In the Matter of

CERTAIN CRYSTALLINE CEFADROXIL MONOHYDRATE

Investigation No. 337–TA–293
Limited Exclusion Order
(Commission Decision of
March 15, 1990)

USITC PUBLICATION 2391

JUNE 1991

United States International Trade Commission
Washington, DC 20436

UNITED STATES INTERNATIONAL TRADE COMMISSION

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United States International Trade Commission
Washington, DC 20436

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

In the Matter of	)	
CERTAIN CRYSTALLINE CEFADROXIL MONOHYDRATE	)	Investigation No. 337-TA-293

NOTICE OF ISSUANCE OF A LIMITED EXCLUSION ORDER AND CEASE AND DESIST ORDERS

AGENCY: U.S. International Trade Commission.

ACTION: Notice.

SUMMARY: Notice is hereby given that the Commission has issued a limited exclusion order and three cease and desist orders in the above-captioned investigation.

FOR FURTHER INFORMATION CONTACT: Marc A. Bernstein, Office of the General Counsel, U.S. International Trade Commission, telephone 202-252-1087.

SUPPLEMENTARY INFORMATION: The authority for the Commission's determination is contained in section 337 of the Tariff Act of 1930 (19 U.S.C. § 1337), as amended by the Omnibus Trade and Competitiveness Act of 1988, Pub. L. 100-418 (Aug. 23, 1988), and in sections 210.56 and 210.58 of the Commission's Interim Rules of Practice and Procedure (19 C.F.R. §§ 210.56, 210.58).

On February 1, 1989, Bristol-Myers Company (since renamed Bristol-Myers Squibb Company) ("Bristol") filed a complaint with the Commission alleging violations of section 337 in the importation and sale of certain crystalline cefadroxil monohydrate. The complaint alleged infringement of claim 1 of U.S. Letters Patent 4,504,657 ("the '657 patent") owned by Bristol.

The Commission instituted an investigation into the allegations of Bristol's complaint and published a notice of investigation in the Federal Register. 54 F.R. 10740 (March 15, 1989). The notice named the following respondents: (1) Biocraft Laboratories, Inc. of Elmwood Park, N.J.; (2) Gema, S.A. of Barcelona, Spain; (3) Kalipharma, Inc. of Elizabeth, N.J.; (4) Purepac Pharmaceutical Co. of Elizabeth, N.J.; (5) Istituto Biochimico Italiano Industria Giovanni Lorenzini S.p.A. of Milan, Italy; and (6) Institut Biochimique, S.A. of Massagno, Switzerland.

On December 15, 1989, the presiding administrative law judge (ALJ) issued an initial determination (ID) finding no violation of section 337 in this investigation. On January 25, 1990, the Commission issued a notice of a decision to review the ID's findings and conclusions that the '657 patent

is invalid for obviousness under 35 U.S.C. § 103. The Commission determined not to review the remainder of the ID, except for two sentences that it determined to strike. 55 F.R. 3282 (Jan. 31, 1990). The ALJ's findings on those issues in the ID that the Commission determined not to review or strike became the determinations of the Commission.

All parties except Gema, S.A. submitted briefs, and later reply briefs, on the issues of remedy, the public interest, and bonding. The Commission additionally received submissions from Zenith Laboratories, Inc. and the Department of Medical Assistance of the State of Georgia.

Having examined the record in this investigation, including the ID, the Commission has concluded that there is a violation of section 337 in the importation, sale for importation, or sale in the United States of the accused crystalline cefadroxil monohydrate.

The Commission has determined that a limited exclusion order and cease and desist orders directed to all U.S. respondents are the appropriate form of relief. The Commission has further determined that the public interest factors enumerated in 19 U.S.C. § 1337(d) and (f) do not preclude the issuance of relief. The Commission has established that respondents' bond under the exclusion order and the cease and desist orders during the Presidential review period shall be in the amount of sixty-eight (68) percent of the entered value of the imported articles.

Copies of the Commission's orders, the opinion issued in connection therewith, 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 202-252-1000. Hearing-impaired persons are advised that information on this matter can be obtained by contacting the Commission's TDD terminal on 202-252-1810.

By order of the Commission.

Kenneth R. Mason
Secretary

Issued: March 15, 1990

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

In the Matter of	)	
CERTAIN CRYSTALLINE CEFADROXIL MONOHYDRATE	)	Investigation No. 337-TA-293

ORDER

On February 1, 1989, Bristol-Myers Company (since renamed Bristol-Myers Squibb Company) ("Bristol") filed a complaint with the Commission alleging violations of section 337 in the importation and sale of certain crystalline cefadroxil monohydrate. The complaint alleged infringement of claim 1 of U.S. Letters Patent 4,504,657 ("the '657 patent") owned by Bristol.

The Commission instituted an investigation into the allegations of Bristol's complaint and published a notice of investigation in the Federal Register. 54 F.R. 10740 (March 15, 1989). The notice named the following respondents: (1) Biocraft Laboratories, Inc. of Elmwood Park, N.J.; (2) Gema, S.A. of Barcelona, Spain; (3) Kalipharma, Inc. of Elizabeth, N.J.; (4) Purepac Pharmaceutical Co. of Elizabeth, N.J.; (5) Istituto Biochimico Italiano Industria Giovanni Lorenzini S.p.A. of Milan, Italy; and (6) Institut Biochimique, S.A. of Massagno, Switzerland.

On December 15, 1989, the presiding administrative law judge (ALJ) issued an initial determination (ID) finding no violation of section 337 in this investigation. On January 25, 1990, the Commission issued a notice of a decision to review the ID's findings and conclusions that the '657 patent is invalid for obviousness under 35 U.S.C. § 103. The Commission determined not to review the remainder of the ID, except for two sentences

that it determined to strike. 55 F.R. 3282 (Jan. 31, 1990). The ALJ's findings on those issues in the ID that the Commission determined not to review or strike became the determinations of the Commission.

The Commission did not request further briefing on the issues under review, but did request written submissions from interested persons on the issues of remedy, the public interest, and bonding. The Commission received such submissions from all parties except Gema S.A. It also received submissions from Zenith Laboratories, Inc. and the Department of Medical Assistance of the State of Georgia.

Having examined the record in this investigation, including the ID, and the arguments submitted by the parties in their petitions for review and replies thereto, the Commission has determined to reverse that portion of the ID concluding that the '657 patent is invalid for obviousness under 35 U.S.C. § 103. Because those portions of the ID that the Commission determined not to review (1) found that Bristol had established all elements of a section 337 violation except for patent validity and (2) rejected respondents' remaining arguments that the '657 patent is invalid or unenforceable, the Commission concludes that there is a violation of section 337 in the importation, sale for importation, or sale in the United States of crystalline cefadroxil monohydrate.

Having determined that there is a violation of section 337, the Commission considered the questions of the appropriate remedy, bonding during the Presidential review period, and whether the statutory public interest considerations preclude the issuance of a remedy. The Commission considered the submissions of the parties, comments received from other interested persons, and the entire record in this investigation. The

Commission has determined that a limited exclusion order and cease and desist orders directed to all U.S. respondents are the appropriate form of relief. The Commission has further determined that the public interest factors enumerated in 19 U.S.C. § 1337(d) and (f) do not preclude the issuance of the aforementioned relief. The Commission has established that respondents' bond under the exclusion order and the cease and desist orders during the Presidential review period shall be in the amount of sixty-eight (68) percent of the entered value of the imported articles.

