Result Than the '035 Process

FF CP 180. Because claim 1 of the '035 patent does not include a recovery step, the product of claim 1 is N-alkylated TZP in a reaction mixture containing water, a polar, water-miscible carbonyl solvent and various salts. CX 1; Taber, Tr. 2183.

FF CP 181. The Profarmaco process produces a solution of N-alkylated TZP in toluene. Taber, Tr. 2183-2184.

FF CP 182. The examples of the '035 patent teach that the N-alkylated TZP obtained as the product of claim 1 of the '035 patent must be isolated, purified, and transferred to another reaction vessel before the manufacture of diltiazem can proceed. CX 1; Piselli, Tr. 1987.

FF CP 183. The product of Profarmaco's sodium carbonate/toluene N-alkylation process provides commercial advantages, for example, convenience, unobtainable using the product of the N-alkylation process claimed in the claim 1 of the '035 patent. Taber, Tr. 2183-2185.

FF CP 184. Because toluene is immiscible with water, the solution of N-alkylated TZP in toluene produced from the N-alkylation step of the Profarmaco process can be directly washed with water to remove byproducts and unreacted DMC, leaving behind a solution in which one can directly carry out the subsequent acetylation reaction. Taber, Tr. 2185.

FF CP 185. The function of the process of claim 1 of the '035 patent is to produce an organic reaction mixture containing N-alkylated TZP in a carbonyl solvent-water mixture. This product will contain water, dissolved

base and salts along with alkylated TZP. To utilize the solubilized N-alkylated TZP, the reaction mixture must be (i) extracted, (ii) washed, (iii) filtered, (iv) concentrated, (v) redissolved, and (vi) transferred to another reactor prior to the subsequently applied steps, including, inter alia, the acetylation and salt-forming steps. RX 3348; Taber, Tr. 2183; Piselli, Tr. 1987.

B. The Abic Process Does Not Infringe Claim 1 of the '035 Patent

1. The Abic Process Is Not Equivalent to Any Process Disclosed Or Claimed By The '035 Patent

FF CA 1. The Abic process does not employ either of the two bases or either of the two organic solvents or any of the five specific base-solvent combinations identified in the '035 patent. See RX 1194; RX 1195.

FF CA 2. Abic's commercial process uses barium hydroxide octahydrate as a base, a biphasic solvent system of methylene chloride and water, and triethylbenzylammonium chloride (TEBA) and is similar to the process described in example 4 of its United States Patent No. 4,466,995 ("the '995 patent"). RX 1701C.

FF CA 3. All the processes used by Abic to manufacture diltiazem hydrochloride were disclosed in the Abic DMF. C RX 1701.

The Bases Are Not Equivalent

FF CA 4. Abic's base is barium hydroxide octahydrate, and not potassium hydroxide or potassium carbonate. RX 1194; Taylor Tr. 2638; RX 1701C.

FF CA 5. The '035 patent does not disclose or suggest barium hydroxide to a person of ordinary skill. Taylor Tr. 2609.

FF CA 6. Barium is an alkaline earth metal, and as such forms divalent cations. Taylor Tr. 2609.

FF CA 7. Among other things, barium hydroxide is less soluble than potassium hydroxide in carbonyl solvents such as acetone and lower alkyl acetates. Taylor Tr. 2610.

FF CA 8. If one of ordinary skill in the art were investigating the interchangeability of other bases with the potassium bases of the '035 patent, one would likely first try sodium hydroxide (NaOH) because sodium hydroxide is more common and substantially less expensive than potassium hydroxide. Taylor Tr. 2626.

FF CA 9. Tanabe tried and abandoned sodium hydroxide in combination with DMSO. RX 1589C.

FF CA 10. As is shown by the Comparative Test Report, Tanabe did try the base/solvent combination of sodium hydroxide and acetone, and concluded that it was not part of the method of the invention of the '035 patent. Tr. 2636; RPX 1146; RX 1096; RX 1344, RX 3225.

FF CA 11. Barium hydroxide would be expected to be less effective than sodium hydroxide in the '035 process because barium is even less soluble than sodium in the carbonyl solvents acetone or ethyl acetate of the '035 patent. Taylor Tr. 2627.

FF CA 12. Consequently, if sodium hydroxide were found to be not as good as potassium hydroxide, one of ordinary skill in the art would not be led to try barium hydroxide, since barium hydroxide would be expected to be even worse in the '035 process, which discloses solvation of the solid base in a carbonyl solvent. Taylor Tr. 2627.

FF CA 13. Accordingly, one of ordinary skill in the art, knowing that even sodium hydroxide was not interchangeable with potassium hydroxide would not have expected that barium hydroxide would be interchangeable with

potassium hydroxide or potassium carbonate. Taylor Tr. 2609-10.

The Organic Solvents Are Not Equivalent

FF CA 14. The organic solvent in Abic's process is methylene chloride. RX 1195; Taylor Tr. 2641; RX 1701C.

FF CA 15. The '035 patent does not teach the use of methylene chloride as an organic solvent to be used in the N-alkylation of the '035 process. See Taylor Tr. 2612.

FF CA 16. The '035 patent disclosed chloroform, a chlorinated hydrocarbon like methylene chloride, but did not disclose its use or the use of any other chlorinated hydrocarbon solvent in its N-alkylation process. CX 1; Gokel Tr. 769-70.

FF CA 17. Acetone is a ketone. Taylor Tr. 2621.

FF CA 18. One of ordinary skill in the art looking to investigate the scope of potentially interchangeable solvents to replace acetone in the '035 process would have looked for solvents which shared the important structural and functional characteristics of the carbonyl solvents of the '035 patent, i.e., would have looked at oxygen-containing, cation-solvating, water-miscible solvents. Taylor Tr. 2624.

FF CA 19. Some common solvents which one might have investigated include methyl ethyl ketone, dioxane, methanol, and DMSO. Taylor Tr. 2621-24; RPX 1155.

FF CA 20. Methylene chloride would not be one of the solvents one would first try since it does not solvate cations well, has no oxygen atoms to act as donors, and is nearly totally immiscible with water. Taylor Tr. 2624.

FF CA 21. If solvents such as dioxane, methanol, and methyl ethyl ketone were not as effective as acetone in a reaction, one would not be led to try

methylene chloride, since that would be going in the "wrong direction," to even more inferior water-immiscible solvents. Taylor Tr. 2624-25.

Tanabe Tried to Extend the Scope of It's Invention in 1981 and Failed

FF CA 22. Tanabe tried sodium carbonate instead of potassium carbonate, but it did not work as well as the '035 bases. RX 3368; Taber Tr. 2134-36.

FF CA 23. Tanabe tried structurally and functionally similar solvents, such as dioxane, methyl ethyl ketone, methanol, and DMSO, and they didn't work as well as the '035 solvents. RX 3361; Gokel Tr. 928-31; RX 2046; Gokel Tr. 676-79; RX 3368; Taber Tr. 2138; RX 1272C; Taylor Tr. 2629-31.

FF CA 24. In fact, Tanabe tested and abandoned the base-solvent combination of potassium carbonate-methyl ethyl ketone (the combination currently employed by Fermion) because Tanabe could not get that combination to work. Taylor Tr. 2629; Gokel Tr. 676-79; RPX-1061a; and RX-2046.

FF CA 25. Tanabe did not try barium hydroxide as a base, methylene chloride as a solvent, or the combination of barium hydroxide and methylene chloride. See Taylor Tr. 2633; RX 1703.

The Liquid-Solid Process of the '035 Patent and the Abic Liquid-Liquid Process Are Not Equivalent

FF CA 26. Each of the organic solvent-water mixtures of the '035 patent forms a single liquid phase, i.e., it is a solution of water in the acetone or lower alkyl acetate organic solvent. Taylor 1804, 2666-68.

FF CA 27. Abic's solvent system is a biphasic solvent system - it consists of two distinct liquid phases - methylene chloride and water. RX 1195; Liotta Tr. 1804-05; Taylor Tr. 2664, 2666-67.

FF CA 28. There is no solid phase present in the Abic process. Schwartz Tr. 2520-21.

FF CA 29. Liquid-liquid phase transfer catalyst processes such as that

used by Abic and solid-liquid processes such as those of the '035 patent are not chemically equivalent. Taylor Tr. 2667; RX-3969 at 108.

FF CA 30. Dr. Liotta wrote in his book that, even when a solid-liquid process and a liquid-liquid process are both phase transfer catalyzed, they are by no means equivalent. RX 3969 at 108.

Abic's Process Is Phase Transfer Catalyzed by TEBA

FF CA 31. Dr. Charles Liotta, complainants' expert with respect to infringement of the '035 patent by the Abic process, submitted a declaration in this investigation in which he stated that:

> Convincing evidence has not been presented by Abic to date that [TEBA] is operating as a phase transfer catalyst in their N-alkylation process step.

RX 1333C, ¶ 6d.

FF CA 32. At his deposition, Dr. Liotta explained how such evidence could be generated:

> Q If I have two experiments, one where I have a phase transfer catalyst present and one where it is exactly the same but I leave out the phase transfer catalyst, and the rate in the one with the phase transfer catalyst is faster than the one without it, does that indicate that a phase transfer catalysis is taking place?
>
> A If you have repeated the experiments so you have reproductibility and stirring speeds are the same in both and everything was the same, the indication is that you have evidence for the operation of phase transfer catalysis.

Liotta Tr. 1832-33.

FF CA 33. Abic carried out a series of such experiments, as described by Dr. Liotta, which are identified as experiments 1, 10, and 14-20 on RPX 1051a. Taylor Tr. 2642-45.

FF CA 34. In experiments 1, 14, 17, 18, the N-alkylation was performed in the presence of TEBA catalyst; experiments 10, 13, 15, 16, 19 and 20 did

not use the TEBA phase transfer catalyst. RPX 1051a.

FF CA 35. The TZP and DMC were allowed to react in the methylene chloride-water biphasic solvent system for 1.5, 3, 6, or 12 hours. RPX 1051a.

FF CA 36. Experiments 14 and 17, 15 and 16 are repeats of each other, and the similar results indicate that the results were reproducible. Taylor Tr. 2645-47.

FF CA 37. The stirring speeds were carefully controlled, and were essentially the same in all experiments. Schwartz Tr. 2524, 2532.

FF CA 38. The Abic experiments met the criteria set forth by Dr. Liotta. Taylor Tr. 2650.

FF CA 39. The results were plotted on a graph which shows that the phase-transfer catalyzed reaction was at least twice as fast as the uncatalyzed reaction. Taylor Tr. 2647-49; RPX 1058.

The Abic Process Functions in a Different Way Than the '035 Process

FF CA 40. In the Abic liquid-liquid biphasic solvent process, the TZP and DMC are in the organic phase (the methylene chloride layer), while the barium hydroxide remains dissolved in the aqueous phase. TEBA, the phase transfer catalyst, is soluble in both phases. The aziridinium ion which, as a cation, is insoluble in methylene chloride, remains in the aqueous layer. Taylor Tr. 2638; RPX 1156.

FF CA 41. The hydroxide ion in the water layer cannot efficiently deprotonate the TZP in the methylene chloride layer, because they are in separate layers, organic and aqueous. The TEBA phase transfer catalyst carries the hydroxide ion as TEBA hydroxide into the methylene chloride layer, where it deprotonates the TZP. The TZP anion can then react with DMC to N-alkylate the TZP N-aryl amide. Taylor Tr. 2638; RPX 1099.

FF CA 42. The methylene chloride phase has an additional function in the Abic process over and above the function of acetone in the '035 process. Taylor Tr. 2641.

FF CA 43. The water-immiscible solvent methylene chloride keeps the TZP and DMC separated from dissolved aqueous barium hydroxide. Taylor Tr. 2641

FF CA 44. Kugita I discloses that TZP can hydrolyze in the presence of aqueous sodium hydroxide, especially at higher temperatures. RX 3806; Kende Tr. 1452-54.

FF CA 45. Abic's experience with biphasic toluene-aqueous hydroxide processes is in accord: at higher temperatures, hydrolysis of TZP was seen. RX 1007C; Haber Tr. 2417-20.

FF CA 46. In the Abic process, the methylene chloride, operating at 40° C, protects the TZP and DMC from hydrolysis by aqueous barium hydroxide. Taylor Tr. 2641.

FF CA 47. Because there is no aqueous hydroxide in the '035 solid-liquid potassium hydroxide/acetone process, hydrolysis is not a problem in the '035 process. Taylor Tr. 2666; Taber Tr. 2173.

Abic's Process Is Not Equivalent to the Potassium Hydroxide-Acetone Process of the '035 Patent

FF CA 48. Abic's expert compared the potassium hydroxide (KOH)/acetone system of the '035 patent and the barium hydroxide/methylene chloride system of Abic's process. Taylor Tr. 2664-65; RPX 1157.

FF CA 49. The bases and solvents are different. Id.

FF CA 50. There is no water in the '035 potassium hydroxide process; there is a separate aqueous layer in the Abic barium hydroxide process. Id.

FF CA 51. There is one solvent phase in the '035 process; there are two solvent phases in the Abic process. Id.

FF CA 52. The alkylating agent in the '035 process is aziridinium ion, and is located in the acetone single solvent phase in the '035 process. CPX 14; RPX 1157; Taylor Tr. 2664.

FF CA 53. In Abic's process, the active alkylating agent, DMC itself, is located in the methylene chloride phase. Taylor Tr. 2665.

FF CA 54. In the '035 process, potassium hydroxide is able to deprotonate TZP because it is somewhat soluble in the acetone solvent. In the Abic process, barium hydroxide, which is not soluble in methylene chloride, is able to deprotonate TZP via phase transfer catalysis. Taylor Tr. 2656, 2668.

FF CA 55. The potassium hydroxide in the '035 system and barium hydroxide in Abic's system do not function the same way to deprotonate TZP. Taylor Tr. 2665.

FF CA 56. The organic solvents in the '035 and the Abic processes have different functions: the function of acetone in the '035 process is to solubilize the KOH base in the organic phase; the solvents in Abic's process have the important function of separating the reagents. Taylor Tr. 2665-66.

FF CA 57. The '035 process is a solid-liquid system while the Abic process is a liquid-liquid system. Taylor Tr. 2666.

FF CA 58. The Abic process uses the phase transfer catalyst TEBA, but there is no phase transfer catalyst in the '035 process. Taylor Tr. 2665.

FF CA 59. Solid-liquid phase-transfer-catalyzed systems and liquid-liquid phase transfer catalyzed systems are not regarded as equivalent in the art. Taylor Tr. 2666-67; RX 3969.

FF CA 60. Abic's liquid-liquid phase-transfer-catalyzed system is even less equivalent to a simple solid-liquid system, i.e., a solid-liquid system without a phase transfer catalyst, such as that of the '035 process. Taylor

Tr. 2667; RX 3969.

FF CA 61. Phase transfer of the hydroxide ion could be effected by heating Abic's system. Unlike catalysis, which selectively increases the rate of hydroxide ion transfer, heating indiscriminately speeds up everything that is going on, thus increasing the potential for side reactions. Taylor Tr. 2668-69; RX 3969.

FF CA 62. Examples of side reactions which could occur in the Abic system as a result of heating to speed up the reaction are: dimer formation, hydrolysis of DMC, and hydrolysis of TZP. Taylor Tr. 2669-70; RPX 1051a.

FF CA 63. In Abic's process, dimer formation is inhibited by use of a phase transfer catalyst. Taylor Tr. 2669-70; RPX-1051a.

FF CA 64. Use of a phase transfer catalyst in Abic's system also enables a reduction in the volume of solvent used. Taylor Tr. 2670-71; RX-1024.

FF CA 65. The elements of Abic's barium hydroxide process, i.e., the base, the two solvents, the alkylating agent, and the phase transfer catalyst, are not the same as the elements of the potassium hydroxide/acetone base/solvent combination of the '035 patent, and the two processes do not function in the same way and are not equivalent. See Taylor Tr. 2672.

FF CA 66. Even if the alkylating agents were the same, and phase transfer catalysis were not taking place, the two processes would still not be equivalent. See Taylor Tr. 2672.

FF CA 67. That the '035 process starts with the same substrate, employs the same alkylating agent, and obtains the same product has no bearing on the equivalence of the base/solvent combinations to the claimed process, because the starting material, alkylating agent and the product are the prior art, not the elements of the claimed improvement. See Taylor Tr. 2672-73.

The Abic Process System Is Not Equivalent to the Potassium Carbonate/Acetone or Potassium Carbonate/Ethyl Acetate Processes of the '035 Patent

FF CA 68. The Abic process is even less similar to the potassium carbonate/acetone or potassium carbonate/ethyl acetate processes of the '035 patent, because the Abic base, barium hydroxide ($Ba(OH)_2$), is not a carbonate base, but a hydroxide base. RPX 1157; Taylor Tr. 2673.

FF CA 69. The Abic process is not equivalent to the potassium carbonate/acetone or potassium carbonate/lower alkyl acetate processes of the '035 patent because those processes cannot be made to work as they are disclosed by the '035 patent. See Taylor Tr. 2675.

FF CA 70. Attempts by Abic to replicate Examples 4 and 5 of the '035 patent (powdery potassium carbonate-acetone and powdery potassium carbonate-ethyl acetate, with no added water) failed. Taylor Tr. 2675; RPX-1051A.

FF CA 71. Abic found that the potassium carbonate/acetone and potassium carbonate/ethyl acetate base/solvent combinations do not work without added water. Taylor Tr. 2676, 2680-81; RX 1272.

FF CA 72. The Tanabe laboratory notebooks produced by Tanabe and in evidence showed that Tanabe knew from experiments conducted in 1981, before it filed its patent application on December 7, 1981, that the potassium carbonate/acetone and potassium carbonate/ethyl acetate combinations did not work consistently without added water. Taylor Tr. 2677; Taber Tr. 2099, 2148.

FF CA 73. Abic's process, which consistently works, is not equivalent to the '035 systems of potassium carbonate/acetone and potassium carbonate/ethyl acetate, which do not work. Taylor Tr. 2678; RX 1272C.

FF CA 74. If, contrary to the evidence, it were assumed that the '035 processes of potassium carbonate/acetone and potassium carbonate/lower alkyl

acetate did work, the Abic process would not be equivalent to either process. See Taylor Tr. 2673, 2680.

FF CA 75. Barium hydroxide and potassium carbonate bases are different, and are non-equivalent ways of deprotonating TZP, because the deprotonating species is hydroxide (OH^-) in the one case, and carbonate ion ($CO_3^=$) in the other. Taylor Tr. 2673-74.

FF CA 76. To make the potassium carbonate and barium hydroxide bases seem more similar, complainants have postulated that the potassium carbonate processes are "hydroxide mediated"; that is, that potassium carbonate forms some hydroxide ion, which then deprotonates TZP. CPX 14; Gokel Tr. 709.

FF CA 77. There is no evidence that the potassium carbonate processes of the '035 patent are hydroxide mediated. Taylor Tr. 2674.

FF CA 78. Dr. Kende testified that he didn't know whether the processes were hydroxide mediated or not, and didn't even know how one would carry out an experiment to determine this. Kende Tr. 3415-16.

FF CA 79. Abic's process is not equivalent to the potassium carbonate/acetone and potassium carbonate/ethyl acetate combinations of the '035 patent for the same reasons it is not equivalent to the potassium hydroxide/acetone combination; and for the additional reasons that these '035 processes employ a different base, and are not hydroxide mediated. See Taylor Tr. 2679.

Abic's Process Is Not Equivalent to the Potassium Carbonate/Acetone-Water and Potassium Carbonate/Lower Alkyl Acetate-Water System of the '035 Patent

FF CA 80. Potassium carbonate processes with added water are similar to the potassium carbonate/acetone or potassium carbonate/ethyl acetate processes of the '035 patent, except that with the small added amount of water they produce satisfactory results. Taylor Tr. 2681-82; RPX 1051A.

FF CA 81. Although there is a small amount of water in the potassium carbonate/acetone-water and potassium carbonate/ethyl acetate-water processes, they are still solid-liquid processes, because the water (a) reacts with potassium carbonate to form solid potassium carbonate sesquihydrate, or (b) dissolves in the acetone or lower alkyl acetate solvent. Taylor Tr. 2682-3; 2687-98.

FF CA 82. For the same reasons that the Abic process is not equivalent to the KOH/acetone processes, or the potassium carbonate/acetone and potassium carbonate-lower alkyl acetate processes, it is not equivalent to the potassium carbonate-acetone-water or potassium carbonate-lower alkyl acetate-water processes. Taylor 2681-82.

FF CA 83. Abic repeated Examples 3 and 7 of the '035 patent, with yields similar to those reported by the '035 patent, and observed only one solid phase and one liquid phase. Schwartz Tr. 2513-15; RX 1175; Taylor Tr. 2682-82; RPX1051a.

FF CA 84. Abic also performed some experiments which showed that the '035 solid-liquid processes, even with added water, and the Abic liquid-liquid processes were fundamentally different. RPX 1051a; Taylor Tr. 2682-86.

FF CA 85. Abic performed an experiment repeating Example 3 of the '035 patent (potassium carbonate/ethyl acetate-water) but in which methylene chloride was substituted for ethyl acetate. After 6 hours (as specified in the '035 example), there was 21.5 percent of unreacted TZP and 77 percent of product. Taylor Tr. 2684; RPX-1051a.

FF CA 86. The yield of '035 Example 3 is reported to be 92.7%. RX 1194.

FF CA 87. The yield of the process is important in determining the equivalence of commercial processes, which require high yields. Gokel Tr. 1116-17.

FF CA 88. Abic performed an identical experiment with the sale difference that a small amount of TEBA phase transfer catalyst was added. After 6 hours, there remained 77 percent of product, but only 2.7 percent of unreacted starting material and a large amount of the dimer side product. Taylor Tr. 2684; RPX1051a.

FF CA 89. Abic also repeated Example 4 of Abic's '995 patent, with and without the TEBA phase transfer catalyst. In Abic's liquid-liquid biphasic solvent process, the results were exactly the reverse: a dimer was formed in the absence of phase transfer catalyst, but no dimer was formed in the presence of the phase transfer catalyst. Taylor Tr. 2685-86; RPX 1051a.

FF CA 90. It is not surprising that the two systems behave in opposite ways, since they are completely different systems. Taylor Tr. 2686.

FF CA 91. Complainants assert that the small amount of water present in these base/solvent combinations of the '035 patent is present as a "surface solvent phase" which complainants attempt to liken to the aqueous phase of Abic's biphasic solvent process. See Taylor Tr. 2698-99.

FF CA 92. Complainants introduced no evidence of such a surface solvent phase under the base-solvent conditions of the '035 patent. See Liotta Tr. 1762-64, and 1779-81.

FF CA 93. The "surface solvent phase" is postulated by complainants to be a very thin layer, approximately 100 angstroms (Å) thick, of indeterminate composition associated with the solid. Gokel Tr. 707, 1053.

FF CA 94. It would take 50,000 of the postulated 100 Å surface solvent

phases laid one on top of the other to make up the thickness of a pencil line. The surface solvent phase would be invisible to the naked eye. Wrighton Tr. 1610.

FF CA 95. Even if there were a surface solvent phase, the two processes would still be non-equivalent, for the reasons set forth above. See Taylor Tr. 2698-99.

FF CA 96. Professor Wrighton of M.I.T., an expert on surface chemistry, testified that the term "surface solvent phase" was not customarily used in surface chemistry, and had no recognized meaning. Wrighton Tr. 1608.

FF CA 97. Before this investigation, Dr. Liotta had never used the term "surface solvent phase" in any publication. Liotta Tr. 1749.

FF CA 98. Before this investigation, Dr. Liotta had never called a surface solvent phase a "biphasic solvent system." It appears that he used that terminology as and analogy to Abic's biphasic solvent system. Liotta Tr. 1705-06.

FF CA 99. The postulated surface solvent phase film, of indeterminant composition, and only 1/50,000th of the thickness of a pencil line, is not the chemical equivalent of the aqueous phase of the Abic methylene chloride-water biphasic solvent system. Taylor Tr. 2700.

FF CA 100. Dr. Liotta performed experiments attempting to prove the presence of a surface solvent phase when water was added to a mixture of potassium carbonate and ethyl acetate. Liotta Tr. 1812-13; CX 636.

FF CA 101. Dr. Liotta's experiments established that the potassium carbonate and water did not form a "surface solvent phase", but formed the well known solid compound potassium carbonate sesquihydrate ($K_2CO_3 \cdot 1.5H_2O$). Taylor Tr. 2687-2697.

FF CA 102. Potassium carbonate sesquihydrate is not a surface solvent phase. Gokel Tr. 1052; Wrighton Tr. 1622; Taylor Tr. 2688.

FF CA 103. Abic repeated Dr. Liotta's experiments, and tested the products by differential scanning calorimetry (DSC). RX 1702.

FF CA 104. Dr. Wrighton testified that the DSC results established that when potassium carbonate was treated with water in ethyl acetate as Dr. Liotta had done, the products were potassium carbonate sesquihydrate, or potassium carbonate sesquihydrate with some residual potassium carbonate. Wrighton Tr. 1602-22.