Accordingly, it is hereby **ORDERED THAT** --

1. Crystalline cefadroxil monohydrate capsules and crystalline cefadroxil monohydrate bulk powder manufactured abroad by Gema, S.A. of Spain; Istituto Biochimico Italiano Industria Giovanni Lorenzini S.p.A. of Italy; and Institut Biochimique, S.A. of Switzerland; or any of their affiliated companies, parents, subsidiaries, licensees, contractors, or other related entities, or their successors or assigns, that is covered by claim 1 of U.S. Letters Patent 4,504,657, are excluded from entry into the United States for the remaining term of the patent, except under license of the patent owner.

2. In accordance with 19 U.S.C. § 1337(1), the provisions of this Order do not apply to crystalline cefadroxil monohydrate capsules or bulk powder imported by or for the United States.

3. The articles identified in paragraph (1) of this Order are entitled to entry into the United States under bond in the amount of sixty-eight (68) percent of their entered value from the day after this Order is received by the President, pursuant to 19 U.S.C. § 1337(j)(3), until such time as the President notifies the Commission that he approves or disapproves this Order, but, in any event, no later than 60 days after the date of receipt of this Order by the President.

4. The attached cease and desist orders are issued to Biocraft Laboratories, Inc., Kalipharma, Inc., and Purepac Pharmaceutical Co.

5. The Commission may amend this Order in accordance with the procedure described in section 211.57 of the Commission's Interim Rules of Practice and Procedure, 19 C.F.R. § 211.57.

6. A copy of this Order shall be served upon each party of record in this investigation and upon the Department of Health and Human

Services, the Department of Justice, and the Federal Trade Commission.

7. Notice of this Order shall be published in the Federal Register.

By order of the Commission.

Kenneth R. Mason
Secretary

Issued: March 15, 1990

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

In the Matter of	)	
CERTAIN CRYSTALLINE CEFADROXIL MONOHYDRATE	)	Investigation No. 337-TA-293

ORDER TO CEASE AND DESIST

IT IS HEREBY ORDERED THAT Purepac Pharmaceutical Co., 200 Elmora Avenue, Elizabeth, New Jersey 07207, cease and desist from marketing, distributing, offering for sale, selling, or otherwise transferring in the United States certain imported crystalline cefadroxil monohydrate in violation of section 337 of the Tariff Act of 1930.

I

(Definitions)

As used in this Order:

(A) "Commission" shall mean the United States International Trade Commission.

(B) "Complainant" shall mean Bristol-Myers Squibb Company, New York, N.Y.

(C) "Respondent" shall mean Purepac Pharmaceutical Co., 200 Elmora Avenue, Elizabeth, New Jersey 07207.

(D) "Person" shall mean an individual, or any non-governmental partnership, firm, association, corporation, or other legal or business entity other than the above Respondent or its majority owned and/or controlled subsidiaries, their successors, or assigns.

(E) "United States" shall mean the fifty states, the District of Columbia, and Puerto Rico.

(F) "The Patent" shall mean claim 1 of U.S. Letters Patent 4,504,657.

II

(Applicability)

The provisions of this Order shall apply to Respondent and to its principals, stockholders, officers, directors, employees, agents, licensees, distributors, controlled (whether by stock ownership or otherwise) and/or majority owned business entities, successors, and assigns.

III

(Conduct Prohibited)

Respondent shall not market, distribute, offer for sale, sell, or otherwise transfer in the United States imported crystalline cefadroxil monohydrate that is covered by the Patent, except under license of the patent owner.

IV

(Conduct Permitted)

Notwithstanding any other provisions of this Order, specific conduct otherwise prohibited by the terms of this Order, shall be permitted if, in a written instrument, such specific conduct is licensed or authorized by Complainant or related to the importation or sale of crystalline cefadroxil monohydrate thereof by or for the United States.

V

(Reporting)

For purposes of this reporting requirement, the reporting period shall commence on the first day of July, and shall end on the following last day of June. The first report required under this section shall cover the period March 16, 1990, through June 30, 1990. This reporting requirement shall continue in force until the date of expiration of the Patent, unless, pursuant to subsection (j)(3) of section 337 of the Tariff Act of 1930, the President notifies the Commission within 60 days after the date he receives this Order, that he disapproves this Order.

Any failure to report shall constitute a violation of this Order.

Within thirty (30) days of the last day of the reporting period, Respondent shall report to the Commission the following:

(A) Its sales or other transfers in the United States, measured in capsules of crystalline cefadroxil monohydrate, and in grams of bulk powder of crystalline cefadroxil monohydrate, for the reporting period in question; and

(B) All contracts, whether written or oral, entered into during the reporting period in question, to sell or otherwise transfer capsules or bulk powder of crystalline cefadroxil monohydrate.

In connection with the sales or other transfers referred to in paragraphs (A) and (B) above, Respondent shall provide the Commission with two copies of all invoices, delivery orders, bills of lading, and other documents concerning the importation or sale in question. Such copies shall be attached to the reports required by paragraphs (A) and (B) above.

VI

(Compliance and Inspection)

(A) For the purposes of securing compliance with this Order, Respondent shall retain any and all records relating to the sale in the United States of crystalline cefadroxil monohydrate referred to in paragraphs (V)(A) and (V)(B) above made and received in the usual and ordinary course of its business, whether in detail or in summary form, for a period of two (2) years from the close of the fiscal year to which they pertain.

(B) For the purpose of determining or securing compliance with this Order and for no other purpose, and subject to any privilege recognized by Federal Courts of the United States, Respondent shall furnish or otherwise make available for inspection and copying to duly authorized representatives of the Commission, and in the presence of counsel or other representative if Respondent so chooses, upon reasonable written notice by the Commission or its staff, all books, ledgers, accounts, correspondence, memoranda, financial reports, and other records or documents in its possession or control for the purpose of verifying any matter or statement contained in the reports required under section V of this Order.

VII

(Service of Cease and Desist Order)

Respondent is ordered and directed to:

(A) Serve, within fifteen (15) days after the date of issuance of this Order, a copy of the Order upon each of its respective officers, directors, managing agents, agents and employees who have any responsibility for the

marketing, distribution, or sale of imported crystalline cefadroxil monohydrate in the United States.

(B) Serve, within fifteen (15) days after the succession of any of the persons referred to in paragraph VII(A), a copy of this Order upon each successor.

(C) Maintain such records as will show the name, title, and address of each person described in paragraph VII(A) and (B) above upon whom this Order has been served, together with the date on which service was made.

(D) The obligations set forth in paragraphs VII (B) and (C) above shall remain in effect until the date of expiration of the Patent, unless, pursuant to subsection (j)(3) of section 337 of the Tariff Act of 1930, the President notifies the Commission within 60 days after the date he receives this Order, that he disapproves this Order.

VIII

(Confidentiality)

Information obtained by the means provided for in sections V and VI of this Order will be made available only to the Commission and its authorized representatives, will be entitled to confidential treatment, and will not be divulged by any authorized representative of the Commission to any person other than duly authorized representatives of the Commission, except as may be required in the course of securing compliance with this Order, or as otherwise required by law. Disclosure hereunder will not be made by the Commission without ten (10) days prior notice in writing to Respondent.

IX

(Enforcement)

Violation of this Order may result in any of the actions specified in section 211.56 of the Commission's Interim Rules of Practice and Procedure, 19 C.F.R. § 211.56, including an action for civil penalties in accordance with section 337(f) of the Tariff Act of 1930 (19 U.S.C. § 1337(f)), and such other action as the Commission may deem appropriate. In determining whether Respondent is in violation of this Order, the Commission may infer facts adverse to Respondent if Respondent fails to provide adequate or timely information as required by this Order.

X

(Modification)

This Order may be modified by the Commission on its own motion or upon motion by any person pursuant to section 211.57 of the Commission's Interim Rules of Practice and Procedure, 19 C.F.R. § 211.57.