FF CA 105. Dr. Ronald Jenkins of the International Center for Diffraction Data testified as to analyses he had performed on the same material that Dr. Wrighton testified about. Dr. Jenkins concluded that the products were potassium carbonate sesquihydrate, or potassium carbonate sesquihydrate, with some residual potassium carbonate. Jenkins Tr. 2945-2953.

2. Abic Independently Developed Its Own Process -- It Did Not Copy the Process of the '035 Patent

Abic's Initial Experiments

FF CA 106. In 1982 Abic decided to market a calcium channel blocker, and chose diltiazem as its goal. Haber Tr. 2402.

FF CA 107. Although there was no patent on diltiazem in Israel, Abic sought a license from Tanabe for sale to other countries. Haber Tr. 2402.

FF CA 108. Tanabe refused to license Abic, or to supply raw material. Haber Tr. 2402-2403.

FF CA 109. As a consequence, Abic began research and development of the overall process for synthesizing diltiazem hydrochloride in December 1982 or very early in 1983. Haber Tr. 2402.

FF CA 110. By early 1983, Abic knew of the '257 patent and its foreign counterparts, but not of the '035 patent or any foreign counterpart of it. Haber Tr. 2403-04.

FF CA 111. There are about seven or eight steps in Abic's procedure to manufacture diltiazem hydrochloride, and the N-alkylation is the fifth or sixth step. Haber Tr. 2404.

FF CA 112. Therefore, it wasn't until May of 1983 that Abic had the starting material in hand to enable it to begin working on the N-alkylation step. Haber Tr. 2408.

FF CA 113. Abic's work on the synthesis of diltiazem hydrochloride, particularly the N-alkylation step, is reflected in Abic's internal periodic reports for 1982 and 1983. Haber Tr. 2409-10; RX 1007C; RX 1008C; RX 1009C; RX 1010C; RX 1013C; RX 1015C.

History of Abic Work on N-Alkylation

Date	Event
May 1983	First N-alkylation NaH/DMSO
August 1983	First phase transfer catalyst work KOH + Methylene Chloride + Water + TBABr Fix on methylene chloride as solvent Fix on TEBA as PTC Try NaOH as base
September - November 1983	NaOH + Methylene Chloride + Water + TEBA
December 1983	Try other than alkali metal bases $Mg(OH)_2$ $Ca(OH)_2$ NH_4OH $CaCO_3$ NEt_3 Knowledge of EPO '035 counterpart
February 1984	Test $Ba(OH)_2 \cdot H_2O$

RPX 1144

FF CA 114. Based on the literature, Abic believed that alkylating the nitrogen on the seven-membered ring would be a straightforward procedure.

Haber Tr. 2406-07.

FF CA 115. Because Abic needed diltiazem precursor for study of the acetylation step, and for further pharmaceutical testing, Abic began alkylating TZP under the conditions already reported in the '257 patent and the Kugita publications, sodium hydride and DMSO. Haber Tr. 2411.

The Early Development of Abic's Phase-Transfer Catalyzed, Methylene-Chloride-Water Processes

FF CA 116. Abic quickly moved away from the sodium hydride-DMSO base-solvent combination by replacing DMSO with DMF. Haber Tr. 2411-12.

FF CA 117. Abic then began to look for alkylation processes which did not employ sodium hydride. Haber Tr. 2412.

FF CA 118. It was known at that time, the summer of 1983, that one could alkylate carbon atoms (C-alkylation) using either harsh conditions or the milder conditions of phase transfer catalysis, in the presence of water, and it was felt that those milder phase transfer catalysis methods could be adapted to the N-alkylation of TZP. Haber Tr. 2412.

FF CA 119. Abic believed that alkylating under milder conditions would minimize the possibility of side reactions. Haber Tr. 2412-13.

FF CA 120. Although there is a large amount of water present in classical phase transfer conditions, Abic was not concerned with potential hydrolysis of the TZP. Haber Tr. 2413-14.

FF CA 121. Similarly, Abic was not concerned with the potential retro-Michael reactions under phase transfer catalyzed conditions because of the particular structure of the TZP molecule. Haber Tr. 2414-15.

FF CA 122. Because Tanabe had not observed O-alkylation at the 3-hydroxyl group of TZP under the harsher conditions of the '257 patent, Abic was not concerned that such O-alkylation was likely to take place under the

milder phase-transfer conditions. Haber Tr. 2415.

FF CA 123. Abic was not concerned about the potential for alkylation at the carbonyl oxygen because in the presence of a base, alkylation occurs almost exclusively at the nitrogen. Haber Tr. 2416.

FF CA 124. Abic was not concerned that DMC would be unstable under Abic's phase transfer conditions because, as with all alkylating agents, conditions can be modified to minimize instability. Haber Tr. 2416-17.

FF CA 125. In August, 1983, Abic tried two phase transfer catalyzed processes, one using potassium hydroxide-methylene chloride-water and the other using potassium hydroxide-toluene-water, both with TEBA bromide as the phase transfer catalyst. Haber Tr. 2413.

FF CA 126. In August, 1983 Abic was not aware of the '035 patent or any of its foreign counterparts. Haber Tr. 2413.

FF CA 127. The phase transfer catalyzed reaction in toluene did not work at low temperatures, and at high temperatures there was some hydrolysis of the lactam. Haber Tr. 2418-19; RX 1007C.

FF CA 128. However, the phase transfer catalyzed reaction in methylene chloride worked well at low temperature, so hydrolysis which could occur at high temperature was not a problem. Haber Tr. 2418-19; RX 1007C.

FF CA 129. Although Abic tried a number of other solvents, none were as good as methylene chloride, so from August, 1983, Abic concentrated on developing the methylene chloride-water phase transfer catalyzed process. Haber Tr. 2422-23.

FF CA 130. Abic also experimented with several phase transfer catalysts, but rapidly settled on TEBA because it gave the best results. Haber Tr. 2423-24.

FF CA 131. The product of the alkylation using potassium hydroxide as the base was somewhat impure. Haber Tr. 2423-25.

FF CA 132. In August 1983, therefore, Abic tried sodium hydroxide as the base, since it was the most similar base to potassium hydroxide. RX 1008; RPX 1144; Haber Tr. 2424-25.

FF CA 133. Sodium hydroxide gave a purer product, but it still contained about 10% of the unidentified impurity. Haber Tr. 2425.

FF CA 134. Abic continued using sodium hydroxide as a base for two to three months to make precursor for use in studying the subsequent acetylation, hydrochlorination and purification processes. Haber Tr. 2425-26.

Abic's Development of Its Phase-Transfer-Catalyzed Barium Hydroxide-Methylene Chloride-Water Process

FF CA 135. Eventually Abic discovered that the impurity obtained with potassium hydroxide and sodium hydroxide was "dimer", which was formed by an alkylation reaction between the solvent methylene chloride and two molecules of TZP. Haber Tr. 2426.

FF CA 136. Abic also was aware of British Patent No. 1,236,467, a counterpart of the '257 patent, as well as other counterparts, claiming alkylation processes employing alkali metal salts. RX 1010C; RX 1700; Haber Tr. 2432.

FF CA 137. In an effort to avoid the formation of dimer, and in an attempt to develop a process using bases other than alkali metal bases which would not infringe the '257 foreign counterpart process patents, Abic in December, 1983 began experimenting with ammonium hydroxide, magnesium hydroxide and calcium hydroxide. Haber Tr. 2429-31, 2434.

FF CA 138. Abic also apparently became aware in December of 1983, for the first time, of the European patent application that was the counterpart of

the '035 patent. Haber Tr. 2429-30.

FF CA 139. Abic was not concerned with potential infringement in Europe, because the European application was restricted to potassium bases, and Abic at the time was using sodium hydroxide. Haber Tr. 2435.

FF CA 140. Ammonium hydroxide and magnesium hydroxide bases did not work in the Abic phase transfer catalyzed methylene chloride-water process. Haber Tr. 2431.

FF CA 141. However, calcium hydroxide in the phase transfer catalyzed methylene chloride-water process gave high purity product without the formation of the unwanted dimer. Haber Tr. 2431-32.

FF CA 142. Neither calcium hydroxide nor calcium carbonate in acetone resulted in N-alkylation. RX 1010C; Haber Tr. 2430-31.

FF CA 143. In February 1984, Abic tested barium hydroxide with its methylene chloride-water-TEBA system and found that barium hydroxide gave good yields, practically no formation of dimer, and fewer side reactions with DMC. Haber Tr. 2436.

FF CA 144. Abic repeated tests of other bases in the methylene chloride-water system with a phase transfer catalyst, and confirmed that potassium hydroxide and potassium carbonate yielded large amounts (20%-30%) of the dimer under those conditions. Haber Tr. 2436-37; RX 1015C.

FF CA 145. For comparative purposes, Abic also tried some of the base-solvent combinations of the EPO 81234 application, but Abic did not pursue those combinations because Abic has a policy of not infringing valid patents. Haber Tr. 2438-39; RX 1013C.

FF CA 146. Abic tried numerous bases in the methylene chloride-water-TEBA system, including, in chronological order, potassium hydroxide, sodium

hydroxide, potassium carbonate, sodium bicarbonate, calcium carbonate, magnesium hydroxide, ammonium hydroxide, triethylamine, and alumina, but in every case Abic obtained either low yields of N-alkylated product or high yields of the unwanted dimer formation. Haber Tr. 2439-40; RPX-1145.

FF CA 147. C

C

Haber Tr. 2440, 2443-43; RX 1145, RX 1024C.

FF CA 148. C

C

C

Haber Tr. 2443-44; RX 1024C.

FF CA 149. C

C

C

C

C Haber Tr. 2445-46; RX 1024C.

FF CA 150. C

C Haber Tr. 2447-48; RX 1024C.

FF CA 151. C

C

C

C Haber Tr. 2449; RX 1024C.

FF CA 152. Abic's process is not a copy of the Tanabe process. Haber Tr. 2452.

FF CA 153. Abic's effort to develop its own process was wholly

independent, and was not stimulated by knowledge of the '035 patent or of any counterpart. Haber Tr. 2452.

FF CA 154. Abic obtained patents on its process in the United States of America, Israel, Japan, Canada and Europe. Haber Tr. 2450.

FF CA 155. In the United States, Abic's patent application was examined by Examiner Bond, who cited the '257 patent and the '035 patent as prior art, and concluded that Abic's process was patentable over those references. Haber Tr. 2450; RX 1195 [CX 632].

FF CA 156. Professor Taylor is an organic chemist specializing in organic synthesis, synthetic methodology, and heterocyclic chemistry with emphasis on the development of new synthetic methods in heterocyclic and medicinal chemistry. Taylor Tr. 2586-87.

FF CA 157. Professor Taylor has been a professor of organic chemistry at Princeton for 41 years. He is currently the A. Barton Hepburn Professor of Organic Chemistry at Princeton. Taylor Tr. 2586.

FF CA 158. Professor Taylor has published over 400 articles, written three books in the field of heterocyclic chemistry, and is editor of a 60-volume series called Chemistry of Heterocyclic Compounds that is generally recognized as the reference series in heterocyclic compounds. He has obtained about 40 patents, and is a past Chairman of the Organic Division of the American Chemical Society. Taylor Tr. 2587-89.

FF CA 159. Professor Taylor is a consultant to chemical companies in the area of process development. Taylor Tr. 2592.

FF CA 160. Professor Taylor was awarded the American Chemical Society Award for Creative Work in Synthetic Organic Chemistry, the Gowland Hopkins Medal, the Fifth International Award in Heterocyclic Chemistry, and recently

the C.Cope Scholar Award for his work in heterocyclic chemistry. Taylor Tr. 2592.

FF CA 161. Professor Taylor was accepted as an expert in the field of organic chemistry, including the subfields of organic chemistry and heterocyclic chemistry, including the seven-membered ring of heterocyclic amide compounds. Taylor Tr. 2593-94.

FF CA 162. Professor Mark S. Wrighton is an expert in surface chemistry and in the interpretation of differential scanning calorimetry curves. Wrighton Tr. 1607; RX 1679.

FF CA 163. Professor Wrighton is Provost and Professor of Chemistry at the Massachusetts Institute of Technology. He has been on the MIT faculty since 1972, and has been a full professor since 1977. Wrighton Tr. 1605.

FF CA 164. Professor Wrighton's general area of research involves surface chemistry, photochemistry and electric chemistry. Virtually all of his current research concerns the property of surfaces. Wrighton Tr. 1605-06. FF CA 165. Professor Wrighton has published more than 400 scientific papers. Wrighton Tr. 1605.

FF CA 166. Professor Wrighton has published papers which contain the results of differential scanning calorimetry analyses. Wrighton Tr. 1606-07.

FF CA 167. Professor Wrighton was accepted as an expert in surface chemistry and in the interpretation of DSC curves. Wrighton Tr. 1607.

3. The Experts

Professor Liotta

FF CA 168. Dr. Liotta submitted a declaration in this investigation, which admittedly had some inaccuracies. The declaration also confused the claims of the patent with the examples cited in the specification. Liotta Tr.

1710-17. In an effort to show that the yield of Abic's process is not affected by the use of TEBA, the phase transfer catalyst, he reported incorrect yields (*id.* at 1713-15). Although Dr. Liotta declared that he had reviewed the prior art relating to the claims, he had only examined the prior art of phase transfer catalysis. Id. at Tr. 1712-13.

FF CA 169. Dr. Liotta referred to his postulated "surface solvent phase" as a "biphasic solvent system" only for purposes of this litigation; he had never referred to it before in those terms, and did it only to draw a comparison between Abic's solvent system and examples in the '035 patent. Liotta Tr. 1705-06.

FF CA 170. Dr. Liotta first concluded that the KOH-DMSO process was not equivalent to the '035 processes; then concluded that the KOH-DMSO process was equivalent; and then changed his mind again and said that they were not equivalent. Liotta Tr. 1708-09.

FF CA 171. Dr. Liotta obtained a patent on his theory of the "omega phase," a "surface solvent phase" which contained a phase transfer catalyst. *Id.* at 1750. In his patent he distinguished such omega phase systems as patentably distinct from conventional phase transfer catalyst processes. *Id.* at 1750-52. He admitted at his deposition that the Abic process is an example of such a conventional phase transfer catalyst process. *Id.* at 1753. But he also alleged that his theory of the omega phase was wrong, and that his patent was wrong. *Id.* at 1755.

FF CA 172. Dr. Liotta could not bring himself to admit that TEBA is a phase transfer catalyst, and kept calling it a "quat" and a "surfactant". Not only did Dr. Taylor testify that it is a phase transfer catalyst but Dr. Baldwin, an expert for complainant, referred to it as a phase transfer

catalyst, as did Dr. Kende. CX 635; Liotta Tr. 1703-04; Kende Tr. 1340.

FF CA 173. Eventually Dr. Liotta admitted that TEBA is one of the most commonly used phase transfer catalysts (Liotta Tr. 1702), because he had written that in his book. RX 3969; Taylor Tr. 2654; RX 3969; Liotta Tr. 1676, 1701; Taylor Tr. 2653.

FF CA 174. Dr. Liotta was forced to admit that there is no experimental data supporting his surfactant theory (Liotta Tr. 1676). He further admitted that he had not done any experiments of his own to show that TEBA is not acting as a phase transfer catalyst in the Abic system, and refused to accept Abic's data which shows increased yield when TEBA is used. Liotta Tr. 1835-37.

FF CA 175. For the above reasons, the Administrative Law Judge declines to accept the opinions of Dr. Liotta in support of complainants' positions.

Professor Atwood

FF CA 176. Dr. Atwood is primarily a single-crystal x-ray crystallographer. Atwood Tr. 3311.

FF CA 177. None of Dr. Atwood's publications is about x-ray powder diffraction. Atwood Tr. 3315, 3260.

FF CA 178. Unlike Dr. Jenkins, he hasn't written text-books about x-ray powder diffraction. Atwood Tr. 3260.

FF CA 179. Unlike Dr. Jenkins, Dr. Atwood does not belong to any organization devoted to x-ray powder diffraction. Atwood Tr. 3311.

FF CA 180. Unlike Dr. Jenkins, Dr. Atwood does not have any patents on x-ray powder diffraction equipment. Atwood Tr. 3317-18, 3260.

FF CA 181. Unlike Dr. Jenkins, Dr. Atwood does not design his own x-ray powder diffraction equipment. Atwood Tr. 3322-3323.

FF CA 182. Because the materials which are of interest in this investigation are powders, x-ray powder diffraction is the more pertinent expertise. Atwood Tr. 3313-14.

Dr. Jenkins' Qualifications

FF CA 183. Dr. Jenkins is currently employed as the principle scientist at the International Center for X-Ray Product Direction Data, a not-for-profit data base organization that archives and supplies about 65,000 powdered refraction patterns. Jenkins Tr. 2936-2937.

FF CA 184. Dr. Jenkins has been involved in X-ray powder refraction for about 35 years. Jenkins Tr. 2937.

FF CA 185. Dr. Jenkins worked for ESSO Research, Limited for 10 years, the last years spent in X-ray powder refraction analysis. He then worked at North American Phillips, where he was involved with the development of instrumentation and software for X-ray powder refraction. He also was involved in the application of the technique and teaching of the method of powder refraction. Jenkins Tr. 2937-2938.

FF CA 186. Dr. Jenkins obtained 6 patents for developmental work at North American Phillips, of which three were on equipment for X-ray powder refraction. Jenkins Tr. 2938

FF CA 187. Dr. Jenkins has published about 80 papers on X-ray powder refraction, and written three books targeted at an audience of material scientists (geologists, mineralogists, chemists). The first book was written in 1972, and sold about 8,000 copies. The second was an audio course done in connection with the American Chemical Society. The third is coming out in March. Jenkins Tr. 2939

FF CA 188. Dr. Jenkins was accepted as an expert in X-ray powder

refraction. Jenkins Tr. 2940.

4. TEBA/Phase Transfer Catalysis

FF CA 189. Dr. Liotta does not have any experimental evidence to support his opinion that TEBA in Abic's process acts as a surfactant. Liotta Tr. 1676.

FF CA 190. There is no documentary evidence of record in this investigation that TEBA acts as a surfactant or is regarded as a surfactant by people of ordinary skill in the art. Liotta Tr. 1701.

FF CA 191. TEBA is one of the most commonly used phase transfer catalysts in chemistry. Liotta Tr. 1701.

FF CA 192. Dr. Baldwin regards TEBA in Abic's system as a phase transfer catalyst. Liotta Tr. 1704-03.

FF CA 193. When TEBA is used in Abic's system, no dimer is formed, whereas when TEBA is not used, dimer is formed. Liotta Tr. 1801-03.

FF CA 194. In example 3 of the '035 patent, if methylene chloride is substituted for ethyl acetate, and no TEBA is present, no dimer forms, whereas, if TEBA is present, dimer forms. Liotta Tr. 1803-04.

FF CA 195. Solid-liquid phase transfer catalysis is different than liquid-liquid phase transfer catalysis. Liotta Tr. 1838.

C. The Fermion Process

FF CF 1. In February 1983, Dr. Lindholm (a Fermion development manager) assigned the project of developing a process for manufacturing diltiazem to Mr. Hytönen (who was then a product development chemist). Hytönen Tr. 2992-2993; Lindholm Tr. 3067.

FF CF 2. Dr. Lindholm testified at the hearing in part as an expert witness. Dr. Lindholm was accepted as an expert in chemical process design.

Lindholm Tr. 3068-3069.

FF CF 3. Fermion's process development effort involved more than the single N-alkylation step. The Fermion diltiazem synthesis procedure today includes nine processing steps. The development effort commenced with the early steps in synthesis. Hytönen Tr. 2994.

FF CF 4. In early September 1983, Mr. Hytönen began working on the N-alkylation step of the diltiazem process. RPX 2022C, RX 2114C and RX 2115C, identified at Hytönen Tr. 2994-2995.

FF CF 5. The first N-alkylation experiment conducted by Mr. Hytönen was using '257 conditions so that he could obtain some N-alkylated TZP and learn how the '257 process worked. Hytönen Tr. 2994-2995.

FF CF 6. Mr. Hytönen conducted many tests with various base/solvent combinations for about one year. In September and October 1984, Fermion experimented with 2-butanone or methy ethyl ketone (MEK), C C in September and October 1984. Hytönen Tr. 2995-3004; RX 2114C and RX 2115C.

FF CF 7. Mr. Hytönen read the '035 patent to exclude the use of MEK as a solvent. He testified as follows:

> Q When you reviewed the '035 patent, was there anything which suggested the use of MEK?
>
> A No, there was not.
>
> Q Why not?
>
> A They had only mentioned acetone, and they had -- not even ketone mentioned. On the other hand, they had determined that the lower alkaline acetate, in the same way they could have determined -- described also the lower ketones, if they had known that the reaction can be done with other ketones than acetone.
>
> Q Is MEK a homolog of acetone?

A Yes.

Q Do I understand that despite the fact that MEK is a homolog of acetone, the '035 patent still do not suggest the use of MEK to you?

* * *

THE WITNESS: It did not suggest any other ketone than acetone.

BY MY. KELLEY:

Q Why not?

* * *

THE WITNESS: I understand that Tanabe's researchers thought that other ketones cannot be used in this reaction.

Hytönen Tr. 3014-3015.

FF CF 8. Butanone is a homolog of acetone, i.e., butanone has an additional methylene group.[1] It is not a lower alkyl acetate. Because of the additional methylene group, butanone has different properties from acetone. At the least, it can be said that butanone is more solvable in hydrocarbons than acetone; it is less solvable in water than acetone, it has a higher boiling point than acetone; it is less polar than acetone. Gokel Tr. 635, 637.

FF CF 9. Normally, if one of ordinary skill in the art wanted to see how far one could extend the N-alkylation of '035 patent, one would try another ketone besides acetone, possibly 2-butanone (or MEK). By the same token, one of ordinary skill in the art familiar with a range of ketones would read the

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[1] A homolog(ue) is defined as:

> Member of a series of compounds whose structure differs regularly by some radical, e.g., $=CH_2$, from that of its adjacent neighbors in the series.

R. Grant & C. Grant, eds. Grant & Hackh's Chemical Dictionary 287 (1987).

'035 patent, notice the specificity and exclusivity of the claim to the use of acetone, and conclude that other ketones were not included because they did not work. Taylor Tr. 2620-2621, 2784-85.

FF CF 10. While at university, Mr. Hytönen tried alternatives to acetone in an alkylation with potassium carbonate. One of the substitutions he tried was MEK for the acetone. He later had better success with another chemical. Although he tried these substitutions, Mr. Hytönen believes that many researchers (including his professor) think that certain alkylation reactions are specific to acetone. Hytönen Tr. 3015-3016, 3045-3046.

FF CF 11. Mr. Hytönen had experience with MEK at Fermion before starting his diltiazem development work. Hytönen Tr. 3016.

FF CF 12. Fermion conducts pilot tests on a scale that is smaller than industrial scale yet larger than laboratory scale, using instruments similar to those used for commercial manufacturing. Hytönen Tr. 3005.

FF CF 13. In October 1984, Fermion conducted a pilot plant test on the N-alkylation process using potassium carbonate/MEK as the base/solvent combination. This pilot plant test was a failure. RPX 2022C; Hytönen Tr. 3004-3005.

FF CF 14. After the October pilot plant failure with MEK, Fermion conducted additional experiments with a mixture of C as the solvent and C as the base; C and either C C , with and without C ; C and either C ; C with either C ; C with C C ; C with C ; and C with C . RX 2114C and RX 2115C (experiments B2449, B2454, B3367(a) and (b), B3371(a) and

(b), B3372(a) and (b), B1048, B1049 and B3370).

FF CF 15. In 1985 Fermion conducted additional testing with the combination of C as the base/solvent combination for the N-alkylation step. RX 2114C and RX 2115C (experiments B1054, B3275(a) and (b), B1058(a) and (b), B3376(a), (b), (c) and (d), B1061, B1062(a), (b) and (c), B1064 and B1065(a), (b), (c) and (d)).

FF CF 16. Mr. Hytönen conducted further experiments in 1985 with the MEK and potassium carbonate process to determine why it had failed in the pilot plant. Hytönen Tr. 3007.

FF CF 17. Fermion also developed an alternative process using potassium carbonate/ethyl acetate, and produced diltiazem for commercial use. Hytönen Tr. 3005-3007.

FF CF 18. Fermion found the potassium carbonate/ethyl acetate combination to be unreliable on a commercial scale because potassium carbonate had to be added twice and one had to follow the reaction to completion, and to add DMC·HCl in different amounts based upon an analysis of the reaction. These procedures required the presence of a skilled chemist. Hytönen Tr. 3006-3007, 3047-3048.

FF CF 19. The operators of Fermion's process are not chemists, or laboratory technicians. They are individuals without formal chemical education. The skill of the operators is taken into account when developing a commercial process. Lindholm Tr. 3089-3090.

FF CF 20. The Finnish counterpart of the '035 patent was not in effect during the time period that Fermion used the potassium carbonate/ethyl acetate combination. Hytönen Tr. 3007, 3047-48.

FF CF 21. In late 1985, Mr. Hytönen thought he had solved the problem

with the MEK and potassium carbonate system, and conducted a second pilot plant test. Hytönen Tr. 3007.

FF CF 22. The second MEK and potassium carbonate pilot plant test was also a failure. Hytönen Tr. 3007.