XI

(Bonding)

With respect to crystalline cefadroxil monohydrate imported prior to March 15, 1990, that was not subject to the entry bond as set forth in the temporary limited exclusion order issued by the Commission in Investigation No. 337-TA-293 on January 10, 1990, the conduct prohibited by paragraph III of this Order may be continued during the period in which this Order is in under review by the President pursuant to section 337(j) of the Tariff Act of 1930 (19 U.S.C. § 1337(j)) subject to Respondent posting a bond in the

amount of sixty-eight (68) percent of the entered value of the crystalline cefadroxil monohydrate capsules or bulk powder in question. This bond provision does not apply to conduct which is otherwise permitted by paragraph IV of this Order. Crystalline cefadroxil monohydrate capsules or bulk powder imported on or after March 15, 1990, are subject to the entry bond as set forth in the limited exclusion order issued by the Commission on March 15, 1990, and are not subject to this bond provision.

The bond is to be posted in accordance with the procedures established by the Commission for the posting of bonds by complainants in connection with the issuance of temporary exclusion orders (53 Fed. Reg. 49133-34 (Dec. 6, 1988)).

The bond and any accompanying documentation is to be provided to and approved by the Commission prior to the commencement of conduct which is otherwise prohibited by paragraph III of this Order.

The bond is to be forfeited in the event that the President approves, or does not disapprove within the Presidential review period, the Commission's Orders of March 15, 1990, or any subsequent final order issued after the completion of Investigation No. 337-TA-293, unless the U.S. Court of Appeals for the Federal Circuit, in a final judgment, reverses any Commission final determination and order as to Respondent on appeal, or unless Respondent exports the products subject to this bond or destroys them and provides certification to that effect satisfactory to the Commission.

The bond is to be released in the event the President disapproves this Order and no subsequent order is issued by the Commission and approved, or not disapproved, by the President, upon service on Respondent of an Order

issued by the Commission based upon application therefor made by Respondent to the Commission.

By Order of the Commission.

Kenneth R. Mason

Secretary

Issued: March 15, 1990

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

In the Matter of	)	
CERTAIN CRYSTALLINE CEFADROXIL MONOHYDRATE	)	Investigation No. 337-TA-293

ORDER TO CEASE AND DESIST

IT IS HEREBY ORDERED THAT Biocraft Laboratories, Inc., 92 Route 46, Elmwood Park, New Jersey 07407, cease and desist from marketing, distributing, offering for sale, selling, or otherwise transferring in the United States certain imported crystalline cefadroxil monohydrate in violation of section 337 of the Tariff Act of 1930.

I

(Definitions)

As used in this Order:

(A) "Commission" shall mean the United States International Trade Commission.

(B) "Complainant" shall mean Bristol-Myers Squibb Company, New York, N.Y.

(C) "Respondent" shall mean Biocraft Laboratories, Inc., 92 Route 46, Elmwood Park, New Jersey 07407.

(D) "Person" shall mean an individual, or any non-governmental partnership, firm, association, corporation, or other legal or business entity other than the above Respondent or its majority owned and/or controlled subsidiaries, their successors, or assigns.

(E) "United States" shall mean the fifty states, the District of Columbia, and Puerto Rico.

(F) "The Patent" shall mean claim 1 of U.S. Letters Patent 4,504,657.

II

(Applicability)

The provisions of this Order shall apply to Respondent and to its principals, stockholders, officers, directors, employees, agents, licensees, distributors, controlled (whether by stock ownership or otherwise) and/or majority owned business entities, successors, and assigns.

III

(Conduct Prohibited)

Respondent shall not market, distribute, offer for sale, sell, or otherwise transfer in the United States imported crystalline cefadroxil monohydrate that is covered by the Patent, except under license of the patent owner.

IV

(Conduct Permitted)

Notwithstanding any other provisions of this Order, specific conduct otherwise prohibited by the terms of this Order, shall be permitted if, in a written instrument, such specific conduct is licensed or authorized by Complainant or related to the importation or sale of crystalline cefadroxil monohydrate thereof by or for the United States.

V

(Reporting)

For purposes of this reporting requirement, the reporting period shall commence on the first day of July, and shall end on the following last day of June. The first report required under this section shall cover the period March 16, 1990, through June 30, 1990. This reporting requirement shall continue in force until the date of expiration of the Patent, unless, pursuant to subsection (j)(3) of section 337 of the Tariff Act of 1930, the President notifies the Commission within 60 days after the date he receives this Order, that he disapproves this Order.

Any failure to report shall constitute a violation of this Order.

Within thirty (30) days of the last day of the reporting period, Respondent shall report to the Commission the following:

(A) Its sales or other transfers in the United States, measured in capsules of crystalline cefadroxil monohydrate, and in grams of bulk powder of crystalline cefadroxil monohydrate, for the reporting period in question; and

(B) All contracts, whether written or oral, entered into during the reporting period in question, to sell or otherwise transfer capsules or bulk powder of crystalline cefadroxil monohydrate.

In connection with the sales or other transfers referred to in paragraphs (A) and (B) above, Respondent shall provide the Commission with two copies of all invoices, delivery orders, bills of lading, and other documents concerning the importation or sale in question. Such copies shall be attached to the reports required by paragraphs (A) and (B) above.

VI

(Compliance and Inspection)

(A) For the purposes of securing compliance with this Order, Respondent shall retain any and all records relating to the sale in the United States of crystalline cefadroxil monohydrate referred to in paragraphs (V)(A) and (V)(B) above made and received in the usual and ordinary course of its business, whether in detail or in summary form, for a period of two (2) years from the close of the fiscal year to which they pertain.

(B) For the purpose of determining or securing compliance with this Order and for no other purpose, and subject to any privilege recognized by Federal Courts of the United States, Respondent shall furnish or otherwise make available for inspection and copying to duly authorized representatives of the Commission, and in the presence of counsel or other representative if Respondent so chooses, upon reasonable written notice by the Commission or its staff, all books, ledgers, accounts, correspondence, memoranda, financial reports, and other records or documents in its possession or control for the purpose of verifying any matter or statement contained in the reports required under section V of this Order.

VII

(Service of Cease and Desist Order)

Respondent is ordered and directed to:

(A) Serve, within fifteen (15) days after the date of issuance of this Order, a copy of the Order upon each of its respective officers, directors, managing agents, agents and employees who have any responsibility for the

marketing, distribution, or sale of imported crystalline cefadroxil monohydrate in the United States.

(B) Serve, within fifteen (15) days after the succession of any of the persons referred to in paragraph VII(A), a copy of this Order upon each successor.

(C) Maintain such records as will show the name, title, and address of each person described in paragraph VII(A) and (B) above upon whom this Order has been served, together with the date on which service was made.

(D) The obligations set forth in paragraphs VII (B) and (C) above shall remain in effect until the date of expiration of the Patent, unless, pursuant to subsection (j)(3) of section 337 of the Tariff Act of 1930, the President notifies the Commission within 60 days after the date he receives this Order, that he disapproves this Order.

VIII

(Confidentiality)

Information obtained by the means provided for in sections V and VI of this Order will be made available only to the Commission and its authorized representatives, will be entitled to confidential treatment, and will not be divulged by any authorized representative of the Commission to any person other than duly authorized representatives of the Commission, except as may be required in the course of securing compliance with this Order, or as otherwise required by law. Disclosure hereunder will not be made by the Commission without ten (10) days prior notice in writing to Respondent.

IX

(Enforcement)

Violation of this Order may result in any of the actions specified in section 211.56 of the Commission's Interim Rules of Practice and Procedure, 19 C.F.R. § 211.56, including an action for civil penalties in accordance with section 337(f) of the Tariff Act of 1930 (19 U.S.C. § 1337(f)), and such other action as the Commission may deem appropriate. In determining whether Respondent is in violation of this Order, the Commission may infer facts adverse to Respondent if Respondent fails to provide adequate or timely information as required by this Order.

X

(Modification)

This Order may be modified by the Commission on its own motion or upon motion by any person pursuant to section 211.57 of the Commission's Interim Rules of Practice and Procedure, 19 C.F.R. § 211.57.

XI

(Bonding)

With respect to crystalline cefadroxil monohydrate imported prior to March 15, 1990, that was not subject to the entry bond as set forth in the temporary limited exclusion order issued by the Commission in Investigation No. 337-TA-293 on January 10, 1990, the conduct prohibited by paragraph III of this Order may be continued during the period in which this Order is in under review by the President pursuant to section 337(j) of the Tariff Act of 1930 (19 U.S.C. § 1337(j)) subject to Respondent posting a bond in the

amount of sixty-eight (68) percent of the entered value of the crystalline cefadroxil monohydrate capsules or bulk powder in question. This bond provision does not apply to conduct which is otherwise permitted by paragraph IV of this Order. Crystalline cefadroxil monohydrate capsules or bulk powder imported on or after March 15, 1990, are subject to the entry bond as set forth in the limited exclusion order issued by the Commission on March 15, 1990, and are not subject to this bond provision.

The bond is to be posted in accordance with the procedures established by the Commission for the posting of bonds by complainants in connection with the issuance of temporary exclusion orders (53 Fed. Reg. 49133-34 (Dec. 6, 1988)).

The bond and any accompanying documentation is to be provided to and approved by the Commission prior to the commencement of conduct which is otherwise prohibited by paragraph III of this Order.

The bond is to be forfeited in the event that the President approves, or does not disapprove within the Presidential review period, the Commission's Orders of March 15, 1990, or any subsequent final order issued after the completion of Investigation No. 337-TA-293, unless the U.S. Court of Appeals for the Federal Circuit, in a final judgment, reverses any Commission final determination and order as to Respondent on appeal, or unless Respondent exports the products subject to this bond or destroys them and provides certification to that effect satisfactory to the Commission.

The bond is to be released in the event the President disapproves this Order and no subsequent order is issued by the Commission and approved, or not disapproved, by the President, upon service on Respondent of an Order

issued by the Commission based upon application therefor made by Respondent to the Commission.

By Order of the Commission.

Kenneth R. Mason

Secretary

Issued: March 15, 1990

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

In the Matter of	)	
CERTAIN CRYSTALLINE CEFADROXIL MONOHYDRATE	)	Investigation No. 337-TA-293

ORDER TO CEASE AND DESIST

IT IS HEREBY ORDERED THAT Kalipharma, Inc., 200 Elmora Avenue, Elizabeth, New Jersey 07207, cease and desist from marketing, distributing, offering for sale, selling, or otherwise transferring in the United States certain imported crystalline cefadroxil monohydrate in violation of section 337 of the Tariff Act of 1930.

I

(Definitions)

As used in this Order:

(A) "Commission" shall mean the United States International Trade Commission.

(B) "Complainant" shall mean Bristol-Myers Squibb Company, New York, N.Y.

(C) "Respondent" shall mean Kalipharma, Inc., 200 Elmora Avenue, Elizabeth, New Jersey 07207.

(D) "Person" shall mean an individual, or any non-governmental partnership, firm, association, corporation, or other legal or business entity other than the above Respondent or its majority owned and/or controlled subsidiaries, their successors, or assigns.

(E) "United States" shall mean the fifty states, the District of Columbia, and Puerto Rico.

(F) "The Patent" shall mean claim 1 of U.S. Letters Patent 4,504,657.

II

(Applicability)

The provisions of this Order shall apply to Respondent and to its principals, stockholders, officers, directors, employees, agents, licensees, distributors, controlled (whether by stock ownership or otherwise) and/or majority owned business entities, successors, and assigns.

III

(Conduct Prohibited)

Respondent shall not market, distribute, offer for sale, sell, or otherwise transfer in the United States imported crystalline cefadroxil monohydrate that is covered by the Patent, except under license of the patent owner.

IV

(Conduct Permitted)

Notwithstanding any other provisions of this Order, specific conduct otherwise prohibited by the terms of this Order, shall be permitted if, in a written instrument, such specific conduct is licensed or authorized by Complainant or related to the importation or sale of crystalline cefadroxil monohydrate thereof by or for the United States.

V

(Reporting)

For purposes of this reporting requirement, the reporting period shall commence on the first day of July, and shall end on the following last day of June. The first report required under this section shall cover the period March 16, 1990, through June 30, 1990. This reporting requirement shall continue in force until the date of expiration of the Patent, unless, pursuant to subsection (j)(3) of section 337 of the Tariff Act of 1930, the President notifies the Commission within 60 days after the date he receives this Order, that he disapproves this Order.

Any failure to report shall constitute a violation of this Order.

Within thirty (30) days of the last day of the reporting period, Respondent shall report to the Commission the following:

(A) Its sales or other transfers in the United States, measured in capsules of crystalline cefadroxil monohydrate, and in grams of bulk powder of crystalline cefadroxil monohydrate, for the reporting period in question; and

(B) All contracts, whether written or oral, entered into during the reporting period in question, to sell or otherwise transfer capsules or bulk powder of crystalline cefadroxil monohydrate.

In connection with the sales or other transfers referred to in paragraphs (A) and (B) above, Respondent shall provide the Commission with two copies of all invoices, delivery orders, bills of lading, and other documents concerning the importation or sale in question. Such copies shall be attached to the reports required by paragraphs (A) and (B) above.

VI

(Compliance and Inspection)

(A) For the purposes of securing compliance with this Order, Respondent shall retain any and all records relating to the sale in the United States of crystalline cefadroxil monohydrate referred to in paragraphs (V)(A) and (V)(B) above made and received in the usual and ordinary course of its business, whether in detail or in summary form, for a period of two (2) years from the close of the fiscal year to which they pertain.

(B) For the purpose of determining or securing compliance with this Order and for no other purpose, and subject to any privilege recognized by Federal Courts of the United States, Respondent shall furnish or otherwise make available for inspection and copying to duly authorized representatives of the Commission, and in the presence of counsel or other representative if Respondent so chooses, upon reasonable written notice by the Commission or its staff, all books, ledgers, accounts, correspondence, memoranda, financial reports, and other records or documents in its possession or control for the purpose of verifying any matter or statement contained in the reports required under section V of this Order.

VII

(Service of Cease and Desist Order)

Respondent is ordered and directed to:

(A) Serve, within fifteen (15) days after the date of issuance of this Order, a copy of the Order upon each of its respective officers, directors, managing agents, agents and employees who have any responsibility for the

marketing, distribution, or sale of imported crystalline cefadroxil monohydrate in the United States.

(B) Serve, within fifteen (15) days after the succession of any of the persons referred to in paragraph VII(A), a copy of this Order upon each successor.

(C) Maintain such records as will show the name, title, and address of each person described in paragraph VII(A) and (B) above upon whom this Order has been served, together with the date on which service was made.

(D) The obligations set forth in paragraphs VII (B) and (C) above shall remain in effect until the date of expiration of the Patent, unless, pursuant to subsection (j)(3) of section 337 of the Tariff Act of 1930, the President notifies the Commission within 60 days after the date he receives this Order, that he disapproves this Order.

VIII

(Confidentiality)

Information obtained by the means provided for in sections V and VI of this Order will be made available only to the Commission and its authorized representatives, will be entitled to confidential treatment, and will not be divulged by any authorized representative of the Commission to any person other than duly authorized representatives of the Commission, except as may be required in the course of securing compliance with this Order, or as otherwise required by law. Disclosure hereunder will not be made by the Commission without ten (10) days prior notice in writing to Respondent.