FF CF 23. Fermion conducted further experiments with the MEK and potassium carbonate process, and conducted a third pilot plant test in January 1986 which was a success. Hytönen Tr. 3008.

FF CF 24. In the accused Fermion process, the N-alkylation step uses TZP, DMC·HCl, K_2CO_3, butanone (or "MEK") and water. Gokel Tr. 624; CX 192C.

FF CF 25. Fermion learned that the amount of C present in the MEK and potassium carbonate process was critical. Mr. Hytönen testified to this point as follows:

> Q Did you determine what the cause of the problem was with your MEK process?
>
> A Yes, we found out.
>
> Q What did you determine caused the failure on the first pilot run?
>
> A In the first pilot experiment, we had too much C in the reaction mixture.
>
> Q Did you determine what the problem was in the second experiment?
>
> A Yes. It had too little C .

Hytönen Tr. 3008.

FF CF 26. The '035 patent contains no teachings that the amount of C in the process is critical. For example, complainants' expert testified as follows:

> Q Nowhere in the '035 patent is there any explicit teaching that C is critical to the success of the reaction, is there?

A I think that's a fair statement.

Kende Tr. 1428.

FF CF 27. The '035 patent provided no guidance to Fermion and Mr. Hytönen in solving the problems encountered with the MEK and potassium carbonate process. In this regard, Mr. Hytönen testified as follows:

Q You testified a few minutes ago that the '035 patent did not provide any help in developing the present Fermion process. Do you recall that?

A That is true.

Q Why didn't it provide you with any help?

A For instance, there was no mention about -- they did not mention the critical nature of C . On the contrary, they had examples in which there were reactions that had no C in them.

Q Did the '035 patent provide you with any help in determining the cause of the failures in the first two pilot plant runs with MEK?

A No, it did not.

Hytönen Tr. 3013-3014.

FF CF 28. Fermion learned that the MEK and potassium carbonate process did not work with either too much or too little added C . Hytönen Tr. 3008.

FF CF 29. After Fermion's success with the MEK and potassium carbonate N-alkylation process in the pilot plant, Mr. Hytönen began to experiment with making the process less sensitive to the amount of C present, and therefore "more reliable." Hytönen Tr. 3009-3010.

FF CF 30. Mr. Hytönen discovered that by reducing the ratio of C C , it was possible to reduce the sensitivity of the MEK and potassium carbonate to the amount of C present. Hytönen Tr. 3010.

FF CF 31. The present Fermion process has C added to the MEK. Hytönen Tr. 3008-3009, Lindholm Tr. 3090.

FF CF 32. Fermion discovered that its present process is extremely reliable, always proceeding to completion, i.e., all the TZP is consumed. Hytönen Tr. 3011; Lindholm Tr. 3075.

FF CF 33. The '035 patent does not provide any teaching that the C C will have any effect on the reaction. Mr. Hytönen testified as follows:

> Q During the time that you were improving the MEK process, did the '035 patent provide any help?
>
> A No, it did not.
>
> Q Does the '035 patent teach a chemist what the effect of varying the relative amount of C will have on the process?
>
> JUDGE HARRIS: You better ask that again.
>
> BY MR. KELLY:
> Q Let me break it into pieces and try to ask that again. Is there any description or teaching in the '035 patent that you will get a more reliable process by reducing the C C ?
>
> A No.

Tr. 3011-3012.

FF CF 34. The '035 patent provided no guidance to Fermion in reducing the ratio of C . Tr. 3011.

FF CF 35. Fermion's experts, Dr. Lindholm and Professor Magnus, testified that Fermion's process works in a different way than the process of the '035 patent claims. Lindholm Tr. 3075, Magnus Tr. 3178.

FF CF 36. Fermion conducted over C N-alkylation experiments between October 1983 and early 1986 in developing its process. Lindholm Tr. 3101; RX 2114C.

FF CF 37. In 1981, Tanabe attempted to use MEK as the solvent in the N-alkylation of TZP. RX 2047C, RX 2046C, RX 2094C and RX 3494C.

FF CF 38. In 1981, Tanabe tested and rejected MEK as the solvent for the N-alkylation of TZP. RX 2047C, RX 2046C, RX 2094C, RX 3494C.

FF CF 39. In 1981, Tanabe's experiments with MEK either resulted in no product or impure product. RX 2047C, RX 2046C, RX 2094C and RX 3494C.

FF CF 40. Fermion introduced evidence that a process which produced impure product would be considered a failure. See Hytönen Tr. 2999.

FF CF 41. The adverse consequence of too little or too much C in the '035 patent's potassium carbonate/ethyl acetate process was experienced by Tanabe in its commercial process, and is demonstrated by Tanabe's later 1991 testing. RX 2237C; Nakao Tr. 384, 420.

FF CF 42. Complainants' expert, Professor Gokel, testified that the way in which the process of the '035 patent claims worked was through a so-called "surface solvent phase" or a boundary phase. Gokel Tr. 941-942, 982.

FF CF 43. Complainants offered no evidence that a surface solvent phase was present in the Fermion process. The only tests offered by complainants were not N-alkylations and lacked both the TZP and DMC·HCl. CX 636, CX 680C and CX 681C.

FF CF 44. Dr. Lindholm testified as follows:

Q Have you reviewed any experiments which were conducted by Professor Gokel and Liotta in connection with this litigation?

A Yes, I have.

Q In your opinion are those experiments relevant in any way to the matters involved in this litigation?

A They are not in my opinion.

Q Why not?

A In these experiments there were no starting material, no reagent that's the TZP or DMC. So in my opinion these experiments does not show anything about what happens when you do the real reaction.

Q Do you recall the testimony by Dr. Gokel that in his experiments he saw or observed a clump of potassium carbonate forming in the experiments with MEK?

A Yes, I remember.

Q Based upon your experience in the Fermion process, does the potassium carbonate form a hard clump upon the addition of water?

A No, it does not. We have not seen the thing occur either in laboratory or on the industrial scale.

Dr. Lindholm Tr. 3095-3096.

FF CF 45. In all of its experiments and commercial experience, Fermion has never observed the results obtained by complainants in complainants' tests in which neither TZP nor DMC·HCl were present. Lindholm Tr. 3095-3096.

FF CF 46. Fermion's expert, Dr. Lindholm, testified that complainants' testing provides no basis for concluding that the Fermion process works in the same way as the process of the '035 patent. Lindholm Tr. 3095-3096.

FF CF 47. Fermion duplicated examples found in the '035 patent, and compared the results obtained with the '035 patent solvents to those obtained when MEK was used as the solvent. CX 394

FF CF 48. Dr. Lindholm, one of Fermion's experts, concluded that based on these experiments, MEK was not equivalent to the '035 patent claim solvents in the N-alkylation of TZP. Dr. Lindholm testified as follows:

Q What is it about CX 394 that further supports your opinion?

A This CX 394 is a test series we run in the laboratory using the '035 patent examples, just as they are described in the patent. And for comparison, these examples, we substituted the solvent mentioned in the examples with MEK.
And if we look at page 3, we see here a comparison of patent

example 2 using either acetone or MEK.
From these experiments, we see that these two reactions run rather similarly. The butanone is a little bit faster than acetone.
If we then go two pages forward and look at patent Example 4, this is now a dry system. We can see here that the acetone process works. After nine hours, there is really nearly no starting material left in the reaction.
But on the other hand, we can see that using MEK, we have virtually no reaction.
Taking these two examples together, as we should do, if these two solvents were equivalent, we would get the same results. We would even have a slightly faster reaction in MEK, as the boiling point is higher.
But as we do not have that, this means that these solvents can't be equivalent. If we turn one page back, we have patent Example 3. This is with ethyl acetate. From the numbers here, we can see that the reaction grows nicely in ethyl acetate.
But on the other hand, we can see that using MEK, the reaction proceeds, but to a very small extent. After six hours reaction time, we have still roughly about 60 percent of the starting material left.
This indicates that or at least shows that MEK and ethyl acetate are not equivalent.

Q When you said the reaction went rather nicely in ethyl acetate, what did you mean?

A I mean that the consumption of starting material was nearly complete.

Lindholm Tr. 3077-3078.

FF CF 49. Dr. Lindholm testified, that with the exception of '035 patent example 2, in all cases the substitution of MEK for the solvent of the patent example provided substantially different results. Lindholm Tr. 3077-3078.

FF CF 50. In patent example 3, the use of ground potassium carbonate in combination with ethyl acetate resulted in an N-alkylation reaction which proceeded to completion as described in the patent, i.e., within six hours. In contrast, with MEK and ground potassium carbonate, after six hours roughly 60% of the starting TZP remained. Lindholm Tr. 3077-3078, Hytönen Tr. 3138-3139.

FF CF 51. In patent example 4, Fermion was able to duplicate the results reported for acetone and powdery potassium carbonate, essentially complete TZP conversion within nine hours. However, when MEK was substituted for the acetone, the reaction did not proceed at all, essentially all TZP remained unreacted. Hytönen Tr. 3077-3078.

FF CF 52. Patent example 5 did not proceed as written. CX 394.

FF CF 53. In patent example 6, the substitution of MEK for the methyl acetate of the example resulted in an N-alkylation which proceeded to completion in two hours, while with methyl acetate the reaction took thirty hours. CX 394.

FF CF 54. Fermion chose to use patent example 3 as exemplary of the '035 patent claim process because this was the sole '035 patent example repeated by complainants' expert, Professor Baldwin. Lindholm Tr. 3086.

FF CF 55. Subsequently, Fermion learned that patent example C closely resembles C process. Lindholm Tr. 3087.

FF CF 56. Complainants had testing conducted by Professors Baldwin, Gokel and Liotta. CX 635, CX 636 CX 680C and CX 681C.

FF CF 57. Professor Baldwin testified that he could not have predicted the results he obtained with MEK, 2-butanone:

> Q Is there any way before this experiment you could have predicted this result?
>
> A What result?
>
> Q That increasing C [with 2-butanone] would increase yield.
>
> A In the particular butanone system, no, I couldn't have predicted that.

RX 2238C.

FF CF 58. The only tests offered by complainants concerning the so-

called "surface solvent phase" were not N-alkylations and lacked both the TZP and DMC·HCl. CX 636, CX 680C and CX 681C; Lindholm Tr. 3095-3096.

FF CF 59. Professor Baldwin's tests demonstrate that the mere substitution of MEK for the '035 patent's solvents did not result in an N-alkylation process which achieved yields and/or productivity comparable to that achieved by the Fermion commercial process. RPX 2004C-A. Lindholm Tr. 3092-3093.

IV. INVALIDITY--CLAIM 1 OF THE '035 PATENT IS INVALID UNDER 35 U.S.C. § 103

A. Background

FF D 1. During the United States prosecution of the '035 patent, Tanabe submitted to the PTO a Statement of Art in which Tanabe described its alleged invention as involving only certain specified base/solvent combinations, specifically stating that the "Applicants' invention" was N-alkylation:

> "[In] the presence of potassium hydroxide in acetone or potassium carbonate in acetone, lower alkyl acetate, water-acetone, or water-lower alkyl acetate."

CX 2, paper 4 at 2-3.

FF D 2. In the Statement of Art Tanabe distinguished its alleged invention over the prior art by arguing that the invention produced yields of no less than 87% as opposed to 65-70% obtained with prior art processes.[2] CX 2, paper 4 at 2-3.

FF D 3. On December 21, 1981, Tanabe filed an application in Europe corresponding to the '035 patent application. RX 3325. On June 1, 1984, Tanabe's EPO application was rejected over the '967 and '257 patents. RX

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[2] Tanabe did not disclose Krapcho's U.S. Patent 3,075,967 (the "'967 patent") to the U.S. Patent and Trademark Office ("PTO") during the original prosecution of the '035 patent. CX 2.

3325.

FF D 4. The '967 patent taught the use of "alkali metal hydroxides" in a variety of solvents including toluene to attach DMC to a benzothiazepinone differing from TZP by only a single R group at the three position of the seven-membered ring. Potassium hydroxide and sodium hydroxide are examples of alkali metal hydroxides. RX 1103; Gokel, Tr. 870-82, 877-78, 881; Taber, Tr. 2159-60. In response to that rejection, on October 1, 1984, Tanabe submitted a twelve page document urging that the application be approved over the '257 and '967 patents. Included in this response were five pages of attorney argument and what Tanabe referred to as a "Comparative Test Report" which, Tanabe claimed, demonstrated the patentability of its claimed process over prior art disclosures that used, inter alia, sodium carbonate and toluene. RX 3929C. Specifically, Tanabe represented that the Comparative Test Report

> "[S]hows that the specific combination of bases and solvents, i.e., potassium hydroxide in acetone or potassium carbonate a solvent selected from acetone, lower alkyl acetate, a mixture of acetone and water and a mixture of lower alkyl acetate and water, leads to surprising results of the method according to the invention."

RX 3929C at 705 (emphasis added).

FF D 5. Tanabe's submission analyzed the experimental data reflected in the Comparative Test Report and explained as follows to the EPO:

> For example, when the condensation reaction was carried out by the use of sodium hydroxide or sodium carbonate as the base, the yield of the product was less than 10% even if acetone was used as the solvent. Moreover, when sodium amide or sodium hydride was used as the base, the yield of the product was not more than 12.4% in the case where toluene or dioxane was used as the solvent. Furthermore, even if potassium hydroxide or potassium carbonate was used as the base, the yield of the product was less than 30% in the case where dioxane, toluene or methanol was used. (RX 3929C at 706.)
> Tanabe further explained that:
>
> [j]udging from the facts (i) that the references cited by the Examining Division teach neither the use of potassium carbonate as the base nor the use of the specific base-solvent combinations to

be employed in the method of the present invention; (ii) that, when the condensation reaction was carried out by the use of sodium hydroxide or sodium carbonate as the base, the yield of the product was less than 10%; and (iii) that, even if potassium hydroxide or potassium carbonate was used as the base, the yield of the product was less than 30% in the case where dioxane, toluene or methanol was used, it is obvious that the above-mentioned advantageous features of the present invention have never been taught nor suggested in the references cited by the Examining Division. Thus, the replacement of sodium hydride and dimethylsulfoxide by the specific base-solvent combinations of the present invention is unobvious over the cited references. Due to the superior and surprising results obtained by the method of the invention, the present application possesses level of inventiveness necessary for its patentability.

RX 3929C (emphasis added).

FF D 6. Tanabe made identical arguments to numerous other patent offices, including those of Israel and Finland. 3338C; 3233C.

FF D 7. Reexamination of the '035 patent was requested by Respondent Abic, and supported by a declaration of Dr. Taylor. RX 1085 (See RX 2193).

FF D 8. The examiner initially agreed with Dr. Taylor, and rejected all the claims of the '035 patent. RX 1603 (RX 2193, RX 2204).

The bases for the rejection included:

(a) The '257 patent showed a conventional method of N-alkylation;

(b) Pachter and subsequent references showed the "widely used" N-alkylation of N-aryl amides with the same bases (potassium hydroxide, potassium carbonate) and the same solvent (acetone) as the '035 patent;

(c) British '119 and Nagarajan showed dimethylaminoethylation (i.e., reaction with DMC) of dibenzoxazepinones;

(d) Johnstone "further illustrat[ed] the value of the Pachter et al. technique."

RX 1603.

FF D 9. In response, Tanabe submitted declarations by Drs. Baldwin and Kende which argued that:

(a) The Pachter technique was not widely known;

(b) Pachter did not render the '035 patent obvious because it (i) disclosed only amides which were not cyclic and (ii) did not disclose DMC as an alkylating agent;

(c) British '119 and Nagarajan were limited to "nitro-substituted" amides, and thus not relevant to N-alkylation of TZP which had no nitro substituent;

(d) Johnstone was not pertinent;

(e) A number of potential side reactions, including retro-Michael reaction, ring-cleavage, O-alkylation, and carbonyl O-alkylation might occur, and might prevent high yields of the '035 patent.

RX 1658, RX 1329.

FF D 10. During the reexamination of the '035 patent, the examiner was presented with about 172 prior art references. RX 1603.

FF D 11. The examiner accepted some of Tanabe's arguments, and in deciding to issue a reexamination certificate, held that the prior art then of record did not establish the obviousness of the '035 patent. RX 1653; RX 1654; Taylor Tr. 2714-15, 2924-26; RPX 1149; RPX 1151.

FF D 12. The N-alkylation process described in the '035 patent is typical of the types of projects that process development chemists would have undertaken in 1981. Pachter Tr. 1495-96.

FF D 13. It is generally accepted that when potassium hydroxide is used to deprotonate an amide, including TZP, water is produced as a side product. Gokel Tr. 103940.

FF D 14. The patent examiner was not told that the prior art disclosed hydrous systems for the N-alkylation of benzothiazepinones. Further, the patent examiner said nothing during the interview which Dr. Baldwin attended to indicate he was aware of the prior art teaching the N-alkylation of benzothiazepine type compounds in hydrous conditions. RX 4038C; Kende Tr.

1431-32.

FF D 15. In his declaration submitted to the examiner during the Reexamination (RX 3132), Dr. Kende did not advise the examiner that in 1981, Yamawaki disclosed hydrous systems involving the use of potassium carbonate, sodium hydroxide and potassium hydroxide as bases which are excellent alternatives to the conventional bases used in N-alkylation methods. Kende Tr. 1355-57.

FF D 16. In granting the request for reexamination, the examiner stated in part as follows:

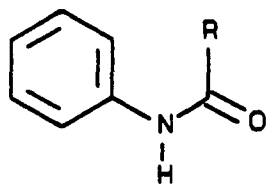
> The arguments concerning the possibility of side reactions by Taylor, Baldwin in [sic] Kende are not seen as having great weight in this particular case one way or another. Nor are the arguments concerning the use of DMC·HCl.

RX 1653.

FF D 17. The chemistry of organic compounds revolves around the chemistry of functional groups. Kende Tr. 526; Taylor Tr. 2780-81.

FF D 18. Functional groups are more important than ring structure in determining chemical reactivity. Taylor Tr. 2780.

FF D 19. The functional group known as an "N-aryl amide," which is part of the structure of TZP, has the following general structure:



Kende Tr. 1457-58; RPX 4023.

FF D 20. One can choose reaction conditions by focusing on the functional group on which one wishes to carry out the chemical transformation. The ring framework to which the functional group is attached plays a minor

role, if any, in the functional group chemistry. In organic chemistry, synthetic reactions depend upon and are focused on the properties of the functional group. Taylor Tr. 2780.

FF D 21. The inventors of the '035 patent knew prior to 1981 that the N-alkylation reaction worked and that commercially feasible methods existed. The only question faced by the inventors was whether cheaper, easier to handle bases or solvents could be used. RX 3739-C; RX 3737-C.

FF D 22. The process claimed in the '035 patent involves the conversion of an N-aryl amide, i.e., TZP or acetyl-TZP, to an N-alkylated amide. RPX 4023; RPX 4015; Kende Tr. 1457-1458; Pachter Tr. 1497.

FF D 23. In attempting to improve on the '257 patent, a person of ordinary skill in the art would have first looked for art related to benzothiazepines. Then, one would have looked for references to work in related systems, which in this case is N-aryl amides, because that is the reactive part of the TZP molecule for alkylation. The person of ordinary skill would have found references such as Pachter et al., "Methylation of Some Amides in Acetone," 74 J. Am. Chem. Soc. 1321-22 (1952)("Pachter reference"); Worley et al., "2-Dialkylphosphonyl- and 2-Alkylidene-3,4-dihydro-3-oxo-2H-1,4-benzothiazepines," 40 J. Org. Chem. 1731-34 (1975)("Worley"); Clark et al., "Synthesis and Analgesic Activity of 1,3-Dihydro-3-(substituted phenyl) imidazo[4,5-b]pyridin-2-ones and 3-(Substituted phenyl)-1,2,3-triazolo[4,5-b]pyridines," 21 J. Med Chem. 965-78 (1978)("Clark"); Nagarajan et al., "Condensed Heterotricycles: Amino & Aminoalkyridibenz[b,f][I,4] oxazepin-II(IOH)-ones," 12 Indian J. Chem. 236-46 (1974)("Nagarajan"); and Latif and Sattar, "A Note on the Alkylation of Amides," 32 J. Indian Chem 489-90 (1955) ("Latif"). Pachter Tr. 1496-97.

FF D 24. In connection with its efforts to synthesize the diltiazem molecule, Abic assembled as many references on benzothiazepines as it could. Significantly, Abic found the field of benzothiazepines relevant, and did not limit its research only to the N-alkylation of TZP. Abic also conducted a chemical structure search. A chemical structure search is a search based on a chemical nucleus, regardless of what structure is attached to it. For this search, Abic selected a six-member ring with a seven-member ring attached to it, the seven-member ring containing sulphur and nitrogen. This search would have included the Krapcho patents, but not the Pachter or Worley references because they do not have the ring structures associated with benzothiazepines. Haber Tr. 2453-59.

FF D 25. It is not clear from the record whether Abic personnel already had knowledge of the Pachter reference before the Abic literature search was conducted. No one at Abic, especially Dr. Haber, is the hypothetical person of ordinary skill in the art who is presumed to have knowledge of all prior art. See Haber Tr. 2453-59.

B. The Prior Art

1. The Kugita '257 Patent

FF D 26. Complainants' expert, Dr. Kende, distinguished the '035 patent over the '257 patent by stating:

> It teaches the use of milder bases than the '257 in that sense certainly it's mild conditions. Mild in this sense means a base which is not so strong that it will be irreversibly deprotonated.

Kende Tr. 1156.

FF D 27. During the Reexamination of the '035 patent, the Examiner issued an Office Action wherein he stated that "Kugita ['257] show the conventional process for production of benzothiazepinones such as diltiazem by

alkylation...." RX 1603(¶4); Taylor Tr. 2706.

FF D 28. In determining to accept Abic's petition for reexamination the examiner concluded that:

> It would be obvious for one of ordinary skill in the art to use the Pachter et al technique in the Kugita et al. ['257] process. Since the desirability of Pachters' technique has been long established, it would be obvious to use it in a process such as that of Kugita et al. One would be motivated to do so in the desire that superior results would be achieved. The chances for success would be excellent.

RX 1603.

FF D 29. The '257 patent teaches the N-alkylation of the identical substrate of the '035 patent, TZP, using the alkyl halide DMC·HCl to yield the identical alkylated product. RX 3652; Taber Tr. 2166; RX 4038C.

FF D 30. The '257 patent discloses a process for the N-alkylation of the identical substrate as the '035 patent using as a base an alkali metal, alkali metal hydride, or alkali metal amide, and as a suitable solvent, for example, dioxane, toluene, xylene, or DMSO. RX 3652.

FF D 31. The N-alkylation reaction disclosed in the '257 patent probably proceeds through the aziridinium. Taber Tr. 2166; Gokel Tr. 850; RX 4038-C.

FF D 32. The '257 patent teaches that benzothiazepinones, which are N-aryl amides, could be alkylated under rigorous conditions. Pachter Tr. 1499.

FF D 33. In looking to improve upon the '257 process, a process development chemist would rapidly realize that the reactive portion of the TZP molecule is what is known as an "N-aryl amide". RPX 4023; Pachter Tr. 1496.

FF D 34. The '257 patent (the only patent cited in the '035 patent) teaches that benzothiazepinones, which are N-aryl amides, can be alkylated under rather rigorous conditions (e.g., NaH/DMSO) using somewhat dangerous bases that can result in explosions, solvents that are inconvenient, and which

result in low yields. Pachter Tr. 1499; RX 1229, 1460.

FF D 35. Given only the '257 patent and the Pachter reference, a person would have had an "excellent" chance (90 percent) of success, i.e., producing some yield even with the possibility of side reactions. Pachter Tr. 1504, 1508-09, 1511-12; Taylor Tr. 2703.

2. The Pachter Reference

FF D 36. The Pachter reference was published in 1952 as a result of work done by Dr. Pachter towards his Ph.D. thesis under the tutelage of Dr. Kloetzel. Pachter Tr. 1499-51; RX 3770; RX 3769.

FF D 37. The N-aryl amide structure, which is a part of TZP, is also a part of each of the substrates alkylated by Dr. Pachter in 1952. Kende Tr. 1458; RPX 3770B; RPX 4023.

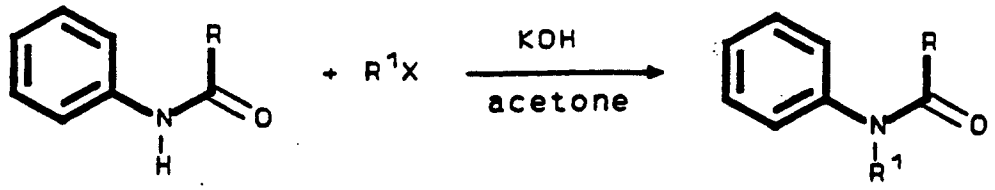
FF D 38. RPX 4023 depicts an N-aryl amide. Pachter Tr. 1497.

FF D 39. The Gabriel synthesis is the alkylation of an activated amide. It is not an N-aryl amide. Every first year organic chemistry student gets to learn what the Gabriel synthesis is. In studying the literature Pachter found that sometimes the Gabriel syntheses is carried out in acetone. RX 3769. The Pachter reference applied the known Gabriel synthesis conditions to N-aryl amides. It worked and he concluded that it appears to have general application to N-aryl amides. Pachter Tr. 1529-30, 1601-02.