IX

(Enforcement)

Violation of this Order may result in any of the actions specified in section 211.56 of the Commission's Interim Rules of Practice and Procedure, 19 C.F.R. § 211.56, including an action for civil penalties in accordance with section 337(f) of the Tariff Act of 1930 (19 U.S.C. § 1337(f)), and such other action as the Commission may deem appropriate. In determining whether Respondent is in violation of this Order, the Commission may infer facts adverse to Respondent if Respondent fails to provide adequate or timely information as required by this Order.

X

(Modification)

This Order may be modified by the Commission on its own motion or upon motion by any person pursuant to section 211.57 of the Commission's Interim Rules of Practice and Procedure, 19 C.F.R. § 211.57.

XI

(Bonding)

With respect to crystalline cefadroxil monohydrate imported prior to March 15, 1990, that was not subject to the entry bond as set forth in the temporary limited exclusion order issued by the Commission in Investigation No. 337-TA-293 on January 10, 1990, the conduct prohibited by paragraph III of this Order may be continued during the period in which this Order is in under review by the President pursuant to section 337(j) of the Tariff Act of 1930 (19 U.S.C. § 1337(j)) subject to Respondent posting a bond in the

amount of sixty-eight (68) percent of the entered value of the crystalline cefadroxil monohydrate capsules or bulk powder in question. This bond provision does not apply to conduct which is otherwise permitted by paragraph IV of this Order. Crystalline cefadroxil monohydrate capsules or bulk powder imported on or after March 15, 1990, are subject to the entry bond as set forth in the limited exclusion order issued by the Commission on March 15, 1990, and are not subject to this bond provision.

The bond is to be posted in accordance with the procedures established by the Commission for the posting of bonds by complainants in connection with the issuance of temporary exclusion orders (53 Fed. Reg. 49133-34 (Dec. 6, 1988)).

The bond and any accompanying documentation is to be provided to and approved by the Commission prior to the commencement of conduct which is otherwise prohibited by paragraph III of this Order.

The bond is to be forfeited in the event that the President approves, or does not disapprove within the Presidential review period, the Commission's Orders of March 15, 1990, or any subsequent final order issued after the completion of Investigation No. 337-TA-293, unless the U.S. Court of Appeals for the Federal Circuit, in a final judgment, reverses any Commission final determination and order as to Respondent on appeal, or unless Respondent exports the products subject to this bond or destroys them and provides certification to that effect satisfactory to the Commission.

The bond is to be released in the event the President disapproves this Order and no subsequent order is issued by the Commission and approved, or not disapproved, by the President, upon service on Respondent of an Order

issued by the Commission based upon application therefor made by Respondent to the Commission.

By Order of the Commission.

Kenneth R. Mason

Secretary

Issued: March 15, 1990

PUBLIC DISCLOSURE VERSION

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

In the Matter of	)	
CERTAIN CRYSTALLINE CEFADROXIL MONOHYDRATE	)	Investigation No. 337-TA-293

COMMISSION OPINION ON THE ISSUE UNDER REVIEW, AND ON REMEDY, THE PUBLIC INTEREST, AND BONDING

I. BACKGROUND

On February 1, 1989, Bristol-Myers Company (since renamed Bristol-Myers Squibb Company) ("Bristol") filed a complaint with the Commission under section 337 of the Tariff Act of 1930 (19 U.S.C. § 1337). The complaint alleged that imports of crystalline cefadroxil monohydrate, an antibiotic drug, infringed U.S. Letters Patent 4,504,657 ("the '657 patent"), owned by Bristol. Bristol concurrently moved for temporary relief.

The Commission published a notice of investigation into Bristol's complaint in the Federal Register on March 15, 1980. The Commission named Biocraft Laboratories, Inc. ("Biocraft"), Gema, S.A. ("Gema"), Kalipharma, Inc. ("Kalipharma"), Purepac Pharmaceutical Co. ("Purepac"), Istituto Biochimico Italiano Industria Giovanni Lorenzini ("IBI"), and Institut Biochimique, S.A. ("IBSA") as respondents. 1/

1/ IBI (a foreign manufacturer of bulk cefadroxil), IBSA (a foreign manufacturer of cefadroxil capsules), Kalipharma (a U.S. importer and marketer), and Purepac (an unincorporated division of Kalipharma), which are represented by common counsel and have proceeded jointly throughout this investigation, will be referred to collectively as "the Kalipharma respondents."

On May 24, 1989, the presiding administrative law judge ("ALJ") issued an initial determination denying Bristol's motion for temporary relief ("the TEO ID") on the grounds that there was no reason to believe that a section 337 violation existed. The TEO ID concluded that it was unlikely that complainant Bristol could demonstrate the existence of a section 337 violation because respondents had established that the '657 patent would likely be proved invalid for obviousness under 35 U.S.C. § 103. The TEO ID also concluded, inter alia, that (1) Bristol had established the existence of a domestic industry; (2) respondents had not established that it was likely that the '657 patent would be proved invalid for anticipation under 35 U.S.C. § 102; (3) if valid, the '657 patent was not unenforceable by virtue of inequitable conduct; and (4) if valid and enforceable, the '657 patent had been infringed by respondents. On June 13, 1989, the Commission issued its determination not to modify or vacate the TEO ID insofar as it denied Bristol's request for temporary relief. 2/ Bristol appealed the Commission's determination to the United States Court of Appeals for the Federal Circuit.

On December 8, 1989, the Federal Circuit issued a decision sustaining the Commission's rulings on anticipation and inequitable conduct, but reversing the ruling on obviousness on the grounds that the ALJ applied an improper legal standard in her analysis. 3/ The court determined that the

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2/ See Certain Crystalline Cefadroxil Monohydrate Temporary Relief Proceeding, Inv. No. 337-TA-293, USITC Pub. 2240 (November 1989), rev'd sub nom. Bristol-Myers Co. v. USITC, App. No. 89-1530 (Fed. Cir. Dec. 8, 1989).

3/ Bristol-Myers Co. v. USITC, App. No. 89-1530 (Fed. Cir. Dec. 8, 1989).

Bristol patent was likely valid and reversed the Commission's denial of temporary relief. 4/

On December 15, 1989, the ALJ issued her initial determination ("ID") on permanent relief. The ID on permanent relief reached substantially the same conclusions as the TEO ID, ruling for Bristol on the issues of domestic industry, anticipation, infringement, and inequitable conduct, but concluding that no violation of section 337 existed because respondents had demonstrated that the '657 patent was invalid for obviousness under 35 U.S.C. § 103.

All parties except Biocraft filed petitions for review of the ID. On January 25, 1990, the Commission issued a notice of a decision to review the ID's findings and conclusions concerning obviousness and ancillary issues. 5/ The Commission determined not to review the remainder of the ID. 6/ The ALJ's conclusions concerning those issues that the Commission determined not to review -- anticipation, inequitable conduct,

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4/ Id., slip op. at 7-13. Pursuant to the Federal Circuit's decision, the Commission granted Bristol temporary relief on January 10, 1990, and issued an opinion concerning its temporary relief orders (the "Temporary Relief Opinion") on January 19, 1990. Certain Crystalline Cefadroxil Monohydrate Temporary Relief Proceeding, Inv. No. 337-TA-293, USITC Pub. ____ (1990). The temporary relief issued was a temporary limited exclusion order (which the Commission approved unanimously) and temporary cease and desist orders against Biocraft, Kalipharma, and Purepac (which the Commission approved by a vote of 4-2, Chairman Brunsdale and Vice Chairman Cass dissenting).

5/ The notice was published in the Federal Register on January 31, 1990. 55 Fed. Reg. 3282 (Jan. 31, 1990).