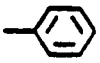
FF D 40. Pachter's process used the same base-solvent combination as the '035 patent, namely, potassium hydroxide and acetone, in hydrous reaction conditions. Pachter Tr. 1502-03; Kende Tr. 1277 and 1286-1287.

FF D 41. The Pachter system is a hydrous system. Kende Tr. 1461.

FF D 42. Pachter disclosed the following N-alkylation of an N-aryl amide using KOH and acetone:



R^1X above represents an alkyl halide. RPX 3770B; Pachter Tr. 1504-05; Kende Tr. 1456-57.

FF D 43. Pachter disclosed successful N-alkylation using methyl iodide as the alkyl halide, in which R was methyl ($-CH_3$) or phenyl  .

RPX 3770B; Pachter Tr. 1504-05.

FF D 44. Pachter's KOH/acetone reaction conditions are hydrous reaction conditions. Kende Tr. 1286-87.

FF D 45. It was important to have as much of the base in solution as possible in order for the reaction to take place rapidly. Therefore, Dr. Pachter chose potassium hydroxide as the base because potassium bases are more soluble in acetone than sodium bases. Pachter Tr. 1527-28.

FF D 46. Dr. Pachter chose acetone as the solvent since he knew he could get his compounds into the acetone solution quite readily and because it would provide a good medium for the reaction. Pachter Tr. 1528.

FF D 47. The Pachter reference discloses the N-alkylation of several N-aryl amides using the base/solvent combination KOH/acetone. Each of the N-alkyklated amides has an aryl, or benzene ring, and a carbonyl. The benzene ring and the carbonyl flank the nitrogen, which is to be alkylated. Pachter Tr. 1504-05; CX 638A; RX 3770; RPX 3770B.

FF D 48. Pachter investigated the N-alkylation of N-aryl amides over a range of conditions, including those in which the amide was activated toward

alkylation, deactivated, and neither activated nor deactivated, thus demonstrating the general applicability of his reaction procedure. Pachter 1504-07; Kende Tr. 1458-59; RX 3770; RPX 3770B.

FF D 49. Using the same KOH/acetone base-solvent combination claimed in the '035 patent, Pachter discovered and disclosed that alkylation can be accomplished "conveniently and in good yield." RX 3770.

FF D 50. In the five specific examples described by Pachter, the yields of N-alkylated amides were from 81% to 90%. RPX 3770B.

FF D 51. Although certain of the N-aryl amides alkylated by Dr. Pachter had potential alternative reaction sites, they did not interfere with the desired reaction of the amide. Pachter Tr. 1508, 1532-33; RPX 3770B.

FF D 52. Some of the compounds alkylated by Pachter were complex. Pachter Tr. 1568.

FF D 53. The (N-methylbenzamido)diphenylamine compounds that Pachter alkylated had two possible sites for alkylation, the amide nitrogen and the amine nitrogen. Alkylation of the amine did not interfere with alkylation of the amide. Pachter Tr. 1508.

FF D 54. Dr. Pachter decided to use potassium hydroxide as the base because he knew it was more soluble in organic solvents like acetone or ethyl acetate than the sodium base. Pachter Tr. 1527.

FF D 55. Dr. Pachter used potassium hydroxide and acetone based upon the teachings of the prior art that alkylation of an amide in what is known as the Gabriel synthesis succeeded with potassium hydroxide, but failed under '257 conditions. RX 3769 at 46-47; Pachter Tr. 1528-30.

FF D 56. In 1952, when Dr. Pachter applied the conditions of the Gabriel synthesis to his own N-alkylation reactions, he was a little less than someone

skilled in the art because he had not yet received his Ph.D. degree. Taylor Tr. 2798.

FF D 57. The person of ordinary skill in the art would do exactly what Dr. Pachter did in 1952 -- if you want to carry out a reaction on a substrate, you look at what's been done that's analogous and see if it can be applied to the system. The closer the analogy, the closer the example from the literature, perhaps the greater confidence one has. But there is a standard way of doing organic chemistry and this is the way people skilled in the art do it. Taylor Tr. 2798-99.

FF D 58. In 1952, Dr. Pachter concluded that the alkylation procedure with potassium hydroxide and acetone seems to have "general application." Pachter Tr. 1530.

FF D 59. Following the publication of the Pachter reference, the Pachter base-solvent combination of KOH/acetone for the N-alkylation of aryl amides became well-known and well-recognized by those of ordinary skill in the art as a generally applicable procedure for the N-alkylation of aryl amides. Taylor Tr. 2737, 2740.

FF D 60. In his declaration submitted to the Patent office during the Reexamination, Dr. Baldwin suggested that a paper by Yamawaki suggested that the Pachter method is not general. RX 1658; Taylor Tr. 2740-2741.

FF D 61. Yamawaki's experiments were not limited to N-aryl amides. Taylor Tr. 2740-2741.

FF D 62. Respondents presented over a dozen references in this investigation which describe Pachter-type N-alkylations of N-aryl amides. Taylor Tr. 2744-2745.

FF D 63. In explaining why the N-alkylation reaction occurs at one

nitrogen rather than another in one of the amides discussed in his reference, Dr. Pachter explained that under neutral conditions both nitrogens are extremely weak bases. However, under basic conditions, only the nitrogen of the N-aryl amide is sufficiently acidic to be deprotonated and form an anion. Pachter Tr. 1532.

FF D 64. Every attempt known to Dr. Pachter to N-alkylate an N-aryl amide using Pachter conditions has succeeded. Dr. Pachter knows of about 100 such N-alkylations. Pachter Tr. 1565, 1567.

FF D 65. The prior art showed that Pachter conditions worked for the N-alkylation of all N-aryl amides and some others. Taylor Tr. 2702.

FF D 66. In 1981, no reference was known of in which Pachter's conditions did not work for the alkylation of an N-aryl amide. Today, no reference is known of in which the use of Pachter's conditions not to work for the alkylation of an N-aryl amide. See Pachter Tr. 1565; Kende Tr. 1286.

FF D 67. Complainants' expert agreed with the remark made by the examiner that by 1981, the "desirability" of the Pachter KOH/acetone technique had long been established. Complainants' expert did not, of course, take the position that the "applicability" of the technique had been established. Kende Tr. 1280.

FF D 68. In Pachter's process, water is formed in the reprotonation step. Kende Tr. 1287.

FF D 69. The alkylation of an amide under Pachter conditions produces water as a side product. Gokel Tr. 1039-40; RPX 1096.

FF D 70. The Pachter reference teaches one of ordinary skill in the art that one can alkylate an amide under hydrous conditions. Kende Tr. 1286-87, 1461; CX 638A.

FF D 71. During the reexamination of the '035 patent, the examiner stated that "Pachter et al. show the widely used alkylation of aryl amides." RX 1603 (PTO Office Action); Taylor Tr. 2706-07.

FF D 72. Several references describe Pachter conditions in general terms, e.g., Worley (RPX 1094), Johnstone (RX 1137), Latif and Sattar (RX 1605), Clark (RPX 1093). Kende Tr. 1290-99, 1306-08, 1380; Pachter Tr. 1509.

FF D 73. The process taught in the Pachter reference was an improvement over earlier processes because it achieved the N-alkylation reaction by switching the known bases and solvents (later disclosed in the '257 patent) to potassium hydroxide/acetone (those later described in the '035 patent). In his paper, Dr. Pachter showed that in relatively short reaction times under very convenient conditions, one could rapidly and in good yield produce the necessary compound. Indeed, Dr. Pachter's paper teaches that some compounds are inactive under '257 conditions, but easily alkylated under Pachter conditions. Kende Tr. 1284-85, 1460-61; Pachter Tr. 1502-04, 1524; CX 1, 638A; RX 3770; RPX 3770B.

FF D 74. The Pachter reference disclosed that the usual method for alkylating N-aryl amides until his publication included the use of dangerous metals, metallic sodium, or sodium hydride in inert solvents (i.e., '257 conditions). Pachter Tr. 1501-02.

FF D 75. Pachter, in 1952, had taught that the substitution of KOH/acetone for the base-solvent combinations used in the '257 patent would avoid the dangers and inconveniences of such bases and solvents and could actually increase yields. RX 3770; Pachter Tr. 1501-03.

FF D 76. The specification of the '035 patent is similar to the first few paragraphs of the Pachter reference, e.g., both describe previous methods

as inconvenient, dangerous, and resulting in low yields. Indeed, Dr. Pachter initially thought the '035 patent drafters "copied paragraph 1" of his paper. Pachter Tr. 1503-04; CX 1; RX 3770.

FF D 77. Pachter recognized the problem which according to complainants, the '035 patent is said to have solved. Pachter disclosed in his 1952 article that, "[t]he usual method for the alkylation of amides, involving metallic sodium and an inert solvent is at best a rather inconvenient and somewhat dangerous procedure." Pachter then suggested replacing the sodium, i.e., a '257 base, with the KOH/acetone system, the same substitution proposed by the '035 patent. RX 3770; CX 1; RX 3652; Pachter Tr. 1503-04; Kende Tr. 1284-85.

FF D 78. Using the same KOH/acetone base-solvent combination claimed in the '035 patent, Pachter disclosed that the N-alkylation can be "accomplished conveniently and in good yield" in a relatively short period of time. RX 3770.

FF D 79. Given the Pachter reference, all the prior art that discusses Pachter as a general procedure, and ignoring the possibility of side reactions, complainants' expert admitted that it would have been obvious that TZP can be alkylated with methyl iodide under Pachter conditions to give at least a yield of 10% of desired product. Kende Tr. 1318-19.

3. Worley

FF D 80. Worley describes the successful N-alkylation of a N-aryl amide lactam under Pachter conditions using alkylating agents methyl iodide and ethyl bromo acetate, reporting a 73% yield. Kende Tr. 1290-92; Pachter Tr. 1510-11; RPX 1094.

FF D 81. Lactams, including TZP, are cyclic amides. Kende Tr. 1290.

FF D 82. Worley taught that Pachter conditions can be applied to a

lactam (a cyclic amide) as well as to Pachter's cyclic amides. Kende Tr. 1291; Pachter Tr. 1510-11.

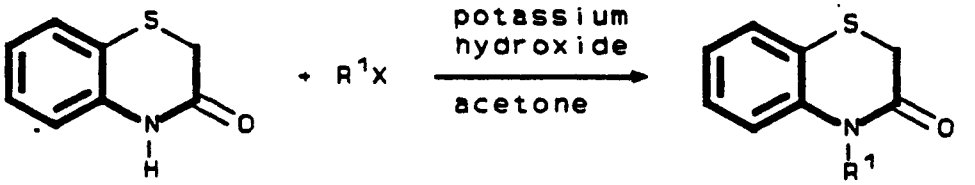
FF D 83. The compound alkylated by Worley had a sulfur atom which, like the sulfur atom of TZP, can transmit its effects through the aromatic ring down to the nitrogen. If the sulfur atom of TZP were to affect the N-alkylation reaction of Pachter, such a deleterious effect would have been seen in Worley. Worley obtained a good yield when using Pachter conditions. Pachter Tr. 1511.

FF D 84. Worley provided assurance that the sulfur atom in the TZP ring would not inhibit the N-alkylation reaction. Taylor Tr. 2703.

FF D 85. The amide group in Worley has approximately the same acidity as the amide group in TZP. Kende Tr. 1304.

FF D 86. Worley is a six-membered ring. In terms of ease of alkylation, a distinction between the six-membered ring of Worley and the seven-membered TZP ring is not necessary. On size alone, complainants' expert would not draw any distinction between six member rings and seven member rings. Kende Tr. 1310.

FF D 87. In 1975, Worley used KOH/acetone in the following N-alkylation reaction, stating that the procedure used was the "general procedure of Pachter and Kloetzel for the alkylation of [N-aryl] amides with potassium hydroxide in acetone" (the N-aryl amide structure shown in bold type):



RX 3824; RPX 3824A; Kende Tr. 1291-93; Pachter Tr. 1509-10.

FF D 88. The Worley compound is a very good model for TZP. Both compounds are N-aryl amides; both compounds have heterocyclic ring systems; both compounds are aromatic and both compounds have sulfur in the same position. Taylor Tr. 2738-2739.

FF D 89. Worley teaches using the "general procedure of Pachter." Pachter Tr. 1509-10; RX 3824 at 1733.

FF D 90. Worley does not report any reaction (or side reaction) of the sulphur atom. Kende Tr. 1303; RPX 1094.

FF D 91. Dr. Taylor believes that Worley, which uses a substrate having a 6-membered heterocyclic ring, is closer prior art to the '035 patent than Nagarajan, which uses a substrate with a 7-membered heterocyclic ring (like TZP) but is an oxazepinone. Taylor Tr. 2708-10.

FF D 92. Given the '257 patent, the Pachter reference, as well as Worley, it would have been even more obvious that one could alkylate TZP under the general Pachter conditions -- chances of success would have increased to 95% since the Worley compound is more similar to TZP in that it is a lactam and it also contains a sulfur atom. Pachter Tr. 1511-12; Taber Tr. 2181-82; Taylor Tr. 2703.

4. Johnstone

FF D 93. In 1969, a technical article, Johnstone et al., "A Rapid Method of N-alkylation of Amides," 16 J. Chem. Soc. 2223-24 (1969)("Johnstone"), reported the use of Pachter conditions to alkylate a substrate that is not an N-aryl amide, calling Pachter "a singular example of easy alkylation of an amide...." RX 3848; Kende Tr. 1294.

FF D 94. In Johnstone, a base/solvent combination of potassium hydroxide/acetone worked, whereas sodium carbonate/acetone did not work.

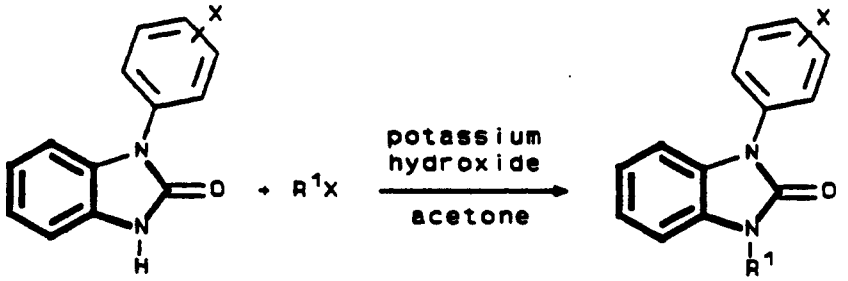
Kende Tr. 1296-97; RX 1137.

FF D 95. The Johnstone use of the Pachter reference and the use of Pachter conditions is one further indication that people working on amides looked to reactions performed on other amides, even if they involved very different substrates. The Johnstone authors managed very successfully to use what they termed an "easy alkylation." Taylor Tr. 2710-11.

FF D 96. Johnstone shows an appreciation of the potential generality of the Pachter technique, and that the Pachter technique was in fact used as a general technique. Taylor Tr. 2711.

5. Clark

FF D 97. In 1978, Clark et al. reported the following N-alkylation reaction, where the N-aryl amide "was alkylated with alkyl halide and refluxing acetone solution in the presence of powdered potassium hydroxide according to the method of Pachter and Kloetzel":



RX 3841 (the N-aryl amide structure is in bold type); Kende Tr. 1306-07.

FF D 98. Clark discloses 40 examples of hydrous reactions on 40 compounds using Pachter conditions (a base/solvent combination of potassium hydroxide/acetone), and reports satisfactory yields. Kende Tr. 1306-08; Taylor Tr. 2772-73; RPX 1093.

FF D 99. The N-alkylation reaction reported in Clark is hydrous. Kende Tr. 1306.

FF D 100. Clark reports the use of Pachter conditions with dialkylaminoethyl chloride: a dialkylaminoethylating agent which, like DMC, reacts through the aziridinium ion. Kende Tr. 1308; Taylor Tr. 2772-73.

6. Latif

FF D 101. Latif refers to Pachter as a general process for the alkylation of amides that is applicable for almost all types of alkyl halides. RX 1605.

FF D 102. Latif observed some limitations for use of the Pachter technique, but not with respect to any N-aryl amide. RX 1605; Pachter 1573-74.

7. Nagarajan

FF D 103. In the May 31, 1994 Notice of Intent to Issue Reexamination Certificate, the examiner stated:

> Perhaps the most pertinent references are the British Patent and Nagarajan et al. Both of these references show the aminoalkylation of lactams which bears some structural relationship to those of Kugita et al. using a process similar to Pachter et al. However, all of the compounds which are amino alkylated contain an activating nitro group when the Pachter-type process is employed. Nagarajan et al. shows that where no activating nitro group is present that the more harsh methods, similar to those of Kugita et al., must be employed. This indicates that where, activating nitro group is not present, the Pachter et al. technique is not operable. This teaches away from the process of Gaino et al. the patent being reexamined here.

RX 1654.

FF D 104. Nagarajan used '257 conditions on the unsubstituted, i.e., no nitro-substitution, compounds because these were the conditions everyone was using. Pachter Tr. 1526.

FF D 105. Nagarajan does not explicitly state that the procedure using potassium carbonate and acetone is not suitable for non-nitro substituted compounds. Kende Tr. 1361. Dr. Kende submitted a declaration during the

reexamination wherein he suggested that the procedure using potassium carbonate and acetone is not suitable for non-nitro substituted compounds of Nagarajan. Dr. Kende read this in by implication. This implication had the obvious effect of misleading the PTO examiner and is totally incorrect. RX 3132; Kende Tr. 1360-61.

FF D 106. Under '257 conditions, a nitro group is a deactivating group. Pachter Tr. 1588.

FF D 107. To state that the presence of the nitro group could make alkylation easier or harder would be speculation. Kende Tr. 1365.

FF D 108. Like Fones, (who came before Pachter) Nagarajan had found that he was unable to alkylate nitro-substituted compounds under '257 conditions, whereas he found the Pachter process worked fine. Pachter Tr. 1526-27.

FF D 109. Nagarajan started with '257 conditions and then switched to Pachter conditions. Pachter Tr. 1587-1588. Nagarajan went to Pachter conditions because alkylation did not proceed under '257 conditions. Pachter Tr. 1542.

FF D 110. Dr. Kende, in his declaration submitted to the examiner during reexamination, on page 17 referenced Nagarajan's discussion of ring cleavage. The ring cleavage discussed in Nagarajan would not occur with TZP. RX 3132; Kende Tr. 1367-68.

FF D 111. Dr. Baldwin, in his declaration submitted to the examiner during the reexamination, stated that "the Nagarajan reference suggested that ring cleavage was a distinct possibility under Pachter base/solvent conditions of seven membered oxazepines. (See, Experimental, page 245(d)). This too would have taught away from the process of the '035 patent." RX 1658. Dr. Kende stated that he did not see the connection between Nagarajan and the '035

substrate. RX 1658; Kende Tr. 1368.

FF D 112. There is no connection between ring opening reported in Nagarajan and alleged ring opening in TZP. Kende Tr. 1375; Taylor Tr. 2720.

FF D 113. As expressly stated in Nagarajan, the ring cleavage in Nagarajan depends upon the presence of the nitro group. There is no nitro group present in TZP. Taylor Tr. 2712, 2720-22.

FF D 114. In his declaration submitted to the PTO, Dr. Baldwin identifies ring cleavage as a consequence of the nitro group. RX 1658; Taylor Tr. 2719. Dr. Baldwin's declaration was misleading regarding Nagarajan, the teaching of ring cleavage, and the possibility that it would suggest ring cleavage in the '035 case where there is no nitro group. Taylor Tr. 2723.

FF D 115. Nagarajan did not report ring cleavage with potassium carbonate and acetone. Kende Tr. 1369.

FF D 116. Nagarajan reported ring cleavage with '257 conditions and no ring cleavage under Pachter conditions. Taylor Tr. 2725-27, 2729-31; Kende Tr. 1369. If there is no nitro group, as there is none with TZP, there is no problem of ring cleavage, and also, under Pachter conditions there is no problem of ring cleavage. Kende Tr. 1369-70; Taylor Tr. 2720-22

FF D 117. Contrary to the examiner's opinion, the Nagarajan paper does not teach that a hydrous system for N-alkylation will not work with compounds that are unsubstituted with the nitro substituent. Pachter Tr. 1523.

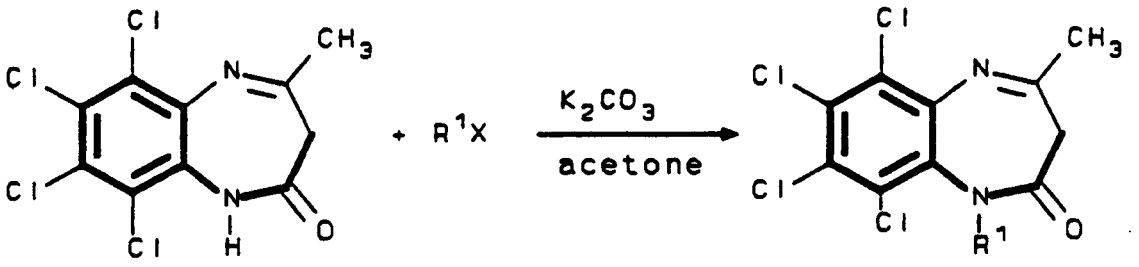
FF D 118. Page 245, Procedure D of Nagarajan shows that Nagarajan, like Fones, attempted to alkylate with DMC using '257-like conditions, heating for a long time (4 hours), resulting in 9% yield, 35% starting material and the remainder as decomposed material. RX 3820; RPX 3820A; Pachter Tr. 1524-25.

FF D 119. Nagarajan (RX 3820) methylated (N-alkylated) with methyl

iodide. After succeeding with methyl iodide, Nagarajan used DMC. Pachter Tr. 1534.

8. Burton

FF D 120. The N-alkylation of aryl amides using the base-solvent combination K_2CO_3-acetone was taught as early as 1968 by Burton et al., "Halogeno-o-phenylenediamines and Derived Heterocycles Part I. Reductive Fission of Benzotriazoles to O-Phenylenediamines," 10 J. Chem. Soc., 1268-73 (1968)("Burton"). Burton disclosed the following N-alkylation reaction using K_2CO_3-acetone:



RX 3794; Taylor Tr. 2273-74.

9. The Branca '522 Patent

FF D 121. Based upon Dr. Baldwin's declaration, the examiner stated that the Pachter reference would have provided little if any guidance, regarding the use of DMC or its hydrochloride salt in the N-alkylations of the '035 patent using a Pachter-type base/solvent combination. The examiner stated that the equivalence of methyl iodide and DMC has not been demonstrated using the conditions of the '035, but only under the harsher conditions employed in

the '257 patent. Taylor Tr. 2764-65.

FF D 122. In connection with the Order Granting Request for Reexamination, dated May 2, 1994, the examiner stated in part as follows:

> The equivalence of methyl iodide and DMC has not been demonstrated using the conditions of '035 but only where more strongly forcing conditions are employed in '257.

RX 1653.

FF D 123. Dr. Taylor's opinion is that prior art not of record before the PTO shows that using the conditions of the '035 patent, and for the purposes of alkylating TZP, methyl iodide and DMC are equivalent. Taylor Tr. 2764-65.

FF D 124. U.S. Letters Patent 4,377,522, issued to Quirico Branca in 1983, is prior art based on its filing date before the Japanese counterpart to the '035 patent. The examiner did not have the '522 patent during the reexamination of the '035 patent. RX 1657; Kende Tr. 1312.

FF D 125. The '522 patent discloses the alkylation of a seven member ring N-aryl amide using potassium carbonate/acetone and the alkylating agents DMC, DEC, or methyl iodide. Taylor Tr. 2757-59; Kende Tr. 1311-13; RX 1657; RPX 1091.

FF D 126. Branca '522 discloses the alkylation of a seven member ring lactam using DMC with a weak inorganic base, such as alkali metal carbonate (e.g., potassium carbonate) in a solvent such as a (e.g., acetone). Kende Tr. 1315-16; Taylor Tr. 2755-56; RX 1657; RPX 1095.

FF D 127. Branca is a N-aryl amide seven-membered ring structure, a benzodiazepine. It is a seven-membered ring benzodiazepinone where the N-aryl amide linkage is the same as it is in TZP. Taylor Tr. 2755-56.

FF D 128. RPX 1027, 1019, 1091, and 1092 are all examples of

benzodiazepines. Gokel Tr. 1012-14.

FF D 129. Benzodiazepines are related to benzothiazepines in that they have a six member ring fused to a seven member ring and they have the amide, however, they lack the sulfur. Gokel Tr. 1014.

FF D 130. The Branca '522 patent discloses an alkylation reaction of a seven member ring N-aryl amide using DEC, DMC or methyl iodide with potassium carbonate and acetone. Kende Tr. 1311-1316; Taylor Tr. 2757-58; RPX 1095.

FF D 131. The Branca patent provides an example of the kind of art the examiner said was not before him, showing the equivalence of methyl iodide and DMC. Branca provides an example of a substrate similar to TZP that is alkylated under '035 conditions with a dialkylaminoethyl halide and methyl iodide. Taylor Tr. 2759.

FF D 132. Prior to the alleged invention of the '035 patent, Burton (RX 3794), Fischli (RX 2130), Branca (RX 1657), Bebenburg (RX 1655), Nagarajan (RX 3820) and Nadzan (RX 3834) disclosed the use of the '035 base-solvent combinations to alkylate N-aryl amides. Taylor Tr. 2773-74.