6/ The Commission did, however, strike two sentences of the ID's discussion on anticipation that contained neither factual findings nor legal conclusions.

infringement, domestic industry, and Bristol's compliance with its duty of candor to the Commission -- became the determinations of the Commission. 7/

The Commission did not request further submissions on the obviousness issue, which all parties had briefed extensively in their petitions for review and responses thereto. The Commission did, however, solicit written submissions from the parties, interested government agencies, and other interested persons concerning the issues of remedy, the public interest, and bonding. Briefs or comments were filed by all parties except Gema, and by the Commission investigative attorney ("IA"), Zenith Laboratories, Inc., a non-respondent U.S. marketer and importer of crystalline cefadroxil monohydrate, and the Department of Medical Assistance of the State of Georgia.

This opinion explains the basis for the following Commission determinations:

(1) We have reversed the ID's conclusion that the '657 patent is invalid for obviousness under 35 U.S.C. § 103. Consequently, we have concluded that a section 337 violation exists in the importation and sale of crystalline cefadroxil monohydrate.

(2) We have issued a limited exclusion order in this investigation, directed at the products of the foreign respondents.

(3) We have issued cease and desist orders against the domestic respondents.

(4) We have concluded that the public interest considerations

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7/ See 19 C.F.R. § 210.53(h).

articulated in section 337(d) and (f) do not preclude the issuance of relief in this investigation.

(5) We have determined that respondents' bond under the exclusion order and cease and desist orders during the Presidential review period shall be in the amount of 68 percent of the entered value of the imported articles.

II. THE ISSUE UNDER REVIEW

The sole issue under review concerns whether the '657 patent is invalid for obviousness under 35 U.S.C. § 103. Respondents have argued that the '657 patent is obvious in light of each of two prior art references -- U.S. Letters Patent 3,781,282 ("the Garbrecht patent") and U.S. Letters Patent 3,985,741 ("the Crast patent"). The ID accepted respondents' arguments. Because we do not believe that the ID's determination on obviousness can be reconciled with the legal analysis required by the Federal Circuit decision in Bristol-Myers concerning our temporary relief determination, we reverse the ID on this issue.

A. The Prior Art at Issue

1. The Claimed Invention

The '657 patent was issued to Bristol on March 12, 1985. The patent contains a single claim for a "novel crystalline monohydrate of cefadroxil and processes for preparing said monohydrate." 8/

Cefadroxil is an antibiotic whose chemical structure places it in a group of compounds known as cephalosporins. 9/ Cefadroxil existed long

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8/ Bristol ex. 20, col. 2, lines 14-16.

9/ See TEO Tr. at 211-17 (Baldwin). Other well-known cephalosporins include cephalexin, cephadrine, and cefaclor. See generally Bristol ex. 10 at 3.

before issuance of the '657 patent. Bristol first formulated cefadroxil in the 1960s, and on January 13, 1970, it was issued U.S. Letters Patent 3,489,752, which covered cefadroxil in any form. 10/

The '657 patent, by contrast, covers a specific cefadroxil structure, viz., a monohydrate with a novel crystalline form that is characterized by a unique 37-line X-ray powder diffraction pattern. 11/ This structure is commonly called the "Bouzard monohydrate" after its inventor, Daniel Bouzard.

2. The Garbrecht Patent

The Garbrecht patent was issued on December 28, 1973, to William Garbrecht, a chemist then employed by Eli Lilly & Co. The Garbrecht patent discloses a method for substantially increasing the yields of and simplifying and enhancing purification procedures for cephalosporin compounds. 12/

Example 7 of the Garbrecht patent illustrates the production of a cefadroxil compound. Example 7 describes a dimethylformanide (DMF) solvate, and indicates that it is to be "treated as in example 1" to remove two "protecting groups" -- the p-nitrobenzyl group and the t-BOC group. These protecting groups, which help effect the necessary chemical reactions, must be removed to enable the compound to function as an

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10/ See ID at 4.

11/ See Bristol ex. 20 at col. 6.

12/ Biocraft/Gema ex. 13, col. 4, lines 11-14.

antibiotic. Example 7 then states that the resulting compound "is treated as in example 5." 13/

The first referenced example, example 1, describes a method for removal of the p-nitrobenzyl group from a cephalexin DMF solvate. Cephalexin is another cephalosporin antibiotic possessing certain structural similarities to cefadroxil. Garbrecht example 1 does not describe removal of the t-BOC group. 14/ The second referenced example, example 5, describes a large-scale purification process for cephalexin. It describes removal of the DMF impurity from a DMF cephalexin solvate, resulting in a cephalexin monohydrate. 15/

3. The Crast Patent

The Crast patent was issued on October 12, 1976, to Leonard Crast and William Gottstein, chemists then employed by Bristol. The patent discloses improved processes for the production, isolation, and purification of cefadroxil. 16/ One such improved purification process for cefadroxil is described in Example 6 of the patent. Part (A) of Example 6 describes preparation of a cefadroxil DMF solvate. 17/ Part (B) of Example 6 describes purification of the DMF solvate to cefadroxil by means of slurrying the solvate in a mixture of 90 percent methanol. 18/

13/ Id., cols. 10-11.

14/ Id., col. 7, line 68 through col. 8, line 45.

15/ Id., col. 9, line 72 through col. 10, line 26.

16/ Biocraft/Gema ex. 10, col. 2, lines 30-34.

17/ Id., col. 10.

18/ Id., col. 11, lines 1-22.

B. The Legal Standard for Determining Obviousness

As the ID stated, there is a statutory presumption that complainant Bristol's '657 patent is valid; respondents must prove invalidity by clear and convincing evidence. 19/ The ID correctly describes the basic inquiries relevant to an obviousness determination as those specified in Graham v. John Deere & Co.: 20/

> 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 inquiries may have relevancy.

The ID's findings concerning the first and third of these factors, pertaining respectively to the relevant prior art and level of ordinary skill, have not been contested by the parties. The ID found that the relevant prior art references were the Garbrecht and Crast patents described above, as well as Bristol's original 1970 patent for cefadroxil. 21/ The ID additionally found that a person with "ordinary skill in the pertinent art" as of 1976, the claimed date of the invention,

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19/ ID at 7; see 35 U.S.C. § 282; Verdegaal Brothers, Inc. v. Union Oil Co., 814 F.2d 628, 631 (Fed. Cir.), cert. denied, 484 U.S. 827 (1987); Astra-Sjuco, A.B. v. USITC, 629 F.2d 682, 688 (C.C.P.A. 1980).

20/ 383 U.S. 1, 17-18, 148 U.S.P.Q. 459, 467 (1966).

21/ ID at 35.

would have been an experienced chemist with at least an undergraduate degree in chemistry and some experience in the field of cephalosporins. 22/

The parties dispute whether the ID's determinations concerning the second factor, the differences between the prior art and the claimed invention, and the fourth factor, the so-called "secondary" or "objective" considerations of nonobviousness, are consistent with Federal Circuit precedent, including Bristol-Myers. We conclude that the analysis provided in the ID is not consistent with Federal Circuit precedent and provide the following analysis and conclusions of the Commission on these issues.

1. Comparison with Prior Art

a. Identifying the applicable legal standard

The ID's determination that the invention of the '657 patent is invalid as obvious stemmed principally from its comparison between the '657 patent and the prior art Crast and Garbrecht patents. In comparing the '657 patent with the prior art, the ID addressed three matters.

First, the ID addressed the issue of motivation to make the claimed invention of the '657 patent, the Bouzard monohydrate. The ID describes this motivation as follows: "In 1976 there was a major incentive for a chemist working in the area of cephalosporins to find a form of crystalline cefadroxil that could be produced commercially." 23/

Second, the ID determined that the prior art Garbrecht and Crast patents

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22/ ID at 35.

23/ ID at 47; see ID at 56.

described various methods for making cefadroxil that were inoperative or unsatisfactory. 24/

Third, the ID concluded that if these prior art methods were modified in a certain manner, using changes obvious to those with ordinary skill in the art, the Bouzard monohydrate would be produced. 25/

In effect, the ALJ concluded that because there was motivation to make a commercially usable form of cefadroxil, and obvious changes to the processes described in the prior art would result in production of the Bouzard monohydrate, which has been commercially successful, the Bouzard monohydrate was obvious under 35 U.S.C. § 103. We do not believe that either the ID's inquiries or its conclusions comport with controlling law. The ID's method of analysis is, in fact, identical to that found in the TEO ID, which the Federal Circuit rejected as:

> irrelevant to whether the Bouzard discovery would have been obvious in terms of § 103. The question before the Commission was not whether the Bouzard crystal form could have been duplicated with experimentation or with even minor chemical process changes; the question was whether this new crystal form, as a composition of matter, would have been obvious from the teachings of the prior art. 26/

We agree with respondents that the Bristol-Myers decision on temporary relief did not and could not dictate how the Commission must rule as to validity of the '657 patent on the basis of the full record compiled during

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24/ See ID at 38 (Garbrecht patent did not suggest enough hydrochloric acid to remove both protecting groups from DMF solvate), 50 (Crast patent did not produce pure product in high yield when followed literally).

25/ See ID at 39-49 (Garbrecht), 53-56 (Crast).

26/ Bristol-Myers, slip op. at 12. See also id. at 13 ("There must be an affirmative suggestion or teaching in the prior art whereby it would have been obvious to make the new monohydrate; not simply the absence of obstacle.")

the permanent relief phase of this investigation. 27/ We also believe, however, that the decision articulates legal doctrines that the Commission must apply in determining whether the '657 patent is valid. 28/ None of the respondents disputes this proposition. 29/ The ID, however, failed to address the issue. Its section on obviousness did not discuss or even cite Bristol-Myers.

In Bristol-Myers, the Federal Circuit directed the Commission to inquire "whether this new crystal form, as a composition of matter, would have been obvious from the teachings of the prior art." 30/ Other portions of the decision similarly indicate that the Commission should examine whether the crystal structure represented by the Bouzard monohydrate is obvious:

> It is insufficient that the prior art shows methods that some (but not all) chemists were able to modify, to produce the Bouzard crystalline

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27/ Nevertheless, we believe respondents' repeated assertions as to the quantum of new evidence introduced during the permanent relief phase of the investigation to be exaggerated. Of the 13 witnesses introduced by respondents during the June and September hearings on permanent relief, only two presented testimony and evidence pertaining to their affirmative cases on obviousness. Because both these witnesses testified concerning the Crast patent, there was no new testimony at all presented concerning respondents' affirmative case as to the Garbrecht patent. The vast bulk of testimony of respondents' witnesses was directed to rebutting Bristol's witnesses, especially as to the seeding issue.

28/ When the Federal Circuit articulates a rule of law in a case, a subordinate tribunal is obliged to follow that rule in subsequent proceedings in that case. See W.L. Gore & Associates v. Garlock, Inc., 842 F.2d 1275, 1279 (Fed. Cir. 1988).

29/ See Biocraft Response to Petitions for Review at 13 ("Biocraft is not suggesting that the Commission is free to disregard the Federal Circuit"), Gema Reply to Petitions for Review at 5 (Commission should "apply[] the correct legal standard as delineated by the Federal Circuit"); Kalipharma Respondents' to Petitions for Review at 8-10 (indicating that determination should address issues raised by Bristol-Myers decision).

30/ Bristol-Myers, slip op. at 12 (emphasis added).

> form. There must be a suggestion in the prior art that the Bouzard crystal structure would or should be made, whether by manipulation of the Garbrecht or Crast II processes, or by any other process. In factual and legal point is In re Cofer, 354 F.2d 664, 668, 148 USPQ 268, 271 (CCPA 1966), wherein the court held that a new crystalline form of a compound would not have been obvious absent evidence that "the prior art suggests the particular structure or form of the compound or composition as well as suitable methods for obtaining that structure or form." 31/

Both the Commission and Biocraft argued in the Bristol-Myers appeal that Federal Circuit precedent did not support the proposition that a crystalline chemical compound was not obvious unless its structure was obvious. As the quoted excerpt indicates, the Federal Circuit disagreed. Biocraft's lengthy argument, in its response to the petitions for review, that the Federal Circuit could not have mandated that the Commission examine the obviousness of the crystal structure of the Bouzard monohydrate is an attempt to refight a battle that it has already lost. 32/ The Commission will abide by the Federal Circuit's decision.

b. Applying the legal standard

Bristol-Myers indicates that in examining the obviousness of the Bouzard monohydrate's crystal structure, we should first determine "the motivation or suggestion in the prior art to produce the new structure; [and] the problem confronting the inventor." 33/ The Federal Circuit determined that the temporary relief record was devoid of any evidence indicating

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31/ Bristol-Myers, slip op. at 10 (emphasis added).

32/ See Biocraft Response at 15-19. The quoted excerpt also rebuts respondents' arguments that to require obviousness of crystalline chemical structures would constitute a major change in the law, and that the Federal Circuit would not have announced such a major change in an unpublished opinion. As the excerpt indicates, the court perceived such a requirement to be consistent with precedent.

33/ Bristol-Myers, slip op. at 7-8.

motivation to produce cefadroxil with the structure of the Bouzard monohydrate. 34/

We do not believe that the record on permanent relief is materially different in this regard. The ID merely determined that motivation existed to produce an improved form of cefadroxil -- not the particular structure represented by the Bouzard monohydrate. Similarly, respondents assert motivation only to produce a cefadroxil monohydrate rather than any specific structure. 35/ Indeed, the record demonstrates that Bristol's initial discovery of the Bouzard monohydrate was not the result of an experimental program designed to yield cefadroxil with a specific structure or qualities. The Bouzard monohydrate was initially formed as a result of a spontaneous conversion of a crystalline cefadroxil trihydrate that had previously been produced by Bristol. 36/ The Federal Circuit specifically cited this fact as supporting a conclusion of nonobviousness. 37/

The Federal Circuit additionally indicated that it is necessary to examine "the nature of the new structure as compared with the prior

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34/ Bristol-Myers, slip op. at 13:

> There must be an affirmative suggestion or teaching in the prior art whereby it would have been obvious to make the new monohydrate; not simply the absence of obstacle. No such suggestion or teaching has been shown.

35/ See Gema Reply at 9-9a; Biocraft Response at 21.

36/ See TEO Tr. at 303-05 (Bouzard).

37/ Bristol-Myers, slip op. at 11-12: "We once again are reminded of the perils of hindsight analysis, wherein that which was achieved after long effort, or perhaps serendipitously, is with hindsight deemed obvious."

art." 38/ The court found that, in contrast to the '657 patent, neither Crast nor Garbrecht claims a specific crystalline form of cefadroxil and that Garbrecht also fails to claim a specific hydration. 39/ The ID similarly found that the relevant portions of the Garbrecht and Crast patents merely taught processes for making purified cefadroxil products and did not reveal products having a specific crystalline form. 40/ The ID further found that:

> the form of cefadroxil could not be predicted accurately until the experiment was made. Dr. Garbrecht expected that the cefadroxil DMF solvate produced by his '282 patent process would be crystalline, and that the final product of the aqueous crystallization procedure would be a solid, but he had no expectations about the nature of its crystallinity or hydration. (Tr. 342-44.) Dr. Baldwin [a Bristol expert witness] agreed with Dr. Garbrecht, and testified that no chemist could predict the form of hydration that a cefadroxil crystal could take. (Tr. 228.) 41/

Respondents have not disputed or contested this finding. To the contrary, one of their own expert witnesses also testified that he would not have been able to predict in advance the form of the Bouzard monohydrate. 42/

Consequently, the record indicates that the prior art did not and could not have suggested the particular structure and form of the Bouzard monohydrate. Respondents argue that the "predictability" of the Bouzard monohydrate has no relevance to a determination on obviousness, and instead direct our attention to the evidence that they submitted and the ID

38/ Bristol-Myers, slip op. at 8.