10. The Bebenburg '887 Patent

FF D 133. U.S. Letters Patent 3,910,887, which issued to Walter von Bebenburg in 1975, was not of record during the reexamination on the '035 patent. It discloses a seven member N-aryl amide ring alkylation using DMC as the alkylating agent, and potassium carbonate/acetone as the base/solvent combination. Kende Tr. 1313-14; Taylor Tr. 2757-58; RX 1655; RPX 1092.

FF D 134. The '887 patent suggests that one can N-alkylate a seven-membered ring using methyl iodide or DMC and a base/solvent of potassium carbonate/acetone. Kende Tr. 1313-14; Taylor Tr. 2761-63; RX 1655; RPX 1092.

11. The '338 Schenker Patent

FF D 135. U.S. Letter Patent 3,644,338, which issued in 1972 to Karl Schenker, is not of record in the reexam. See Taylor Tr. 2747. Schenker discloses the alkylation of a compound which, although not an aryl amide, is an amide with a seven-membered ring. The reaction uses DMC as one of the possible alkylating agents, potassium carbonate as a possible base, and acetone as a possible solvent. Taylor Tr. 2747-49, 2751, 2754; RX 1656; RPX 1095.

FF D 136. The Schenker substrate has the nitrogen and the carbon double bond oxygen reversed in position from that of an N-aryl amide, so now the C double 10 group is attached to the aromatic ring and the nitrogen is not. The substrate is called a benzamide, which is an amide. Taylor Tr. 2747.

FF D 137. Dr. Pachter testified that benzamides were substrates with which his conditions did not always work. Taylor Tr. 2747-48.

The Schenker patent teaches that:

> The reaction is advantageously performed in the presence of a solvent such as a polar solvent, for example in a lower alkanol such as methanol or ethanol or in a lower alkanone such as acetone and especially in the presence of a condensing agent such as a weak inorganic base such as sodium or potassium carbonate, or in weak organic base such as a tertiary amine . . . .

Taylor Tr. 2749; RX 1656; RPX 1095.

FF D 138. The solvents referred to in Schenker are the kind of solvents that are capable of solvating potassium, such as a polar solvent. Taylor Tr. 2749.

FF D 139. Schenker also teaches that one should avoid strong bases (such as those found in the '257 patent) because their use results in low yields. Taylor Tr. 2749-50; Kende Tr. 1315-16; RX 1656.

FF D 140. Example 2 of Schenker discloses finely grounded potassium carbonate in acetone, with DMC·HCl. Taylor Tr. 2751-52; RX 1656.

FF D 141. Example 5 of Schenker discloses finely ground potassium carbonate in acetone, with DMC·HCl. Taylor Tr. 2752-53; RX 1656.

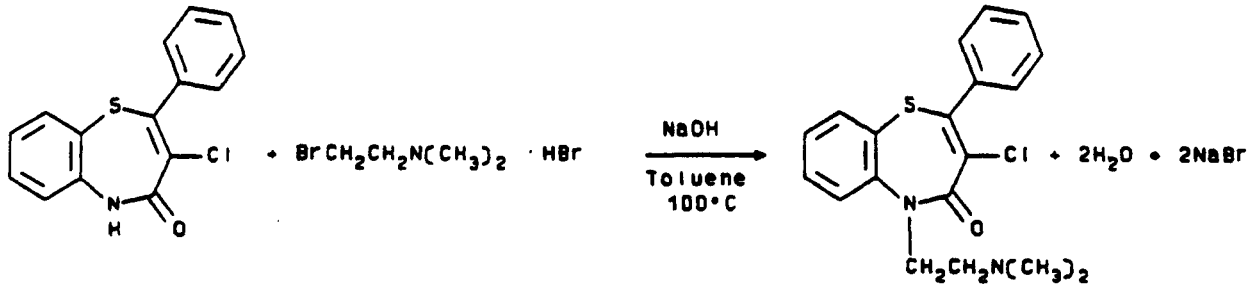
FF D 142. Abic's expert is of the opinion that Schenker is closer art to the '035 patent than the Nagarajan article. Schenker discloses the same base/solvent combination and alkylating agent disclosed in the '035 patent, whereas Nagarajan used sodium hydroxide (a different base) and acetone in a homogenous solution. Taylor Tr. 2754-55.

FF D 143. Abic's expert is of the opinion that Schenker is closer to the '035 patent than any reference of record. Taylor Tr. 2754-55.

12. The Krapco '006, '889, '967 and '902 Patents

FF D 144. The '006 and '889 patents, which contain an identical Example 1B, teach the N-alkylation of benzothiazepinones using sodium hydroxide and toluene in a system that generates water. RX 3669; RX 3673; Taber Tr. 2160; Gokel Tr. 886-93; RX 4038C; Kende Tr. 1430-31.

FF D 145. The reaction described in Example 1B of the '006 and '889 patents is illustrated as follows:



RPX 3673A; Gokel Tr. 887.

FF D 146. An organic chemist of ordinary skill back in 1980-81 would have recognized that the N-alkylation reaction in Example 1B of the '889 and '006 patents was carried out in a hydrous system as opposed to an anhydrous system. This is true even if "great pains" were taken to dry the toluene,

glassware and other equipment of the reaction system. RX 4038C.

FF D 147. The starting material in Example 1B of the '006 and '889 patents contains a phenyl group at the two position of the benzothiazepine molecule, and column 1 of those patents also describes a methoxyphenyl at the two position, which is the identical substituent contained at the two position of TZP. Taber Tr. 2161; Gokel Tr. 888.

FF D 148. Dr. Baldwin believes that if TZP was used as the starting material in the N-alkylation process of Example 1B of the '006 and '889 patents, that process would be equivalent to the process of the '035 patent. RX 4038C.

FF D 149. Dr. Baldwin doesn't "know one way or the other" whether a chemist with the '889 patent in front of him would have tried the reaction in Example 1B with TZP. Dr. Baldwin agreed that "[i]t is a possibility" that the chemist would have tried the reaction with TZP, having seen that the starting substrate in Example 1B was "analogous" to TZP. RX 4038C.

FF D 150. The following question and answer occurred at Dr. Baldwin's October 6, 1994 deposition:

> Q So if you had a series of reactions in which various analogous substrates were treated with the same reaction conditions, same base, same solvent, same alkylating agent, same temperature, same stirring conditions, then you would be able to hazard a guess as to what another one of the set of analogous structures would do under the same conditions?
>
> A I think you might be in a position to make some guesses, yes.

RX 4038C

FF D 151. The reaction disclosed in Example 1B of the '889 and '006 patents would involve the aziridinium ion as the alkylating agent. Gokel Tr. 895; RX 4038C; Taylor Tr. 2775.

FF D 152. The reaction system in Example 1B of the '006 and '889 patents is a "reversible" reaction system. RX 4038C.

FF D 153. The alkylating agent used in Example 1B of the '889 and '006 patents, dimethylaminoethyl hydrobromide, is one of the alkylating agents encompassed by claim 1 of the '035 patent, specifically because claim 1 of the '035 patent broadly states "dimethylaminoethyl halide." Gokel Tr. 888; RX 4038C.

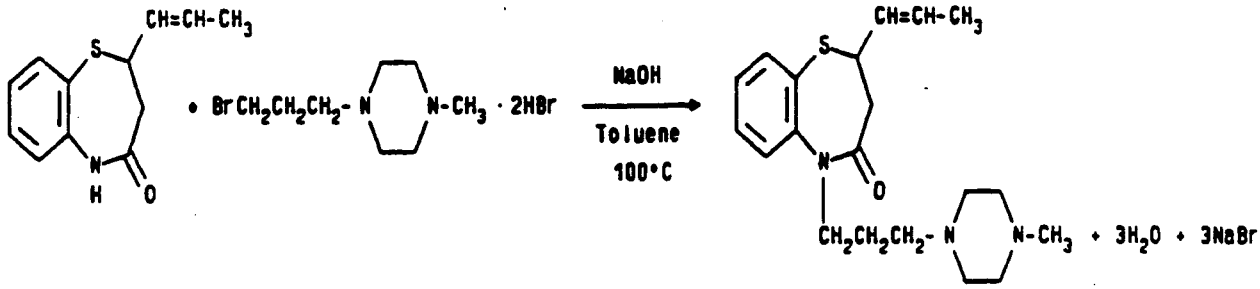
FF D 154. Example 1B in the Krapcho '889 and '006 patents is illustrated on RPX 3669A showing the alkylation of a benzothiazepinone using sodium hydroxide and toluene as the base/solvent. The patents identify the bases as alkali metal hydroxides. Taber Tr. 2160.

FF D 155. The substrate in Example 1B of the '889 and '006 patents has a benzene group bonded to the 2 position. However, column 1 of the patents contemplates a methoxyphenyl at the 2 position, just as in TZP. Taber Tr. 2161.

FF D 156. Example 1B of the '889 and '006 patents teaches that the alkylating agent used in the N-alkylation reaction was sufficiently stable under the hydrous reaction conditions to alkylate the benzothiazepinone substrate and obtain a yield of N-alkylated product. Gokel Tr. 896; RX 4038C.

FF D 157. The '902 patent describes the use of sodium hydroxide and toluene in a hydrous system for the N-alkylation of a 2,3-dihydrobenzothiazepinone. RX 3647; Taber Tr. 2161-62.

FF D 158. The N-alkylation reaction described in Example 4 of the '902 patent may be illustrated as follows:



FF D 159. The Krapcho '902 patent, example 4, describes N-alkylating the N-aryl amide of a benzothiazepinone with an aminopropyl halide with sodium hydroxide and toluene. Taber Tr. 2161; RPX 3647.

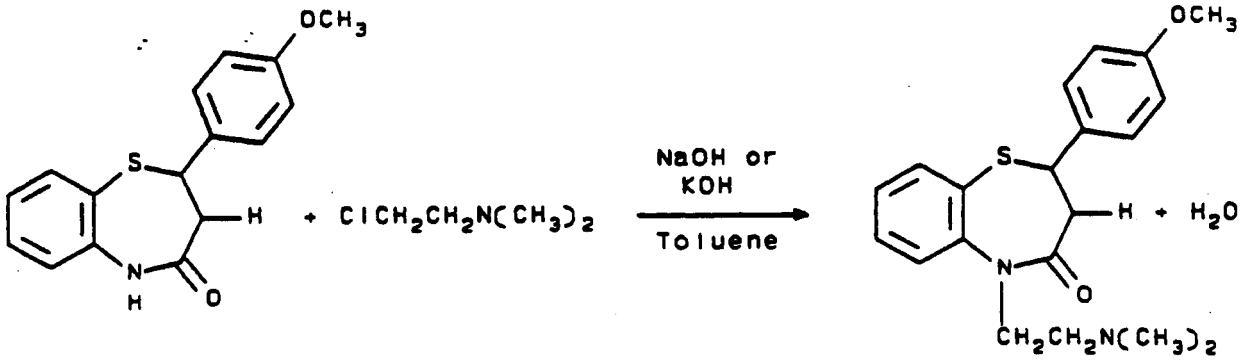
FF D 160. The substrate in example 4 of the '902 patent is a 2,3-dihydrobenzothiapinone, like the structure of TZP. Taber Tr. 2161-62.

FF D 161. In order to get a retro-Michael side reaction using the substrate of example 4 of the '902 patent, the proton would have to be removed at either the 2 or 3 position. However, the protons at 2 and 3 are not sufficiently acidic to remove even under the extreme conditions of sodium hydroxide and toluene. Taber Tr. 2163-63.

FF D 162. Nothing in the '902 patent suggests that side reactions will occur during N-alkylation. Taber Tr. 2162-63.

FF D 163. The '967 patent teaches the use of an "alkali metal hydroxide" in combination with toluene to N-alkylate a 2,3-dihydrobenzothiazepinone using dimethylaminoethyl chloride (DMC) as the alkylating agent. An alkali metal hydroxide would include sodium hydroxide or potassium hydroxide. RX 3632, RX 3125; Taber Tr. 2159-60, 2162; Gokel Tr. 870-72, 877-78, 881.

FF D 164. The general Formula II of the '967 patent includes the following 2,3-dihydrobenzothiazepinone (shown in the '967 N-alkylation reaction):



RPX 3125A, RX 1125; Gokel Tr. 879-81; Taber Tr. 2158-60.

FF D 165. The substrate for the N-alkylation reaction of the '967 patent differs from TZP (the substrate of the '035, '257, and the accused processes) only by the substitution of hydrogen (H) for hydroxyl (OH) at the 3 position of the TZP molecule. Taber Tr. 2159; Gokel Tr. 881; RPX 3125A.

FF D 166. Stereochemistry is the disposition of atoms and molecules in three dimensional space (as compared with a two dimensional piece of paper). Kende Tr. 1175. Claim 1 of the '035 patent does not refer to stereochemistry. Gokel Tr. 882; Taber Tr. 2177; CX 1.

FF D 167. At page 7 of his declaration submitted to the PTO during the Reexamination, Dr. Baldwin argued that subjecting TZP to basic conditions might have destroyed the "stereochemical" integrity of the molecule. Dr. Baldwin stated that such stereochemistry in diltiazem is critical to its pharmacological activity. RX 1658.

FF D 168. The definition of the alkylating agent provided in the '967 patent includes dimethylaminoethyl chloride (DMC). RX 3125; Taber Tr. 2159; Gokel Tr. 877-78.

FF D 169. All of the examples of the '967 patent describe the use of toluene as a solvent for N-alkylation. RX 3125; Taber Tr. 2159; Gokel Tr. 872.

FF D 170. The reaction drawn on poster RPX 3125A is "a reaction in which water would be produced," specifically, by the hydroxide ion of sodium hydroxide reacting with the hydrogen ion attached to the nitrogen on the benzothiazepinone substrate. In addition, if the hydrochloride salt of DMC was used as the alkylating agent in the N-alkylation reaction, as disclosed as a possible alkylating agent in the '967 patent, two molecules of water would be produced for each molecule of alkylated product. Gokel Tr. 882-83.

FF D 171. The N-alkylation reaction disclosed in the '967 patent, using alkali metal hydroxide as the base, is hydroxide mediated, just as complainants' expert, Dr. Gokel, testified that the N-alkylation step of the Profarmaco process, using sodium carbonate as the base, also is hydroxide mediated. Gokel Tr. 709, 882-83; Taylor Tr. 2775.

FF D 172. "Hydroxide-mediation" means that the hydroxide ion carries out the conversion of TZP to its anion, in contrast to when carbonate ion acts as the base to convert TZP to its anion. Taylor Tr. 2775.

FF D 173. Complainants' expert, Dr. Gokel, would agree that the Profarmaco process is an N-alkylation process practiced with a benzothiazepinone and 2-dimethylaminoethyl hydrochloride in the presence of sodium carbonate in a mixture of toluene and water. The sodium carbonate undergoes a reaction to produce sodium hydroxide, thus making the N-alkylation reaction in the Profarmaco process hydroxide mediated, as is the N-alkylation process disclosed in the '967 patent. RX 3125; Gokel Tr. 709, 882-83; Gokel Witness Statement.

FF D 174. Complainants' expert, Dr. Gokel, does not recall whether the '967 patent discloses any warnings or precautionary statements that the alkylating agent, DMC, would be unstable in a hydrous system containing sodium

hydroxide or potassium hydroxide. Nor does he recall the '967 patent containing any warning or precautionary information about the possibility of a retro-Michael reaction using a hydrous system in the presence of sodium hydroxide or potassium hydroxide. Nor does he recall whether the '967 patent contains any warning or precautionary information about the possibility of alkylation of the amide oxygen when using sodium hydroxide or potassium hydroxide in a hydrous system. RX 3125; Gokel Tr. 884-85.

FF D 175. In the N-alkylation reactions described by Krapcho in the '967, '889, '006, and '902 patents, each of which occurred in hydroxide bases under hydrous conditions, no hydrolysis of the amide bond was reported. Taber Tr. 2165.

FF D 176. The N-alkylation reactions disclosed in the Krapcho '967, '889, '006 and '902 patents are hydrous reactions, for at least two reasons. First, when the base, sodium hydroxide, deprotonates TZP, water is produced. Second, hydrogen chloride or hydrogen bromide from the alkylating agent will react with the sodium hydroxide to produce water. Taber Tr. 2163; Kende Tr. 1430-31; Taylor Tr. 2776.

FF D 177. None of the Krapcho patents contains any comment regarding possible negative side-reactions. Taber Tr. 2165.

FF D 178. There is no suggestion or warning in the '967 (RX 3125), '889 (RX 3673), '006 (RX 3669), or '902 (RX 3647) Krapcho patents, which disclosed N-alkylation of benzothiazepinones in hydrous reactions, that amide carbonyl O-alkylation would occur under hydrous conditions using sodium hydroxide and toluene. Taber Tr. 2163-64.

FF D 179. The Krapcho patents (U.S. Letters Patent 3,895,006; U. S. Letters Patent 3,948,889; U.S. Letters Patent 3,075,967; U.S. Letters Patent

3,455,902) describe the N-alkylation of benzothiazepinones. Taber Tr. 2168; RX 1233, 1375, 1609.

FF D 180. TZP is a 2,3-dihydrobenzothiazepinone. Taber Tr. 2162.

FF D 181. The subject matter of the Krapcho patents has "to do with the alkylation of benzothiazepinones in general." RX 4038C.

FF D 182. During the reexamination of the '035 patent, the examiner relied upon the testimony of Dr. John Krapcho, which was included in Tanabe's response to the November 18, 1994 Office Action, stating:

> Dr. Krapcho is virtually the founder to the entire field of 1,5-Benzothiazepine-4-ones (as well as other closely related compounds ... Contrary to requestor's argument Dr. Krapcho's testimony is seen as relevant. This relevancy is shown by the pioneering nature of Dr. Krapcho's work as evidenced by the Krapcho patents of record and Reexam 90/003,044. The fact that such an expert in this field should be surprised that the process in Gaino et al. '035 should work with a dramatic and consistent increase in yields is entitled to considerable weight. If such an expert should be surprised, just how would such a process be so obvious to one or ordinary skill in the art (as requestor would have us believe)?

RX 1653 (¶¶7 and 10); Kende Tr. 1378-79.

FF D 183. Dr. Krapcho stated to the PTO that he was extremely surprised, since he had worked solely with anhydrous alkylating conditions, that alkylation could take place under hydrous conditions such as the '035. RX 1653; Taylor Tr. 2733-2734.

FF D 184. Complainants used the term "hydrous" during the Commission proceeding to include a system having a base or solvent that contains a small amount of water. Dr. Kende defined anhydrous as completely free of water and hydrous as not completely free of water. Kende Tr. 1162.

FF D 185. The Patent Reexamination Examiner expressed the opinion that if Dr. Krapcho, who is a great expert in the field of benzothiazepine chemistry, could be surprised, it is not possible that one of ordinary skill

not be surprised. RX 1653; Taylor Tr. 2734.

FF D 186. Dr. Krapcho's alleged "surprise" that a hydrous (water-containing) as opposed to an anhydrous system could be used for the N-alkylation of a benzothiazepine played an important and decisive role in the Reexamination Examiner's decision. RX 1653; Kende Tr. 1379; Taylor Tr. 2733.

FF D 187. Dr. Krapcho did not specifically bring any of his patents to the attention of the patent examiner during the reexamination proceeding. RX 3048C.

FF D 188. The Krapcho '889 patent, in particular Example 1B, would have been a useful piece of information for the patent examiner in evaluating Dr. Baldwin's representation in ¶20 of his declaration that the stability of DMC under the hydrous conditions was unpredictable prior to the '035 invention. RX 4038C.

FF D 189. The Krapcho patents taught the use of hydrous systems for the N-alkylation of benzothiazepines. Kende Tr. 1430-1431.

FF D 190. A chemist who understood the teaching of Pachter, Worley, and Nagarajan could not be surprised that N-aryl amides could be alkylated under Pachter-type hydrous conditions of potassium hydroxide and acetone or potassium carbonate and acetone. Taylor Tr. 2735.

FF D 191. In Dr. Taylor's opinion, the examiner should not have been surprised that TZP could be alkylated under hydrous conditions. Taylor Tr. 2735-2736.

FF D 192. A bench chemist may find one process that works for him and continue to use it over and over. Pachter Tr. 1541.

FF D 193. Nothing in Dr. Krapcho's work required him to change to Pachter conditions. Pachter Tr. 1542.

13. Kugita I, II, III and IV

FF D 194. In 1970, Tanabe scientists, in Kugita I, reported treating TZP with hot aqueous hydroxide to the destruction of the molecule. From the results reported in Kugita I, Profarmaco's expert concluded that the stereochemistry of TZP was not disrupted under these conditions. RX 3806; Taber Tr. 2176-77.

FF D 195. In his declaration submitted to the patent examiner during the reexamination proceeding, Dr. Baldwin stated:

> [I]n Pachter, only methylation with methyl iodide is performed on non-lactam substrates. Pachter does not alkylate with any amide with the highly reactive and unstable DMC or any closely related alkylating agent. Alkylation conditions used for methyl iodide could not have been extrapolated to dissimilar alkylating agents such as DMC because of the differences in the structure stability and reactivity of the different alkylating agents.

RX 1658.

FF D 196. The examiner during reexamination found that the equivalence of methyl iodide and DMC had not been demonstrated under '035 conditions. RX 1653; Taylor Tr. 2764-2765.

FF D 197. The process of claim 1 of the '035 patent uses dimethylaminoethyl halide, such as DMC, as the alkylating agent. CX 1; Pachter Tr. 1512.

FF D 198. DMC is an alkyl halide. Pachter Tr. 1558.

FF D 199. The mechanism of alkylation is almost irrelevant to the expectation that methyl iodide and DMC will both act as alkylating agents. Differences between mechanism of alkylation with DMC and methyl iodide are not important for determining whether the '035 processes are obvious. Taylor Tr. 2704, 2710.

FF D 200. When medicinal chemists begin to develop reactions for their

compounds, the first alkylating agent they usually use is the simplest alkylating agent, namely methyl iodide or methyl sulfate. This methylation reaction serves as a model. Chemists work out reaction conditions with the simplest compound possible. After working out reaction conditions, medicinal chemists then use DMC or other related alkylating agents using the same procedures as used with methyl halide to make the desired compound. Pachter Tr. 1512-13; Taylor 2704.

FF D 201. DMC is used to alkylate TZP in order to allow the compound to dissolve in water and thus enter the bloodstream either orally or by way of injection. Pachter Tr. 1513-14.

FF D 202. DMC and related alkylating agents are among the most common of side chains put on drug molecules. Thousands of examples exist in the literature of alkylation with DMC and related dialkylaminoalkyl halides. Pachter Tr. 1513-14.

FF D 203. Chemists use the same conditions for alkylating with methyl iodide and DMC, and at least for the purposes of experimentation and development, do not worry about aziridinium or loss of alkylating agent. DMC and related compounds have been used in medicinal chemistry for over 50 years. Pachter Tr. 1534-35.

FF D 204. Dr. Pachter knows of no examples related to a pharmaceutical compound where a chemist started the alkylation reaction by using methyl iodide and then switched to DMC and the desired result was not obtained. Pachter Tr. 1535.

FF D 205. Tanabe scientists first used methyl iodide as the alkylating agent followed by using DMC as the alkylating agent, both with a 20 percent excess of alkylating agent, thus indicating that Tanabe scientists believed

there to be no difference between the two for the purpose of conducting test reactions. Pachter Tr. 1533-1534.

FF D 206. Using conditions other than those of the '035 patent, Kugita II (RX 3807) used methyl iodide as the alkylating agent, and Kugita III (RX 3809) used DMC as the alkylating agent. The results in these cases were comparable. Pachter Tr. 1593.

FF D 207. Eleven years before the priority date of the '035 patent, Tanabe scientists had concluded that when sodium hydride was used as a base in the N-alkylation reaction, low yields and numerous side reactions resulted. In Kugita et al., Chem. Pharm. Bull., 19(3), 595-602 (1971) ("Kugita III"), the author stated that "[r]eaction of 2-aryl-3-hydroxy-2,3-dihydro-1,5-benzothiazepin-4(5-ones (I) with dialkylaminoethyl halides and dioxane using sodium hydride as a base afforded the N-dialkylaminoalkyl derivatives (II) in low yields." Table I reported the result of numerous N-alkylation reactions, and those in which sodium hydride was used as the base, the yields were low. RX 3809.

FF D 208. The Kugita III article states that "[t]he reaction in the presence of dimethylsulfinyl carbanion and dimethylsulfoxide resulted in a remarkable increase in the yields (Table I)." RX 3809; RPX 3809.

FF D 209. During the reexamination of the '035 patent, Complainants' expert, Dr. Baldwin, submitted a declaration to the PTO in which he speculated that the following side reactions might occur (i) the so-called "retro-Michael reaction," (ii) alkylation of the amide oxygen, (iii) alkylation of the 3-hydroxyl, (iv) dehydration between that 2 and 3 position, (v) hydrolysis of the amide bond, and (vi) alkylation at the 1 and 2 positions under "certain conditions." Dr. Baldwin also speculated that dimethylaminoethyl halide

alkylating agents might have been unstable under '035 conditions, thus reducing the yield of the reaction. RX 1658.

FF D 210. In a 1973 publication by Tanabe, Kugita IV, N-alkylation of TZP with DMC was reported with a very high yield, thereby indicating that no major side reactions occurred. Kende Tr. 1274-76; RX 1641; RX 1641a.

FF D 211. Kugita I (published by Tanabe in 1970), a paper of which both Drs. Baldwin and Kende were not aware, clearly shows that under aqueous alkaline conditions you do not get a retro Michael-reaction. Pachter Tr. 1520-22; RX 2148; RPX 3806A.

FF D 212. Kugita I (which cites the Mills and Whitworth retro Michael paper) were trying to see whether they could get retro-Michael like Mills using TZP -- however no retro Michael occurred. Pachter Tr. 1521-22; Taber Tr. 2175-76; RX 2148; RX 2152.

FF D 213. A chemist who was aware of Kugita 1 would "absolutely not" have expected a retro-Michael reaction using Pachter conditions to alkylate TZP using DMC. Pachter Tr. 1519, 1522; Taber Tr. 2176-77; RX 2148. Dr. Taylor agrees with Dr. Pachter, "Michael -- reverse Michael is a dead horse." Taylor Tr. 2704.

FF D 214. None of the Kugita papers reported a retro-Michael. Kende Tr. 1335, 1452-54.

FF D 215. In a 1970 article published by Tanabe scientists (referred to as "Kugita I") (RX 3806), Kugita et al. referred to the work of Mills and Whitworth. Tanabe scientists reported that under the conditions used by Mills and Whitworth, i.e., heating TZP with aqueous sodium hydroxide until destruction of the molecule, no retro-Michael occurred with the TZP molecule. RX 3806; Pachter Tr. 1520-22; Kende Tr. 1452-54; Taber Tr. 2177.

FF D 216. Kugita I (RX 3806) taught that hydrolysis of the lactam ring can occur yet would be minor, with respect to the amount of by-product occurring. RPX 3806; Pachter Tr. 1572.

FF D 217. There was no reported retro-Michael reaction in any of the Tanabe scientific papers by Kugita. Kende Tr. 1335.

FF D 218. Tanabe scientists, in one of the Kugita papers, taught that O-alkylation occurs only after the amide nitrogen has been alkylated. Kende Tr. 1338.

14. Jarrousse

FF D 219. In a 1951, Jarrousse, "Comptes rendues des séances de l'Académie des sciences" Apr. 9, 1951, p. 1424 ("Jarrousse"), DMC is subjected to extremely harsh basic, aqueous conditions without significant decomposition. RX 2145; Pachter Tr. 1518-19.

15. Finkelstein

FF D 220. In a 1951 article by Finkelstein and Linder, Studies in Phenanthridine Chemistry" 73 J. Amer. Chem. Soc. 302-04 (1951)("Finkelstein"), an N-alkylation procedure (previously described by Graebe and Wander, 276 Ann. 245 (1893)) was conducted under extremely harsh conditions, using DMC and a large excess of molten potassium hydroxide at 150° for five hours. A high yield was reported, and no decomposition of the DMC was reported. RX 4025; RPX 4025A; Pachter Tr. 1515-17, 1519.

FF D 221. Finkelstein based his alkylation reaction using DMC on the same alkylation reaction reported by Graebe in 1893 using methyl iodide. RX 4025; RPX 4025(A); Pachter Tr. 1516-17.

FF D 222. The Pachter conditions, used in the '035 patent, are much milder than the Jarrouse or Finkelstein conditions, yet the reaction in both

Jarrouse and Finkelstein was stable enough to produce what both investigators called "excellent yields." Pachter Tr. 1519.

16. Price and Iyer

FF D 223. The Price article (RX 3817) and Iyer article (RX 3132C), articles cited by Dr. Kende in his declaration submitted to the PTO during Reexamination, clearly teach that the aziridinium ion will be of sufficient stability and that the N-alkylation will proceed at a sufficient rate that one would have a reasonable expectation of success under the '035 conditions. Taber Tr. 2171-72.

FF D 224. In 1981, the Price (RX 3817) and Iyer (RX 3132C) articles taught that aziridinium is stable enough to allow N-alkylation without any difficulty. Taber Tr. 2173.

FF D 225. If the concentration is a tenth of what it used to be, the reaction will take 100 times as long. In Price (RX 3817), the reaction is conducted under conditions of high dilution, so one would expect that bimolecular reactions would be disfavored. Taber Tr. 2170.

17. Tanabe's KOH/DMSO Process

FF D 226. Prior to 1981, Tanabe used the base-solvent combination KOH/DMSO for the N-alkylation of TZP in the manufacture of diltiazem. RX 3607; RX 3737-C.

FF D 227. In 1981, the inventors of the '035 patent had as their goal the improvement of the commercial manufacturing process using KOH/DMSO as the base-solvent combination in the N-alkylation of TZP. RX 3737-C; RX 3742-C.

FF D 228. The inventors hoped to obtain a yield equal to that which had been obtained with the KOH/DMSO method. RX 3742-C.

FF D 229. The inventors were also attempting to produce diltiazem having

the same purity as that made by the KOH/DMSO process. RX 3739-C.

FF D 230. The problem faced by Tanabe at the time of the development of the process claimed in the '035 patent was to select a solvent which was easier to recover than the DMSO solvent used in Tanabe's existing commercial process. RX 3793-C; RX 3737-C.

FF D 231. The first change made to the KOH/DMSO process involved changing the solvent DMSO. RX 3737.

FF D 232. Acetone was the first solvent chosen by the inventors to replace DMSO. RX 3739.

FF D 233. Potassium hydroxide was the very first base selected as an alternative when Tanabe began to scale up production from the KOH/DMSO process. RX 3793-C.

FF D 234. More than one year prior to the filing of the application for the '035 patent (beginning in 1973), Tanabe manufactured diltiazem using a trade secret process which used KOH as the base and DMSO as the solvent. During this time period, Tanabe sold the diltiazem into a number of countries, including the United States. RX 3607; CX 646.

FF D 235. During reexamination of the '035 patent, Tanabe submitted to the PTO declarations of alleged patent law experts, including that of James Gambrell, Esq., in support of its position that Tanabe's KOH/DMSO process was not prior art to the '035 patent. During the course of preparing his declaration, Mr. Gambrell communicated with Pennie & Edmonds and deleted certain material from his draft declaration. Specifically, Mr. Gambrell deleted the final underlined sentence in the following paragraph:

> It is my opinion that the public use and on sale sections of 35 U.S.C. § 102(b) are limited by the statutory term '*in this country*.' Therefore, the language of § 102(b) does not include the practice of a process in a foreign country (whether secret or otherwise) as

> prior art. However, this is not necessarily true if the product produced by the foreign process is used or sold in the United States without restriction. In re Cavaney, [761] F.2d 671 (Fed. Cir. 1985) (emphasis added).

This sentence and the accompanying citation was apparently deleted between August 19, 1993 and August 24, 1993.

FF D 236. Potassium hydroxide (KOH) is one of the bases claimed in the '035 patent. CX 1.

FF D 237. Tanabe argued to the examiner during the reexamination that the '035 patent was distinguishable from the prior art because, inter alia, it was a hydrous rather than anhydrous system. RX 1638; RX 4038C.

FF D 238. The production of diltiazem using the base-solvent combination KOH/DMSO is a hydrous system. Kende, Tr. 1386-87.

FF D 239. During the time Dr. Baldwin was present at the interview with the patent examiner, the examiner was never told about the KOH/DMSO process. RX 4038C. The examiner also was not told during the interview that Tanabe regarded alkylation processes that used bases and solvents other than those specifically identified in the '035 patent to be equivalent to those in the '035 patent. RX 4038C.

FF D 240. During reexamination of the '035 patent, the examiner was presented with about 172 prior art references. RX 1603.

FF D 241. Rather than expressly disclosing the KOH/DMSO process to the Examiner during Reexamination, Tanabe submitted a book, entitled, Diltiazem from Birth to Today, that contained over 250 pages, of which one sentence on one page referenced the KOH/DMSO process. That page (RX 1104, page 33) was not pointed out to the Examiner. RX 1087; RX 1690; Taylor, Tr. 2767-2768.

FF D 242. In the "Information Disclosure Statement Under 37 C.F.R. §1.555," submitted to the PTO by Tanabe's counsel, Tanabe requested that the

Examiner take particular note of specified patents and publications. The book Diltiazem from Birth to Today was not one of those references. RX 1087.

FF D 243. The one page of Diltiazem from Birth to Today reads in pertinent part as follows:

> The N-alkylation of the lactam was also studied through close collaboration between the Organic Chemistry Research Laboratory, Onoda Factory and the Pharmaceutical Technics Division. They found that the reaction proceeds easily by the use of potassium carbonate and ethyl acetate in place of potassium hydroxide and dimethylsulfoxide. These two improvements were accomplished at the same time that diltiazem was being introduced overseas and greatly contributed to a plan for a plant with increased output and more efficient production.

RX 1104.

FF D 244. The passage from Diltiazem From Birth to Today even if found by the Examiner would not have revealed the significance of the KOH/DMSO process in particular that the process was a hydrous process. Taylor, Tr. 2795-2796.

FF D 245. That sentence from Diltiazem From Birth to Today does not disclose that the material made by the KOH/DMSO process had been imported into the United States. Rather it leaves the impression that Tanabe was building a plant for potassium carbonate/ethyl acetate to make the compound to send to the United States. Taylor, Tr. 2770.

FF D 246. The passage from Diltiazem From Birth to Today found on page 33 of RX 1104 does not explain that the KOH/DMSO process, like the '035 process, was hydrous. Taylor, Tr. 2770-2771.

FF D 247. As a matter of PTO practice, the placement of Examiner's initials next to a cited reference indicates that the reference was expressly considered by the examiner. Manual of Patent Examining Procedure ("MPEP") § 609.

FF D 248. Examiner Bond placed his initials next to the reference, Diltiazem From Birth To Today., which specifically discloses Tanabe's prior KOH/DMSO process. CX 638A.

FF D 249. Without knowing what he was looking for, Dr. Taylor believes that the one page (RX 1104) would have been extremely difficult to find. Taylor, Tr. 2768-2769.

FF D 250. Yields obtained by KOH/DMSO and KOH/acetone were "about the same." RX 3742. See Nakao Tr. 378-79; 398-99.

FF D 251. A May, 1981 Tanabe report stated that the yield using the KOH/DMSO method was C . RX 3327; Nakao Tr. 398-99.

FF D 252. In 1981, the inventors of the '035 patent sought to find a solvent to replace DMSO because it was difficult to recover. They kept KOH as the base and quickly settled on acetone. RX 3739.

FF D 253. In May 1981, Messrs. Iijima and Gaino reported that the reaction using acetone as a solvent proceeds to the same degree as it does using DMSO. RX 3314. In June 1981, Messrs. Iijima, Nakao and Gaino reported that "alkylation can take place in the same manner when KOH/DMSO is replaced with KOH/acetone." RX 3361.

FF D 254. During the Reexamination of the '035 patent, complainants also did not inform their expert, Dr. Baldwin, about Tanabe's KOH/DMSO process. Dr. Baldwin first learned about the KOH/DMSO process in May 1994, four months after he had prepared and signed his declaration. RX 4038.

FF D 255. Assuming the KOH/DMSO process was conducted under hydrous conditions -- which it was -- Dr. Baldwin agreed that it was relevant to his declaration. RX 4038C.

FF D 256. Dr. Baldwin believes that the patent examiner would have

wanted to know that Tanabe had used the KOH/DMSO process for a number of years prior to the '035 process. RX 4038C.

FF D 257. If Dr. Baldwin had known about the KOH/DMSO process, he would have told the patent examiner about it. RX 3048C.

FF D 258. The base-solvent combination KOH/DMSO is a heterogenous system. Kende, Tr. 1355-56. The '035 system is also heterogeneous. Taylor, Tr. 2613.

FF D 259. The KOH/DMSO system used by Tanabe for the commercial manufacture of diltiazem falls somewhere between '257 and '035 conditions in terms of reactivity. The KOH/DMSO system thus falls in the middle of the reactivity of compounds tested by Dr. Pachter. Thus, in Dr. Pachter's opinion, because KOH-DMSO and '257 conditions succeeded, so should '035 conditions. Pachter, Tr. 1537.

FF D 260. Both the KOH/DMSO process and the '035 process use the TZP substrate, the base and solvent of the KOH/DMSO process are interchangeable with the '035 bases and solvents, DMC and the aziridinium ion are present in both the KOH/DMSO process and the '035 process, water is present in the KOH/DMSO process and the '035 process, and the KOH/DMSO process and the '035 process are hydroxide mediated. RPX 1153; Taylor, Tr. 2774-77, 2791-92.

FF D 261. The KOH/DMSO process and the '035 process work in the same way. Taylor, Tr. 2793-2794.

FF D 262. Tanabe sold DMC·HCl produced using the KOH/DMSO process to MMD in the United States pursuant to various supply agreements from approximately 1976 through approximately 1984. Fogel Tr. 71-72; Joint Stipulation Nos. 22-26.

FF D 263. MMD received formal FDA approval to market its first DZM-HCl

Cardizem® products to the general public in or about November 1982. RX 1249.

FF D 264. Given the '257 patent, Pachter, and the KOH/DMSO process, one would have been 98% certain of success using Pachter conditions on TZP since the KOH/DMSO process showed success using the identical substrate under aqueous KOH basic conditions with no side reactions. Pachter Tr. 1536-37; Taylor Tr. 2703, 2766-67.

C. Additional Findings Concerning Side Reactions

FF D 265. In their declarations submitted to the PTO during the Reexamination of the '035 patent, Drs. Baldwin and Kende described the retro-Michael reaction pointing out that the first step of the retro-Michael reaction involves removal of a hydrogen atom from the carbon at the 3-position. RX 3132; RX 1658.

FF D 266. The retro-Michael reaction shown by Drs. Baldwin and Kende in their declarations occurs in a molecule which, unlike TZP, does not have a hydroxyl group at the 3-position. RX 3132; RX 1658; RPX 4030; Taber Tr. 2174.

FF D 267. For the retro-Michael to proceed, a base would have to remove the hydrogen from the carbon at position 3. Taber Tr. 2175.

FF D 268. The presence of the hydroxyl at the 3 position renders the hydrogen atom at the C-3 position difficult to remove (non-acidic). Taber Tr. 2175.

FF D 269. The proton of the hydroxyl group attached at the C-3 position of TZP is much more acidic than the proton directly bonded to the carbon at the C-3 position. Taber Tr. 2175; RX 3048C.

FF D 270. If retro-Michael were going to occur, it should have occurred under '257 conditions. Taber Tr. 2175.

FF D 271. In the '257 patent where there is a 3-hydroxyl group on TZP,

there is no reported retro-Michael reaction. Kende Tr. 1332; 1401-02; RPX 2011A.

FF D 272. In order for the retro-Michael reaction to occur, the base would have to ignore the more acidic amide NH and 3-OH and find the much less acidic 3-CH, remove the hydrogen and kick out the S minus. This on its face is unlikely. Taber Tr. 2175.

FF D 273. The prior art taught one of skill in the art how to avoid a retro-Michael reaction under '257 conditions. Kende Tr. 1335.

FF D 274. The only two references complainants rely on for the possibility of a retro-Michael reaction are (1) Mills and Whitworth and (2) Krapcho, Spitzmiller and Turk reference. Kende Tr. 1330; RX 1658; RX 2152, RPX 1009.

FF D 275. In Mills and Whitworth no alkylating agent was present, Pachter conditions were not used, and 10% potassium hydroxide dissolved in ethanol and water was used. Kende Tr. 1330-32; RPX 1011; RPX 1009; RX 1658.

FF D 276. In 1963, the Krapcho prior art avoided the retro-Michael reaction by the use of dimethylaminoethyl bromide as the alkylating agent. RX 3788; Kende Tr. 1334-35; Pachter Tr. 1583-1584.

FF D 277. In subsequent patents, such as the '967 and '902 patents, Dr. Krapcho described the N-alkylation of 2,3-dihydrobenzothiazepinones using sodium hydroxide and toluene in hydrous systems without reporting a retro-Michael reaction. Taber Tr. 2163-64.

FF D 278. In internal Squibb memorandums describing N-alkylation of a dihydrobenzothiazepinone (thiazesim) using sodium hydroxide and toluene, it is reported that no S-alkylated material, i.e., retro-Michael, is observed. Kende Tr. 1439-42.

FF D 279. In the '257 patent, no-retro Michael reaction was reported. Kende Tr. 1332; RX 1229.

FF D 280. The compound of Mills and Whitworth was significantly different from the compound of the '035 patent because the Mills and Whitworth compound did not have a hydroxy group. Kende Tr. 1451.

FF D 281. Krapcho, Spitzmiller and Turk used '257 conditions (sodium hydride/toluene) instead of Pachter conditions and only reported retro-Michael when they used the alkylating agent dimethylamino propyl chloride (which can not form an Az^{+}) but reported no-retro Michael when they used DMC. Kende Tr. 1333-34; RPX 1011; RX 1658.

FF D 282. Krapcho, Spitzmiller and Turk reported that retro-Michael did not occur when DMC was used. Kende Tr. 1334-35.

FF D 283. However in a separate paper, Krapcho, Spitzmiller and Turk taught that if you wanted to avoid retro-Michael, one should use the alkylating agent dimethylaminoethyl bromide, instead of dimethylamino propyl chloride. Kende Tr. 1334.

FF D 284. In order to get a retro-Michael reaction, one would have to abstract a hydrogen from a carbon. Abic was not concerned with possible retro-Michael reaction on TZP. TZP has a nitrogen with a proton on it, an acidic proton with nitrogen. TZP also has a hydroxyl group. The hydroxyl is far more vulnerable to attack than a carbon group. Haber Tr. 2414-15.

FF D 285. At page 8 of his declaration submitted to the PTO during the Reexamination of the '035 patent, Dr. Baldwin speculated that a possible side reaction might have been the elimination of water (i.e., dehydration) under basic conditions. He shows a side reaction in which hydroxyl at the 3 position and the hydrogen at the 2 position are removed, leaving a double bond

between the 2 and 3 carbon atom. RX 1658.

FF D 286. Dr. Baldwin described a hypothetical side reaction involving alkylation at the 3-hydroxyl group at the top of page 7 in his declaration submitted to the PTO during the Reexamination. RX 1658.

FF D 287. Complainants also submitted a declaration by Dr. Kende to the PTO during the Reexamination of the '035 patent. In paragraph forty-two (42) of his declaration, Dr. Kende cited to a reference by Floyd to support complainants' theory that alkylation at the 3-hydroxyl of TZP is possible. The Floyd reference is not prior art. RX 3132; Kende Tr. 1338.

FF D 288. The '257 patent taught that alkylation at the 3 hydroxyl group did not compete with alkylation at the amide nitrogen. Taber Tr. 2173.

FF D 289. In the '257 patent, when sodium hydride and DMSO were used for alkylation, the predominant reaction was alkylation at the amide nitrogen. Kende Tr. 1449-50.

FF D 290. Alkylation at the 3-hydroxyl group was not reported in the '257 patent, Tanabe's trade secret KOH/DMSO process or the '035 patent. Kende Tr. 1401; RPX 2011A.

FF D 291. The first paragraph of the Pachter reference cites a prior reference by Fones which teaches that some compounds containing nitro groups are completely inactive under '257 conditions. RX 3770; Pachter Tr. 1502, 1524.

FF D 292. The Pachter reference reported that the nitro-substituted compound which Fones could not get to react under '257 conditions produced an 80% yield using potassium hydroxide and acetone. Kende Tr. 1524, 1459-61; RX 3770.

FF D 293. Under '257 conditions, compounds have the reverse reactivity

as under '035 conditions. The nitro compound of Pachter is the least reactive under '257 conditions. Pachter Tr. 1506-07.

FF D 294. Tanabe argued to the examiner during the reexamination that the possible side reactions set forth in Dr. Baldwin's declaration had the potential of reducing the yield. RX 1638.

FF D 295. Every reaction proceeds in less than 100 percent yield but that does not make the reaction less useful. Pachter Tr. 1572.

FF D 296. Even if side reactions occur, the reaction may still yield product. Kende Tr. 1468.

FF D 297. Dr. Baldwin agreed that even if alkylation occurred at sites on the TZP molecule other than at the amide nitrogen, the reaction process could still be very commercially important. RX 4038C.

FF D 298. The possibility of side reactions would not be determinative of the question of obviousness. If there is a functional group elsewhere in a molecule that one suspects is going to interfere, or which does interfere, you can take care of the problem by standard methods, such as protecting the functional group. Taylor Tr. 2781.

FF D 299. Even if side reactions take place one would not be deterred from trying the N-alkylation reaction. Organic chemists are flexible enough to take care of them. Taylor Tr. 2797.

FF D 300. Obviousness can be found even though yield cannot be predicted. Taylor Tr. 2781.

FF D 301. In his declaration submitted during the reexamination, Dr. Kende cited to an article by Yamawaki to suggest that O-alkylation was possible. RX 3132. Dr. Kende did not inform the Examiner that Yamawaki cites to Challis, which is a chapter in a book titled The Chemistry of Amide, which

teaches that alkylation at the amide nitrogen can be expected. Kende Tr. 1351-53. The Chalice book (pg. 927) teaches those in the art that you can expect alkylation at the nitrogen atom (and says nothing about the oxygen atom) under basic conditions. Kende Tr. 1352-53; RPX 1012.

FF D 302. If a base is used in an N-alkylation reaction, as in the '035 patent, N-alkylation is always obtained. Pachter Tr. 1553.

FF D 303. Benzothiazepinones have been alkylated for a long time and there has never been any suggestion that alkylation occurs at the amide carbonyl oxygen. The alkylation occurs on the nitrogen where the nucleophilic reactivity is. Taber Tr. 2164.

FF D 304. The Nadzan reference relied on by complainants to show O-alkylation alkylates quinolones, not amides, under '257, not '035 conditions. Kende Tr. 1344-45; RPX 1029A.

FF D 305. Of the many alkylations reported in Clark, there was only one O-alkylation. That occurred when tert-butyl bromide was used as the alkylating agent. Tert-butyl bromide is one of the worst alkylating agents to use in that alkylation. Nevertheless, N-alkylated product was obtained. The yield of N-alkylated product was only 3 percent. However, that was almost 3 times the amount of O-alkylated product. Taylor Tr. 2934.

FF D 306. Dr. Gokel believes that due to its rigidity, the Nagarajan substrate is more likely to undergo O-alkylation than N-alkylation. CX 606; see Kende Tr. 1346-48. However, Nagarajan reports no O-alkylation. Kende Tr. 1346-47.

FF D 307. Abic was not concerned with O-alkylation at the 3 carbon when it was developing its process. This was a theoretical possibility. But, knowing of Tanabe's experience with conditions such as disclosed in the '257

patent without any reports of O-alkylation occurring, the possibility of such occurrence, was negligible if at all. Haber Tr. 2415.

FF D 308. Abic was not concerned with O-alkylation at the 3 carbon when it was developing its process because Abic had an aromatic amide, in the presence of base. In Abic's view, if there were no base, O-alkylation at the 3 carbon is a possibility. If base is present, there is exclusive N-alkylation, except in the presence of silver. Haber Tr. 2416.

FF D 309. No known art exists showing the O-alkylation of a benzothiazepinone. Kende Tr. 1341-42.

FF D 310. Complainants' experts cannot give a prior art example of an O-alkylation of a any simple amide. Kende Tr. 1349.

FF D 311. At page 6 of his declaration submitted to the PTO during the reexamination, Dr. Baldwin refers to a possible side reaction involving alkylation of the amide oxygen (at position 4). He does not discuss how this reaction would occur or under what conditions. RX 1658.

FF D 312. Dr. Kende also submitted a declaration to the PTO during Reexamination which postulated the possibility of carbonyl O-alkylation. RX 3132.

FF D 313. The amide carbonyl is the carbon double bonded to the oxygen which is adjacent to the nitrogen. Taber Tr. 2164.

FF D 314. In his declaration Dr. Kende gave no example of carbonyl O-alkylation. RX 3132; Kende Tr. 1342.

FF D 315. Both Dr. Kende and Dr. Baldwin know of no example of carbonyl O-alkylation of a benzothiazepinone. Kende Tr. 1342; RX 4038C.

FF D 316. Alkylation at the amide oxygen was not reported in the '257 patent, Tanabe's trade secret KOH/DMSO process or the '035 patent. Kende Tr.

1401; RPX 2011A.

FF D 317. Complainants cite no prior art, known to one of ordinary skill in the art, in support of their argument that a hydrolysis side reaction might occur when TZP is alkylated under Pachter conditions. See Kende Tr. 1336.

FF D 318. Abic was not concerned with possible hydrolysis when it was developing its process. It was known that if you take diltiazem and compounds similar to it, you have an acetyl group on the hydroxyl group of position 3. You could hydrolyze off that acetyl group by using a base such as sodium hydroxide and water, hydrolyze off of that acetate without attacking the lactam ring. So that was known to show that this would not be a danger. Haber Tr. 2413-14.

FF D 319. Abic knew that the acetyl group could be hydrolyzed, but that reaction would not also cause hydrolysis of the amide linkage. It was also known to every organic chemist that if you have an ester (acetyl is an ester) and an amide in the same compound, the amide is fairly stable and the ester is not. This fact was published, and therefore it was known that in using such conditions, hydrolysis would not happen to any large extent. Haber Tr. 2414.

FF D 320. When hydrolysis occurred with toluene and high temperature, Abic still obtained the desired product, a 7% yield. Haber Tr. 2421-22; RX 1044.

FF D 321. Complainants admit that the art they rely on to allegedly show the possibility of a hydrolysis under Pachter conditions is not prior art. Kende Tr. 1336-38.

FF D 322. At page 9 of his declaration submitted to the PTO during the Reexamination, Dr. Baldwin illustrated the reaction involving hydrolysis of the amide bond under basic conditions. RX 1658.

FF D 323. Hydrolysis of the amide bond occurs where the hydroxide ion, which is a nucleophile, adds to the amide carbonyl breaking the carbonyl-nitrogen bond, kicking out the amide, breaking the ring. Taber Tr. 2165.

FF D 324. Complainants' expert, Dr. Kende, did not know of any prior art showing the hydrolysis of the amide bond in TZP. Kende Tr. 1336.

FF D 325. In their declarations submitted to the PTO during the reexamination, Drs. Baldwin and Kende discussed the potential instability of the alkylating agent used in the '035 patent, contending that DMC is converted to an aziridinium ion, which is subjected to hydrolysis in the presence of water. RX 1658; RX 3132; Pachter Tr. 1514.

FF D 326. Even if an alkylating agent is destroyed or undergoes hydrolysis during the course of a reaction, the situation is normally remedied by adding an excess of the alkylating agent. Gokel Tr. 896-897; Pachter Tr. 1597-1598; RX 3048C.

FF D 327. Any alkylating agent, including DMC, could react with water. For example, the halogen could hydrolyze off the chlorine to form a hydroxyl group, or, under certain conditions, the DMC could react with itself to create what has been termed a dimer. One can expect a little bit of it. However, one can provide for it. One has to change conditions in order to minimize it. For example one might add more of the material to take care of any that is lost. Haber Tr. 2416-17; 2491-92.

FF D 328. Side reactions, even if they do occur, merely reduce yield of desired product. Some, if not a significant amount, of desired product may still be produced, even with side reactions. Kende Tr. 1169, 1468.

FF D 329. Although almost every reaction known produces less than 100% yield (indicating a side reaction or by-product), that does not make the

reaction any less useful. Pachter Tr. 1572.

FF D 330. The possibility of 3 hydroxyl alkylation is negated based upon the '257 patent, which teaches that the 3 hydroxyl does not compete with the 5 nitrogen. Taber Tr. 2173.

FF D 331. If one were to see side-reactions, one would expect to see them under the harsh conditions of the '257 patent. However, the '257 patent does not report any of the potential side-reactions posited by complainants. Taber Tr. 2168-69; RX 1193.

D. One of Ordinary Skill in the Art

FF D 332. The person of ordinary skill would be an industrial, process development chemist, like Dr. Piselli, rather than a discovery chemist, like Dr. Krapcho. Taber Tr. 2151-56.

FF D 333. In 1981, chemists known as "bench chemists" had different objectives than those of a "process development" chemist when developing a compound. Bench chemists had as their objective the preparation of small quantities of material, not worrying initially about yield. Once a product showed promise, it was given to process development chemists whose objective was to develop procedures that would provide a more practical synthesis. Kende Tr. 519; Pachter Tr. 1495.

FF D 334. In 1981, the field of organic process development was a sophisticated technology. Pachter Tr. 1497-98.

FF D 335. The level of ordinary skill in the art at the time of the alleged invention claimed in the '035 patent, December 7, 1981, was very high. A person of ordinary skill in the art was a Ph.D. with process development experience. Pachter Tr. 1497-98; Kende Tr. 1150; Taber Tr. 2151-56.

FF D 336. The person of ordinary skill would be familiar with the

literature of organic chemistry and would be especially familiar with the patent literature in his or her field of study. Taber Tr. 2151-56.

V. UNENFORCEABILITY

A. The Tanabe KOH/DMSO Process Is Material, and Was Intentionally Concealed

FF E 1. In September, 1993, complainants made the following admission in this proceeding: "Diltiazem prepared by Tanabe in Japan using KOH and DMSO, then a trade secret, was sold to MMD more than one year prior to the filing of the '035 patent." RX3607; Findings of Fact, Section VIII(B)(3).

FF E 2. At the time Tanabe filed its Japanese application counterpart to the '035 patent, Tanabe had used its KOH/DMSO N-alkylation process for nearly 10 years to make commercial bulk diltiazem hydrochloride which was sold, inter alia, to MMD in the United States. RX 1406; RX 3607C.

FF E 3. Tanabe also had drafted a patent application for the KOH/DMSO process claiming that it possessed the same advantages over the '257 patent as those ascribed to the process of the '035 patent. RX 1346C; RX 1248; RX Ct; RX 1579C.

FF E 4. The Tanabe application designated P-3348 (1) covered the KOH/DMSO process, and the application designated P-3348 (2) covered the '035 process. RX 1586; RX 1346C; RX 1248; RX 1579C.

FF E 5. The introductory sections of the Japanese KOH/DMSO and '035 patent applications, setting forth the background of the invention, are strikingly similar, differing in only a few words. RX 1579C at 132-36.

FF E 6. The Japanese application on the KOH/DMSO commercial process described that invention, in particular the benefits derived from it, in language virtually identical to that of the '035 patent:

> The above method of the present invention uses less expensive potassium hydroxide that is easier to use compared with the conventional sodium hydride. Another advantage is that it is free from the worry of explosive accidents. It is safe and excellent for industrial use.

RX 1346; RX 1194.

FF E 7. Consequently, by December 7, 1981, when Tanabe filed its two Japanese N-alkylation applications, Tanabe was well aware that the prior commercial KOH/DMSO process had, some ten years earlier, solved the disadvantages of cost and danger of explosion ascribed to the '257 process.

FF E 8. The Tanabe KOH/DMSO process was material because it solved the disadvantages of the '257 process, because it used KOH, one of the bases of the '035 patent, on TZP, the same starting material as the '035 processes, with DMC, the alkylating agent of the '035 processes, and it was a "hydrous" process as complainants have applied that term to the processes of the '035 patent. See Kende Tr. 1387; Pachter Tr. 1536-37.

FF E 9. When Tanabe filed its U.S. Application for the '035 patent in December 1982, Tanabe asserted that it was the '035 base-solvent combination which solved these problems. RX 1194.

FF E 10. Tanabe intentionally withdrew its Japanese application for its KOH-DMSO process. Tanabe maintains that it did so because it wished to keep that process a trade secret. RX 1579.

FF E 11. In the reexamination of the '035 patent, Tanabe submitted to the examiner a copy of Tanabe's book Diltiazem From Birth to Today, which, on one page of the book, contains a brief, one-sentence reference to the secret potassium hydroxide-DMSO process. Information Disclosure Statement Under 37 C.F.R. § 1.555 and Notification of Litigation Under 37 C.F.R. § 1.565, List of References Cited by Patent Owner at 7 of 7, Ref. No. 65 of "Other References"

(CX 607); CX 638A.

FF E 12. The book Diltiazem From Birth to Today, is not listed in the reexamination certificate. CX 637.

FF E 13. No effort was made to point out the Tanabe KOH/DMSO process referred to at p. 33 of Diltiazem From Birth to Today. No effort was made to point out that the Tanabe KOH/DMSO process was "hydrous," as contrasted with the "strictly anhydrous" conditions of the '257 patent. The examiner was not told that diltiazem hydrochloride made by the Tanabe KOH/DMSO process was sold in the United States many years prior to the December 1981 critical date. CX 638.

FF E 14. There is no claim limitation in claim 1 of the '035 patent regarding the order of addition of the reagents. CX 1.

FF E 15. The sale in the United States, prior to the critical date, of diltiazem hydrochloride made using the Tanabe KOH/DMSO process is not described in the Tanabe book. CX 638.

FF E 16. Having only the book, which Tanabe asserted was not prior art, the examiner had no way of learning of the prior art sales.

FF E 17. The text of Diltiazem From Birth to Today, including cover, index, forwards and appendices, contains some 267 pages, (Production Nos. T1877-2143), and the single reference to the potassium hydroxide-DMSO process appears on page 33 of that text (Production No. T1933), as follows:

> They found that the reaction proceeds easily by the use of potassium carbonate and ethyl acetate in place of potassium hydroxide and dimethyl sulfoxide.

RX 1690.

FF E 18. There is nothing in any of Tanabe's submissions to the PTO which expressly called page 33 of Diltiazem From Birth to Today to the

attention of the examiner. CX 638A and 638B.

FF E 19. Diltiazem From Birth to Today was one of some 172 references in a September 1993 Information Disclosure Statement ("IDS"), and a November 1993 Supplemental IDS. RX1690 [RX 2193], RX 1691 [RX 2193].

FF E 20. There is no reference in Diltiazem From Birth to Today to the fact that the KOH/DMSO process was ever used commercially in the making of diltiazem hydrochloride for sale in the United States. RX 1690; Taylor Tr. 2770.

FF E 21. Tanabe submitted to the PTO declarations of patent experts, James Gambrell Esq. and Martin Adelman Esq., which referred generally to the process used by Tanabe which "differed from the '035 process" (Gambrell at ¶ 11) or "is not disclosed in" the '035 patent (Adelman at ¶ 9), but otherwise was not identified. Neither the Gambrell declaration nor the Adelman declaration identified the process as the commercial Tanabe KOH/DMSO process, or the fact that it was a hydrous process. RX 1560; RX 1660; CX 607.

FF E 22. Tanabe also apparently withheld the identity of its prior commercial process from its experts until after the reexamination certificate was issued. See, e.g., RX 4038C, page 15.

FF E 23. Complainants' expert, Dr. Baldwin, conceded that this process should have been disclosed to the PTO. RX 4038C, page 335.

FF E 24. Another of complainants experts, Dr. Liotta, testified on deposition that he considered the Tanabe KOH/DMSO process to be equivalent to the process of the 035 patent. Liotta Tr. 1708.

FF E 25. Tanabe had to be aware of the significance of the KOH/DMSO process as prior art at the time of the reexamination in light of the September 30, 1993 motion by the Fermion respondents for summary determination

of invalidity based on that process. See RX 2001C.

FF E 26. Although certain papers from this proceeding were submitted in the reexamination, Tanabe disclosed neither the KOH/DMSO process nor the Permion motion based on it to the PTO. See CX 638A, 638B.

FF E 27. Tanabe argued that "the '035 patent discloses the 'dramatic improvement' of its processes over those in the '257 patent," but did not tell the examiner that the Tanabe KOH/DMSO secret prior process had provided Tanabe with the same "dramatic improvement" and the same yield as the KOH/acetone process of the '035 patent. CX 638A (KOH-acetone yield 86.3%); RX 3327; Nakao Tr. 398-99 (KOH/DMSO yield 85%).

FF E 28. A Tanabe report from June 1981 states that "[i]t became clear that alkylation can take place in the same manner when KOH/DMSO is replaced with KOH-acetone in the reaction." RX 3361.

FF E 29. Another Tanabe report from 1981 states that "[n]ormally DMSO is used as a solvent, however, the reaction proceeds to the same degree (y. 70 - 86%) with acetone. Acetone is considered advantageous since the reaction fluid has a light coloring, and the collection and disposal of the solvent is simple." RX 3328.

FF E 30. Tanabe repeatedly argued that the solvent systems disclosed and claimed in the '035 patent were hydrous and directly contrary to the strictly anhydrous systems of the '257 patent, yet Tanabe did not tell the examiner that the secret prior process also was hydrous. CX 638A; RX 1658; RX 4038C; Kende Tr. 1386-87.

FF E 31. Tanabe also asserted that "[t]o [Dr. Krapcho] the aqueous processes of the '035 patent that resulted in a 90 percent yield were 'a total surprise' and 'violated all that [he] knew.'" Yet, Tanabe did not tell the

examiner that the prior Tanabe KOH/DMSO process was aqueous. CX 638A.

FF E 32. Tanabe argued that "the chemoselective alkylation of the processes of the '035 patent is critical to the industrial scale production of diltiazem," while failing to advise the examiner that the same chemoselective alkylation was possessed by its prior process for the "industrial scale production" of diltiazem hydrochloride, which was then sold in this country prior to the critical date. CX 638A.

FF E 33. Tanabe's counsel sent a draft declaration to James Gambrell, Esq., which stated that diltiazem manufactured by Tanabe in Japan by a trade secret process was sold or provided free of charge to MMD for the purposes of obtaining FDA approval, and inter alia, included the following paragraphs:

> 4. It is my opinion that the public use and on sale sections of 35 U.S.C. § 102(b) are limited by the terms "*in this country*", which is in the text of the statute. Therefore, the language of § 102(b) does not include the practice of a trade secret process abroad as prior art, since such a practice is not "*in this country*". In my opinion, this is true, even if the product from that process has been shipped to the United States.
>
> 5. For these reasons, it is my further opinion that the trade secret process used by Tanabe in Japan to manufacture diltiazem which was supplied to MMD, is not a public use or sale of the process "in this country," within the meaning of 35 U.S.C. § 102(b) and/or § 103.
> 6. Thus, it is my opinion that Tanabe's trade secret process is not prior art to United States Patent No. 4,438,035 under 35 U.S.C. § 102 and/or § 103.

RX 1694.

FF E 34. Gambrell revised his declaration, and changed the paragraphs quoted above to read as follows:

> 4. It is my opinion that the public use and on sale sections of 35 U.S.C. § 102(b) are limited by the statutory term "*in this country.*" Therefore, the language of § 102(b) does not include the practice of a process in foreign county (whether secret or otherwise) as prior art. However, this is not necessarily true if the product produced by the foreign process is used or sold in the United States without restriction. In re Caveney, 751 F.2d 671

(Fed. Cir. 1985).

5. It is my opinion that the process used by Tanabe in Japan to manufacture diltiazem which was supplied to MMD for the purpose of seeking FDA approval would not be a public use or sale of the process or its product within the meaning of 35 U.S.C. § 102(b) and or § 103 under the principles outlined in TP Laboratories v. Professional Positioners, Inc., 724 F.2d 765 [sic] (Fed. Cir.), cert. denied, 469 U.S. 826 (1984).

6. .....

RX-1694.

FF E 35. Gambrell revised his draft of the declaration. He modified but retained a paragraph stating his understanding that diltiazem was sold or provided free of charge for the purposes of obtaining FDA approval. However, he deleted, among other things, the citation to In re Caveney, and the sentence immediately preceding the citation. Thus, his declaration now stated that "the language of § 102(b) does not apply to the practice of a process in a foreign country (whether secret or otherwise); hence it cannot be prior art against a U.S. patent."

Therefore, his declaration contained a statement of the law that he and Tanabe counsel knew to be overly broad. Gambrell deleted the caveat (that he had written and sent to Tanabe's counsel) which had immediately followed, which stated that "[t]his is not necessarily true if the product produced by the foreign process is used or sold in the United States without restriction and claims covering the same product have been granted in a U.S. patent," with citation to Federal Circuit authority in In re Caveney. His declaration now left the erroneous impression that products manufactured overseas are outside the purview of section 102(b), regardless of whether their distribution in the United States was experimental or commercial. Facsimile of Jim Gambrell to Lori Gentile, dated Aug. 24, 1994 (8:51 a.m.)(marked with deletions and

additions). RX 1694.

FF E 36. A copy of the August 24 revision of his declaration was sent by facsimile to James B. Gambrell at the Regal Royale hotel in New York City, where he was staying in room 2312.

FF E 37. A final declaration was prepared, attached to a curriculum vitae, and executed by James B. Gambrell. The declaration was forwarded to counsel for complainants with a cover letter stating, inter alia, as follows:

> Please let me know if this satisfies your needs for submission to the Patent Office. As you can tell, I have changed it in some respects as I told Lori Gentile as much on Friday when I spoke with her.

RX 1694.

FF E 38. Complainants' counsel submitted the Gambrell declaration without mention of the controlling Federal Circuit authority, In re Caveney, or the original view of its expert. CX 638.

FF E 39. The declaration of Martin J. Adelman states that it is his understanding that Tanabe sold or provided free of charge the diltiazem made by the Tanabe KOH/DMSO process from approximately 1976 to approximately 1983. CX 607.

B. Pattern of Misconduct

FF E 40. Tanabe distinguished the '035 process from that of the '257 patent on the grounds that the processes of the '035 patent were "aqueous, which is diametrically opposed to the anhydrous systems of the '257 patent " CX 638A; RX 2193 [RX 2205].

FF E 41. Tanabe also represented that Dr. Krapcho used only anhydrous processes, while concealing from the examiner the fact that Krapcho used alkali metal hydroxides as bases in combination with aprotic solvents, a system which complainants here assert is not anhydrous. CX 638A.

FF E 42. For example, Tanabe twice told the PTO that the '967 patent, which it referred to as "the Krapcho reference cited by Dr. Taylor" disclosed N-alkylations of benzothiazepines using "anhydrous" conditions; yet complainants here assert that the reference also discloses aqueous conditions. CX 638A; RX 2193 [RX 3205].

FF E 43. The '967 patent discloses the use of alkali metal hydroxides to perform the N-alkylation of a benzothiazepinone. Kende Tr. 1429.

FF E 44. The '967 patent conditions are "hydrous" conditions, as complainants use that term. Kende Tr. 1428-31; Taylor Tr. 2776; RX 4038C; RX 3632; RX 3673; RX 3669. Tanabe effectively concealed from the PTO the other Krapcho patents disclosing the use of "hydrous" conditions. CX 638A.

FF E 45. DMSO is an aprotic, water-miscible solvent. Kende Tr. 1397.

FF E 46. British Patent No. 1,106,119 ("the British '119 patent") published 1968, discloses alkali metal hydroxides generally, including potassium hydroxide, and also discloses the use of acetone-water mixtures as the solvent. RX 1136 [RX 2136, RX 3686]; RPX 1069; RPX 1154 [RX 2128, RX 3844].

FF E 47. The '967 patent discloses and claims the drug "thiazesim," a "parent" of diltiazem. RX 1249; Kende Tr. 1436-37.

FF E 48. The '967 patent which claims thiazesim also discloses that alkali metal hydroxides, a class which includes potassium hydroxide, can be used in the N-alkylation of benzothizepines. RX 1134.

FF E 49. Tanabe's application for its '257 patent, which claims diltiazem, expressly acknowledges thiazesim as prior art. RX 1193.

FF E 50. Claims to an N-alkylation process which were presented in the application for the '257 patent were rejected by the U.S. PTO over, inter

alia, the Krapcho '967 patent, and then cancelled by Tanabe. RX 1252 [RX 2026, RX 3345, RX 3863].

FF E 51. In March 1983, while the application for the '035 patent was pending, the European Patent Office identified the '257 patent and the '967 patent as relevant prior art to the EPO counterpart of the '035 patent. RX 1134; RX 1140; RX 1095.

FF E 52. Tanabe did not at that time, or at any time during the initial prosecution of the '035 patent, cite the Krapcho '967 patent in the PTO. RX 1195 [RX 3118].

FF E 53. The European Patent Office rejected the European application as unpatentable over the '257 patent in view of the Krapcho '967 patent. The Israeli and the Finnish Patent Offices also rejected the respective '035 counterparts as unpatentable over the Krapcho '967 patent. RX 1096 [RX 1122, RX 1344, Rx 3225], RX 1098 [RX 1123] and RX 1100 [RX 3232].

FF E 54. Inasmuch as the Tanabe patent department was not knowledgeable about the disclosure requirements of the U.S. Patent and Trademark Office, it was the policy of Tanabe to submit all potentially relevant information to their U.S. attorneys, so that the U.S. attorneys could determine what should be disclosed. RX 1586C.

FF E 55. Tanabe did not submit the '967 patent to its U.S. attorneys. RX 1685C.

FF E 56. A Tanabe witness and inventor listed on the '035 patent, Shoji Nakajima, was unable to explain why Tanabe did not follow its general policy with respect to the '967 patent. RX 1586C.

FF E 57. Another Tanabe witness, Hisayoshi Hashimoto, testified that Tanabe did not cite the '967 patent to the PTO. He testified that Tanabe

believed the '257 patent to be more relevant because it disclosed a process for the manufacture of diltiazem. RX 1583.

FF E 58. An inference can be drawn that Tanabe knew that the '967 patent was material to its '035 patent application, and intentionally withheld it.

Supposed Side-Reactions

FF E 59. The examiner stated as follows:

> The arguments concerning the possibility of side reactions . . . are not seen as having great weight in this particular case one way or another. Nor are the arguments concerning the use of DMC·HCl.

RX 1653.

FF E 60. Tanabe made at least two misleading arguments regarding side reactions. They were the arguments that ring cleavage or the retro-Michael reaction of TZP might take place under Pachter ('035 conditions). Taylor Tr. 2723-24; Pachter Tr. 1519-20.

Ring Cleavage

FF E 61. Dr. Baldwin in his declaration submitted to the examiner, stated at paragraph 47, as follows:

> In addition, the Nagarajan reference suggested that ring cleavage was a distinct possibility under Pachter base/solvent conditions of seven-membered oxazepines (see Experimental,p. 245(d)). This too would have taught away from the processes of the '035 patent.

RX 1658.

FF E 62. In the "Conclusions" section of his declaration, Dr. Baldwin stated in part as follows:

> Fifth, British '119 and Nagarajan, viewed together, also taught the distinct possibility of ring cleavage in using a Pachter-type base/solvent system, and for this reason, would have suggested that this system be avoided in the N-alkylation reactions of the '035 patent. Indeed, when a substrate was N-alkylated which was not highly activated, the Pachter system was changed to a system

similar to that of the '257 patent.

RX 1658.

FF E 63. The passage referred to by Dr. Baldwin (at ¶ 47 of his declaration) as occurring at p. 245(d) of Nagarajan does not in fact refer to Pachter base-solvent conditions, but rather to '257-type conditions of sodium amide and DMF. Kende Tr. 1369; Taylor Tr. 2720-21; 2725.

FF E 64. Complainants' attorneys submitted a letter to the PTO, in which they attempted to "amend" Dr. Baldwin's declaration, changing "Pachter base-solvent combination" to "Pachter-like base solvent combination" and changing the page reference to page 244(iii). RX 1693.

FF E 65. However, Dr. Baldwin never submitted an amended declaration to the United States Patent Office. CX 638A, 638B; Coggio Tr. 2727-28.

FF E 66. The conditions on page 244(iii) are not Pachter-like conditions either. They are not potassium hydroxide in acetone, but sodium hydroxide in dioxane, which is one of the solvents of the '257 patent. Kende Tr. 1372, Taylor Tr. 2595.

FF E 67. In fact, as Dr. Kende admitted, the ring cleavage described by Nagarajan was a reaction which one would never see with TZP. There is no connection with TZP. Kende Tr. 1367-68, 1374-5.

FF E 68. Moreover, the Nagarajan ring opening (which one would never see with TZP) occurs under '257 conditions but not under '035 conditions. Kende Tr. 1369.

FF E 69. Nagarajan expressly reported that ring cleavage occurred only with nitro-substituted N-aryl amides. Taylor 2712; Kende 1369-70; RX 1145 [RX 2155, RX 3820]; RPX 1131.

FF E 70. Moreover, Nagarajan expressly states that ring cleavage is

observed under '257 conditions, but not under Pachter-type conditions. RX 1145 [RX 2155, RX 3820]; Kende 1369-70; Taylor Tr. 2726-27.

FF E 71. Dr. Kende testified that he would not have drawn any connection between the ring cleavage reported in Nagarajan's nitro-substituted compounds under '257 conditions and the possibility of ring cleavage of TZP under '035 conditions. Kende Tr. 1367-68.

FF E 72. Nagarajan cannot be fairly read to suggest that ring cleavage was a distinct possibility under Pachter base-solvent conditions. Taylor Tr. 2728.

FF E 73. It was misleading for Dr. Baldwin to suggest to the examiner that Pachter base-solvent conditions or Pachter-type conditions led to ring cleavage. Taylor Tr. 2723, 2731.

Retro-Michael

FF E 74. Both the Kende and Baldwin declarations suggest that the possibility of retro-Michael reaction of TZP might deter chemists from attempting the N-alkylation under Pachter/'035 conditions. RX 1329 [RX 1189, RX 3112, RX 3132]; RX 1658.

FF E 75. Dr. Kende testified that an article by Mills and Whitworth suggested that retro-Michael reaction might take place with TZP. Kende Tr. 1183-1185.

FF E 76. However, Tanabe scientists published in 1970 their experiments showing that TZP did not undergo retro-Michael reaction under the same conditions which Mills and Whitworth suggested that other benzothiazepinones might undergo retro-Michael reaction. Kende Tr. 1450-1454.

FF E 77. Tanabe should have known from its own 1970 publication that there was no retro-Michael reaction of TZP under the conditions of Mills and

Whitworth, and should not have raised the possibility of such reaction as an argument to the examiner.

VI. IMPORTATION AND SALE

FF F 1. Respondent Abic manufactures diltiazem HCl in Israel and supplies it to various generic drug manufacturing companies through its subsidiary, respondent Plantex, for importation into and sale in the United States. Abic Proposed Finding of Fact 15; Complaint, ¶¶ 15-16, pp. 4-5, Exh. E.

FF F 2. Respondent Plantex is a New Jersey corporation, and a subsidiary of respondent Abic. Plantex imports diltiazem HCl and other products produced by Abic. Plantex sells in the United States the diltiazem that it imports from Abic. Plantex's Resp. to Comp. ¶22A; Abic Proposed Finding of Fact 15.

FF F 3. Respondent Fermion manufactures diltiazem HCl in Finland and supplies bulk diltiazem to respondents Interchem, Copley and Rhone-Poulenc Rorer for importation and sale in the United States. The Fermion Respondents' Prehearing Statement at 5-6.

FF F 4. Respondents Copley purchases in the United States bulk diltiazem HCl that is produced abroad by respondent Fermion and converts the bulk diltiazem into pharmaceutically acceptable forms suitable for human dosage. The Fermion Respondents Prehearing Statement at 6.

FF F 5. Respondent Interchem imports into the United States bulk diltiazem HCl produced by respondent Fermion and acts as Fermion's exclusive United States sales representative. See Complaint, ¶ 20, p. 6; Exh. K.

FF F 6. Rhone-Poulenc Rorer imports diltiazem HCl into the United States obtained from respondent Fermion and converts the bulk diltiazem into pharmaceutically acceptable forms suitable for human dosage, and sells

diltiazem in the United States. The Fermion Respondents Prehearing Statement at 5-6.

FF F 7. Profarmaco manufactures bulk diltiazem in Italy for importation into and sale in the United States. Russolo Tr. 1914. Profarmaco was purchased by an American company, Cambridge Corporation, shortly before the hearing. Mylan Profarmaco's Proposed Finding of Fact 6; Russolo Tr. 1913.

FF F 8. The Mylan respondents (Mylan Pharmaceuticals and Mylan Laboratories) convert the bulk diltiazem HCl manufactured by Profarmaco into pharmaceutically acceptable forms for sale in the United States. Mylan/Profarmaco's Proposed Finding of Fact 6. Complaint, ¶ 18, p. 6; Exh. D.

FF F 9. Gyma is the exclusive United States distributor for Profarmaco since January 1985. Gyma sells imported bulk diltiazem HCl to respondent Mylan. Russolo Dep. Tr. 111; Complaint, ¶ 21, pp. 6-7.

VII. DOMESTIC INDUSTRY

FF G 1. The parties have entered into stipulations of fact regarding the domestic industry. CX 728; Proposed Findings of Fact and Conclusions of Law of the Commission Investigative Staff at 122.

FF G 2. MMD's Kansas City facilities occupy over C square feet. CX 728.

FF G 3. Currently, MMD has over C square feet of its Kansas City facilities dedicated to Cardizem products made from bulk diltiazem supplied by Tanabe. Fogel Tr. 77; CX 527.

FF G 4. Hypothetically, if Tanabe changed its current process for manufacturing bulk diltiazem to Tanabe's trade secret KOH/DMSO process as practiced by Tanabe for production of diltiazem prior to 1984, or to any other process, provided that such process was appropriately qualified by MMD with

the relevant regulatory authorities, MMD's manufacturing and warehousing facilities in Kansas City which are devoted to the production and storage of diltiazem products could be used, without substantial modification, to produce and store diltiazem products from bulk diltiazem manufactured by Tanabe under the KOH/DMSO process or other process. CX 728.

FF G 5. MMD has invested C million in plant and equipment at Roche Products, Inc. ("RPI") in Puerto Rico where Cardizem products are produced. CX 728.

FF G 6. Hypothetically, if Tanabe changed its current process for manufacturing bulk diltiazem to Tanabe's trade secret KOH/DMSO process as practiced by Tanabe for production of diltiazem prior to 1984, or to any other process, provided that such process was appropriately qualified by MMD with the relevant regulatory authorities, the plant and equipment at RPI in Puerto Rico in which MMD has invested could be used, without substantial modification, to produce and store diltiazem products from bulk diltiazem manufactured by Tanabe under the KOH/DMSO process or other process. CX 728.

FF G 7. MMD leases C square feet from RPI in Puerto Rico; approximately C square feet are used for the production of Cardizem products. CX 728.

FF G 8. Hypothetically, if Tanabe changed its current process for manufacturing bulk diltiazem to Tanabe's trade secret KOH/DMSO process as practiced by Tanabe for production of diltiazem prior to 1984, or to any other process, provided that such process was appropriately qualified by MMD and the relevant regulatory authorities, the floor space which MMD leases from RPI in Puerto Rico for the production of Cardizem products could be used, without substantial modification, to produce and store diltiazem products from bulk

diltiazem manufactured by Tanabe under the KOH/DMSO process or other process. CX 728.

FF G 9. MMD leases C direct labor employees from RPI; C of these individuals are working on the production of Cardizem CD/SR. CX 728.

FF G 10. Hypothetically, if Tanabe changed its current process for manufacturing bulk diltiazem to Tanabe's trade secret KOH/DMSO process as practiced by Tanabe for production of diltiazem prior to 1984, or to any other process, provided that such process was appropriately qualified by MMD and the relevant regulatory authorities, the direct labor employees who work on the production of Cardizem CD/SR which MMD leases from RPI in Puerto Rico could, without any substantial retraining or modification of their activities, work on the production of Cardizem CD/SR from diltiazem manufactured by Tanabe under the KOH/DMSO process or other process. CX 728.

FF G 11. In 1992, MMD employed approximately C full-time associates in Kansas City, of which approximately C were devoted full-time to the production of Cardizem products. CX 728.

FF G 12. Hypothetically, if Tanabe changed its current process for manufacturing bulk diltiazem to Tanabe's trade secret KOH/DMSO process as practiced by Tanabe for production of diltiazem prior to 1984, or to any other process, provided that such process was appropriately qualified by MMD and the relevant regulatory authorities, the full time associates employed at MMD's Kansas facility who are devoted to full-time production of Cardizem products could, without any substantial retraining or modification of their activities, work on the production of Cardizem products from bulk diltiazem manufactured by Tanabe under the KOH/DMSO process or other process. CX 728.

FF G 13. Hypothetically, if Tanabe changed its current process for

manufacturing bulk diltiazem to Tanabe's trade secret KOH/DMSO process as practiced by Tanabe for the production od diltiazem prior to 1984, or to any other process, provided that such process was appropriately qualified by MMD and the relevant regulatory authorities, the procedures for manufacturing Cardizem CD could be used, without substantial modification, for the production of Cardizem CD from bulk diltiazem manufactured by Tanabe under the KOH/DMSO or other process. CX 728.

FF G 14. Diltiazem tablets are manufactured by MMD according to the procedures set forth in CX 553C. CX 728.

FF G 15. Cardizem SR is manufactured by MMD in conjunction with Elan in Ireland according to the procedures set forth in CX 555C. CX 728.

FF G 16. MMD is a licensee of Elan under U.S. Patent No. C which is directed to finished dosage forms of diltiazem. CX 728.

FF G 17. Hypothetically, if Tanabe changed its current process for manufacturing bulk diltiazem to Tanabe's trade secret KOH/DMSO process as practiced by Tanabe for production of diltiazem prior to 1984, or to any other process, provided that such process was appropriately qualified by Elan and the relevant regulatory authorities, the procedures for manufacturing Cardizem SR in conjunction with Elan in Ireland could be used, without substantial modification, for the production of Cardizem SR from bulk diltiazem manufactured by Tanabe under the KOH/DMSO process or other process. CX 728.

FF G 18. Cardizem IV is manufactured for MMD by Sanofi Winthrop in the United States according to the process set forth in the NDS (CX 556C). CX 728.

FF G 19. Hypothetically, if Tanabe changed its current process for manufacturing bulk diltiazem to Tanabe's trade secret KOH/DMSO process as

practiced by Tanabe for production of diltiazem prior to 1984, or to any other process, provided that such process was appropriately qualified by Sanofi Winthrop and the relevant regulatory authorities, the procedures for manufacturing Cardizem IV in conjunction with Sanofi Winthrop in the United States could be used, without substantial modification, for the production of Cardizem IV from bulk diltiazem manufactured by Tanabe under the KOH/DMSO process or other process. CX 728.

FF G 20. On October 1, 1976, Tanabe and MMD entered into an agreement entitled Option and License Agreement. CX 728.

FF G 21. Hypothetically, it would be possible to manufacture Cardizem product formulations from bulk diltiazem made by a process other than the '035 process, given appropriate quality controls, and assurances, quantity assurances, and subject to appropriate qualification by MMD, the bulk manufacturer, and the relevant regulatory authorities. CX 728.

FF G 22. MMD does not manufacture bulk diltiazem by any process. CX 728.

FF G 23. Neither MMD nor Tanabe practices the '035 patent in the United States. CX 728.

FF G 24. Tanabe has not licensed MMD or anyone to practice the '035 patent in the United States. CX 728.

FF G 25. The claimed invention of the '035 patent was not developed in the United States. CX 728.

FF G 26. MMD's Cardizem products are made from imported bulk diltiazem that is manufactured by Tanabe at its facilities in Onoda, Japan. Fogel Tr. 68; Peterson Tr. 126; Nakao Tr. 357-358.

FF G 27. An exclusive supply agreement exists between Tanabe and MMD

whereby Tanabe can only supply bulk diltiazem to MMD and MMD can only purchase bulk diltiazem from Tanabe. Klett 240-241; CX 467; CX 728.

FF G 28. Tanabe and MMD have had a long-term exclusive supply relationship regarding bulk diltiazem. Klett Tr. 241; CX 467.

FF G 29. Diltiazem is a very short-acting product. If bulk diltiazem is administered to a patient, it would not be a pharmacologically effective because the human body would consume it too quickly. Therefore, bulk diltiazem must be formulated into dosage forms for human consumption before it can be effectively administered to patients. Kelly Tr. 164-165.

FF G 30. Cardizem products constitutes MMD's largest product line. Fogel Tr. 68.

FF G 31. Cardizem products are channel blockers which inhibit the influx of calcium into a cell. Kelly Tr. 165-166.

FF G 32. Cardizem products are taken by people who have angina (restricted blood flow in the coronary arteries) and hypertension (high blood pressure). Fogel Tr. 108; Kelly Tr. 165-167.

FF G 33. MMD's Cardizem products include Cardizem CD, Cardizem tablets, Cardizem SR and Cardizem IV which are different dosage forms of Cardizem. Fogel Tr. 68, 70-71.

FF G 34. Cardizem CD is MMD's most significant diltiazem preparation. Fogel Tr. 70.

FF G 35. A company may exploit more than one patent at a time. Burrows Tr. 2360.

FF G 36. Cardizem CD is produced in Kansas City and Puerto Rico. Fogel Tr. 69.

FF G 37. Cardizem tablets are produced in Kansas City. Fogel Tr. 70.

FF G 38. Pursuant to contractual agreements between MMD and Tanabe, MMD has been receiving bulk diltiazem from Tanabe since the late 1970's. Fogel Tr. 71-72; CX 728.

FF G 39. MMD and Tanabe have developed a relationship over the years throughout which Tanabe has consistently supplied MMD with high quality product in the quantities necessary for MMD to maintain a supply of product in the marketplace. Fogel Tr. 72; Peterson Tr. 123.

FF G 40. After MMD receives Tanabe's imported bulk diltiazem, it is sampled, tested, and released to manufacturing upon meeting specification criteria. Fogel Tr. 68-69.

FF G 41. Because of FDA requirements, MMD's processes and equipment are carefully qualified to work in combination with Tanabe's formulated bulk diltiazem. Fogel Tr. 72.

FF G 42. MMD conducts research and development related to its Cardizem products in order to comply with FDA requirements. Klett Tr. 247-248.

FF G 43. MMD cannot immediately purchase bulk diltiazem from a source other than Tanabe and produce its Cardizem preparations. Fogel Tr. 73.

FF G 44. Any change in the process for making the bulk diltiazem would require evaluation, qualification, validation, and stability tests by MMD in order to comply with FDA requirements. Fogel Tr. 72-74; Peterson Tr. 122.

FF G 45. If the process to make bulk diltiazem used in MMD's Cardizem preparations were changed, MMD would have to amend its NDA, submit a new Drug Master File to the FDA, and wait for approval, an overall process that would take somewhere between one and a half and four years. Fogel Tr. 74; Peterson Tr. 122-123.

FF G 46. Changes in Tanabe's process for manufacturing bulk diltiazem

could affect MMD's final formulated Cardizem product. Tests would be necessary in order to verify any changes. Peterson Tr. 117-118, 136-137.

FF G 47. MMD could, however, change its supplier of bulk diltiazem if it made financial sense and if it did not violate an outstanding contract or supply agreement. Fogel Tr. 109.

FF G 48. From 1984-92, MMD spent over C million on research and development including FDA approval, clinical trials, formulation research, and research and development to support the marketing for its Cardizem products in the United States. CX 728C.

FF G 49. The pharmaceutical industry is a research and development intensive business. In addition to the basic research required to develop and identify new chemical entities, pharmaceutical companies must also engage in research and development to meet FDA requirements. Klett Tr. 247-49; CX 535; CX 541.

FF G 50. Without such research and development, a pharmaceutical company could not commercialize and sell its products in the United States. Thus, in that context, MMD's research and development relating to its finished Cardizem formulations is required and is critical to the exploitation of the products manufactured according to the processes of the '035 patent. Klett Tr. 247-48; Burrows Tr. 2349-50.

FF G 51. Unlike other businesses, there are certain distinctive characteristics of the marketing and promotional activities in the pharmaceutical businesses. In this regard, MMD's product support and marketing activities have significant educational aspects. In addition, there are technical aspects of MMD's marketing and promotional activities. For example, claims made regarding MMD's Cardizem products must be supported by

data from various research and development activities, including clinical and comparative studies. Klett Tr. 250-51, 254; Kelly Tr. 172.

FF G 52. In 1991, MMD spent C million on research and development. CX 728C.

FF G 53. In 1992, MMD spent approximately C million on research and development. CX 728C.

FF G 54. In 1991 and 1992, MMD spent over C million in material costs alone for research and development of new formulations of diltiazem. CX 728C.

FF G 55. MMD's Research and Development Department consists of several groups: C

C

C CX 496C; CX 649C.

FF G 56. The C is further segmented into five functional areas: C

C

C These C conduct a wide variety of research and development work, including, inter alia, toxological, carcinogenic, dose range, and pharmacokinetic studies in animals; drug-drug and food interactions; bioavailability, bioequivalency and stability studies; the manufacture of clinical supplies and dosages for early phase studies; projects devoted to the transition from clinical supply manufacture to large scale manufacture; analytical chemistry support and support to analyze the scientific data collected throughout the drug development process. CX 496C.

FF G 57. The C is responsible for the research and development activities relating to FDA-required clinical testing from development phase 1 through phase 3. In phase 1, a drug is first introduced

into healthy human volunteers. During phase 2, the drug is introduced to small well-controlled patient populations. In phase 3, the clinical studies are expanded to larger patient populations. At the end of phase 3, the drug is submitted to the FDA for approval. CX 728C; CX 649C.

FF G 58. The C is responsible for assuring that the research, development, manufacturing, testing, marketing and distribution of MMD's drugs all comply with governmental regulations. This group interprets and advises MMD on existing and future governmental regulations and verifies and inspects operational programs in light of such regulations and MMD's standard operating procedures. CX 496C.

FF G 59. The C is responsible for late phase research of drug products. Late phase research includes those products for which FDA approval is pending (phase 3B) and for those products which have already been approved (phase 4). CX 728C; CX 496C; CX 649C.

FF G 60. MMD has conducted studies to support the filing of its various New Drug Applications (NDA) with the Food and Drug Administration for Cardizem CD and SR capsules, Cardizem tablets, and Cardizem injectable. CX 500C.

FF G 61. The C at MMD is responsible for research and development activities relating to FDA-required clinical testing from development phase 1 through phase 3. CX 728C.

FF G 62. MMD submitted its NDA for Cardizem CD capsules for the treatment of hypertension in February 1989, and the NDA was approved in December 1990. CX 728C.

FF G 63. The formulation work on Cardizem CD capsules began in 1985 and continued until MMD submitted its NDA for Cardizem CD capsules for hypertension in February 1989. Fogel Tr. 74-76; CX 728C.

FF G 64. From 1985 to 1989, MMD employed approximately C research associates full-time on the development of Cardizem CD capsules; several additional MMD associates devoted a portion of their time to such activities. CX 728C.

FF G 65. MMD spent C million to obtain FDA approval for Cardizem CD capsules for the treatment of hypertension. CX 728C.

FF G 66. As part of the research for its NDA for Cardizem CD capsules for hypertension, MMD conducted three large multi-center clinical trials involving over 460 patients. CX 728C.

FF G 67. The clinical trials for the NDA for Cardizem CD capsules for hypertension included a pilot study, a dose response trial, and a dose titration trial. CX 728C; CX 649C; CX 509.

FF G 68. The studies for MMD's NDA on Cardizem CD for hypertension monitored approximately 50 patients over a two-week period. The dose response trial involved approximately 220 patients at 16-20 sites over a six-month period. The dose titration trial involved approximately 120 patients at 8-10 sites throughout the United States. CX 728C.

FF G 69. The clinical trials conducted by MMD to support its NDA for Cardizem CD capsules for hypertension involved approximately C MMD associates on a full time basis and C on a part-time basis. CX 728C.

FF G 70. The data from the three clinical trials for MMD's NDA on Cardizem CD for hypertension, comprising approximately 100 volumes, were submitted to the NDA in February 1989. This NDA was approved in December 1990. CX 728C.

FF G 71. In January 1992, MMD submitted its NDA for Cardizem CD for the treatment of angina. This NDA was approved in September 1992. CX 728C.

FF G 72. MMD expended C million to obtain FDA approval for Cardizem CD capsules in the treatment of angina. CX 728C.

FF G 73. For its NDA on Cardizem CD for angina, MMD conducted two large multi-center clinical trials, a dose response study and a clinical evaluation of Cardizem CD in patients receiving concomitant anti-angina therapy. CX 728C; CX 649C.

FF G 74. The clinical trials for the NDA on Cardizem CD for angina were conducted at 35-40 sites across the United States, involving 350-400 patients at a cost of C million. CX 728C.

FF G 75. Approximately C MMD associates worked full time on the clinical trials to support the NDA for Cardizem CD for angina and numerous other MMD associates were involved on a part-time basis. CX 728C.

FF G 76. MMD also conducted extensive research and development at significant cost to support its NDA for Cardizem injectables. Additional Cardizem injectable research and development included the development of a lyophilized infusion package and certain drug compatibility studies. CX 495.

FF G 77. There is continuing interaction between MMD and the FDA relating to MMD's Cardizem products. CX 728C; CX 649C.

FF G 78. Recently, MMD initiated a study comparing C with Cardizem CD for the treatment of hypertension. CX 728.

FF G 79. The clinical trials for the C diltiazem study will cost MMD over C per patient and involve C patients with hypertension. CX 728C.

FF G 80. MMD is also considering a similar study comparing the use of C with Cardizem CD capsules in the treatment of angina. This study will involve additional expenditures by MMD. CX 728C.

FF G 81. MMD will be making further substantial investments in comparing its Cardizem products to other drugs used in the treatment of various cardiovascular conditions. This study will involve both internal and external costs. Approximately C MMD associates will be involved full time in this study. The clinical trials will cost MMD approximately C per patient and approximately 100 patients will be included. In addition, approximately 80 patients will be included at a higher per patient cost. CX 649C.

FF G 82. MMD is conducting research toward the C C of Cardizem. MMD has expended over C million in material costs alone for this research in both 1991 and 1992. Fogel Tr. 76; CX 728C.

FF G 83. During 1989-90, MMD conducted research on a C product containing diltiazem C . CX 728.

FF G 84. During 1989-90, MMD also conducted research on a C C CX 728C.

FF G 85. MMD is currently conducting research on formulating a C C of Cardizem. CX 728C.

FF G 86. MMD's research and development on Tanabe's diltiazem has led to the development of Cardizem CD and Cardizem SR. Fogel Tr. 75-76.

FF G 87. MMD provides extensive marketing and promotion related to its Cardizem product line through a trained sales force which includes comparative test studies, product support, and educational information. Kelly Tr. 166-167, 173-174, 177; Klett Tr. 250; CX 728.

FF G 88. None of MMD's marketing efforts expressly refer to the '035 patent. Kelly Tr. 199-200; CX 728 at ¶ 41, 49.

FF G 89. The articles protected by the '035 patent are the final dosage

forms of Cardizem produced by MMD in the United States. See Klett Tr. 239-240.

FF G 90. A nexus exists between the bulk diltiazem produced by Tanabe according to the '035 patent in Japan and MMD's activities related to its Cardizem products in the United States. See Klett Tr. 239-241.

FF G 91. A rough approximation of a value added analysis resulted in a calculation of over C . Klett Tr. 255-256, 261-262; CPX 12, 13.

FF G 92. From an economic perspective, a domestic industry exists in the United States with respect to the '035 patent. See Klett Tr. 236-237.

FF G 93. A domestic industry exists even though claim 1 of the '035 patent does not cover the subsequent step of acetylating N-alkylated TZP to produce diltiazem. See Klett Tr. 262-263.

FF G 94. Tanabe's DMF relating to its current process for manufacturing bulk diltiazem HCl was filed with the FDA on July 7, 1993. Nakao Tr. 371; CX 726.

FF G 95. Complainants currently practice the process disclosed in Tanabe's 1993 DMF (CX 726) to manufacture diltiazem HCl which consists of the following: C

C

C Peterson Tr. 115-117, 124; Nakao 366-367, 373; CX 726, 727; CPX 20.

FF G 96. Tanabe's DMF to manufacture bulk diltiazem describes the N-alkylation process and the acetylation process as C

C . Nakao Tr. 427-430; Kende Tr. 496; CX 726; CPX 20.

FF G 97. Tanabe's N-alkylation step to convert TZP into N-alkylated TZP involves C

C Nakao Tr. 428; CX 726.

FF G 98. Under Tanabe's process, a C

C

C

C Nakao Tr. 429.

FF G 99. Tanabe's acetylation step to convert N-alkylated TZP into diltiazem HCl consists of C

C Nakao Tr. 428; CX 726.

FF G 100. If Tanabe were given only the part of the DMF relating to the N-alkylation step (pp. 41-43), and were not given the part of the DMF corresponding to the acetylation step (pp. 44-45), Tanabe would not know how to carry out the acetylation step. Nakao Tr. 429-450.

FF G 101. Tanabe has not changed its current base solvent combination C since 1984. Peterson Tr. 116, 121; Nakao Tr. 369.

FF G 102. In 1993 Tanabe modified its process for manufacturing bulk diltiazem (and thus submitted a new DMF to the FDA) by C

C

C . Peterson Tr. 159; Nakao 379-380.

CONCLUSIONS OF LAW

1. The United States International Trade Commission has jurisdiction over the parties and the subject matter of this investigation. Op. at 5.

2. Claim 1 of the '035 patent is invalid for obviousness. Op. at 119.

3. The '035 patent is unenforceable due to inequitable conduct during the reexamination proceedings at the PTO. Op. at 133-134.

4. Complainants have failed to prove that any of the respondents infringe the '035 patent. Op. at 56-57, 68, 73-74.

5. Respondents have imported, sold for importation or sold within the United States after importation products made by the accused processes. Op. at 134.

6. Complainants have established the existence of a domestic industry. Op. at 146.

7. It has not been established that a violation of section 337 has occurred in the importation, sale for importation or sale within the United States after importation of certain diltiazem hydrochloride. Op. at 334.

Based on the foregoing opinion, findings of fact, conclusions of law, the evidence, and the record as a whole, and having considered all pleadings and arguments as well as proposed findings of fact and conclusions of law, it is the Administrative Law Judge's INITIAL DETERMINATION ("ID") that no violation of § 337 exists in the importation of certain diltiazem hydrochloride and diltiazem preparations, or in their sale, by reason of infringement of claim 1 of U.S. Letters Patent No. 4,438,035.

The Administrative Law Judge hereby CERTIFIES to the Commission this ID, together with the record of the hearing in this investigation consisting of the following:

1. The transcript of the hearing, with appropriate corrections as may hereafter be ordered by the Administrative Law Judge; and further

2. The exhibits accepted into evidence in this investigation as listed in the attached exhibit lists.

In accordance with Commission Interim Rule 210.44(b), all material found to be confidential by the Administrative Law Judge under Rule 210.6 is to be given in camera treatment.

The Secretary shall serve a public version of this ID upon all parties of record and the confidential version upon counsel who are signatories to the protective order issued by the Administrative Law Judge in this investigation, and the Commission Investigative Attorney. To expedite service of the public version, counsel are hereby ordered to serve on the Administrative Law Judge by no later than February 10, 1995, a copy of this ID with those sections considered by the party to be confidential bracketed in red.

This ID shall become the determination of the Commission 45 days after its date of service unless the Commission within those 45 days shall have ordered review of this ID, or certain issues herein, pursuant to Commission Interim Rule 210.54(b) or 210.55.

Sidney Harris
Administrative Law Judge

Issued: February 1, 1995