39/ Bristol-Myers, slip op. at 4, 5.

40/ See ID at 8 (Garbrecht), 35 (Garbrecht), 49 (Crast).

41/ ID at 8-9.

42/ TEO Tr. 617-18, 644-45 (Gema witness Dunitz).

discussed concerning the obviousness of the modifications to the Crast and Garbrecht patents needed to produce the Bouzard monohydrate. The Federal Circuit, however, has ruled that "predictability" does matter, and that respondents' reliance on the obviousness of changes to prior art processes is in vain:

> The patentability of a new chemical structure is independent of how it is made. See, e.g., In re Hoeksema, 332 F.2d 374, 377, 141 USPQ 733, 736 (CCPA 1964) (product patentable, although the process was unpatentable for obviousness). Expert witnesses for both sides, Dr. Dunitz for the intervenors and Dr. Baldwin for Bristol-Myers, agreed that the Bouzard crystal structure was not predictable from the known forms of cefadroxil. 43/

We believe that the record does not contain clear and convincing evidence, or any evidence at all, that the crystal structure of the Bouzard monohydrate was obvious from the prior art Crast or Garbrecht patents. Consequently, respondents have not made the showing required by Bristol-Myers to support a conclusion that the '657 patent is obvious in light of the prior art.

2. Objective Criteria of Obviousness

The Supreme Court decision in the John Deere case states that consideration of "secondary," or "objective," criteria of obviousness "might have relevancy." Subsequent Federal Circuit precedent has given greater prominence to the objective criteria, indicating that evidence concerning them should be considered whenever present. 44/ These criteria

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43/ Bristol-Myers, slip op. at 12-13.

44/ E.g., Fromson v. Advance Offset Plate, Inc., 755 F.2d 1549, 1555 (Fed. Cir. 1985); Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 1538 (Fed. Cir. 1983).

include commercial success, long-felt but unresolved need for the claimed invention, copying, unexpected properties, and industry acquiescence. 45/

The ID examined objective criteria, but accorded them little weight in light of what it concluded was strong evidence of nonobviousness resulting from the comparison of the Bouzard monohydrate with the prior art Crast and Garbrecht patents. 46/ The legally flawed prior art comparison thus taints the ID's conclusions concerning the objective criteria as well. We therefore reexamine those criteria and the weight that they should be given.

Commercial Success. The ID found that "there is evidence of commercial success" for the Bouzard monohydrate. 47/ Although the ID does not fully explain the basis for this finding, it is supported by ample evidence in the record. As the ID indicated, Bristol commercially markets the Bouzard monohydrate under the trade names DURICEF and ULTRACEF. 48/ In 1988, before respondents began to market their allegedly infringing products, DURICEF and ULTRACEF had sales exceeding $100 million and were Bristol's largest selling prescription pharmaceutical products. 49/

45/ See Akzo, N.V. v. USITC, 808 F.2d 1471, 1480 (Fed. Cir. 1986), cert. denied, 482 U.S. 909 (1987); Customs Accessories, Inc. v. Jeffrey-Allan Industries, Inc., 807 F.2d 955, 960 (Fed. Cir. 1986).

46/ See ID at 64 ("If it is clear that one with ordinary skill in the art would be likely to make the product rather easily, in a number of different ways, then the secondary considerations or indirect objective evidence of obviousness may not be as important as they might otherwise be.").

47/ ID at 64.

48/ Staff ex. 3 at 16; see TEO Tr. 104 (Bristol witness Ross).

49/ TEO Tr. at 105 (Ross).

The foregoing facts establish that (1) Bristol markets a commercially successful product and (2) that product is the invention claimed in the '657 patent. Federal Circuit precedent indicates that such facts are sufficient to establish a prima facie showing of commercial success. 50/

Respondents, however, argue that the record does not establish commercial success. Gema maintains that Bristol cannot establish commercial success unless it also demonstrates that its claimed invention has unexpected properties. 51/ As the foregoing discussion indicates, this is simply an incorrect statement of the law. Biocraft and the Kalipharma respondents argue that, to support a finding of commercial success, Bristol must show that the popularity of DURICEF and ULTRACEF stems from some quality that distinguishes the Bouzard monohydrate from other forms of cefadroxil. 52/ The Federal Circuit, however, has indicated that, to establish commercial success, a patentee need only prove a prima facie case and need not disprove that extraneous factors other than the claimed invention are responsible for a product's success in the market. It is the parties challenging the patent that have the burden of producing evidence showing that extraneous factors are responsible for the product's success. 53/ Respondents have not satisfied this burden.

50/ See Demaco Corp. v. F. von Langsdorff Licensing Ltd., 851 F.2d 1387, 1392 (Fed. Cir.), cert. denied, 109 S. Ct. 395 (1988).

51/ Gema Reply at 46.

52/ Biocraft Response at 36; Kalipharma Response at 51.

53/ See Demaco, 851 F.2d at 1393-94.

Consequently, we conclude that the record supports the ID's finding of commercial success. The Federal Circuit has held that commercial success is a strong factor favoring nonobviousness. 54/

Long-Felt Need. The ID also found that the Bouzard monohydrate satisfied a long-felt but unresolved need. It determined that there was a substantial need to find a commercially-usable form of cefadroxil, and noted that the record indicated numerous attempts and failures by Bristol scientists to obtain such a product between the time that Bristol first developed cefadroxil and the time it discovered the Bouzard monohydrate. 55/

The only respondent to attack this finding is Biocraft, which argues that Bristol had produced two commercially viable forms of cefadroxil prior to making the Bouzard monohydrate. 56/ The record, however, indicates that these prior forms of cefadroxil were difficult to compact into pills or had stability problems. 57/ The Bouzard monohydrate, by contrast, has a greater bulk density than prior forms of cefadroxil, which facilitates pill production and packaging. 58/ It also has greater stability, making it preferable for aqueous suspension dosages. 59/ Moreover, neither Bristol

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54/ Akzo, 808 F.2d at 1481; see Demaco, 851 F.2d at 1391.

55/ See ID at 64-65.

56/ Biocraft Response at 35.

57/ TEO Tr. at 302-05, 318 (Bristol witness Bouzard).

58/ TEO Tr. at 305 (Bouzard); Bristol ex. 45, serial no. 931,800 file wrapper at 162.

59/ Bristol ex. 45, serial no. 931,800 file wrapper at 163.

nor any other firm has ever attempted to market commercially these prior art forms of cefadroxil. A reasonable inference from these facts is that the Bouzard monohydrate was the first form of cefadroxil that entirely satisfied commercial marketing requirements.

As the ID found, and no party contests, Bristol engaged in considerable experimentation before its discovery of the Bouzard monohydrate. The record therefore supports the ID's conclusion that the Bouzard monohydrate satisfied a long-felt but unresolved need. This provides further support for a conclusion of nonobviousness. 60/

Copying. The ID found, and no party disputes, that respondents have marketed cefadroxil products that copy the Bouzard monohydrate notwithstanding the availability in the public domain of other forms of cefadroxil that do not infringe the '657 patent. The ID further found that one reason that respondents have copied the Bouzard monohydrate is that copying facilitates the process of obtaining approval from the Food and Drug Administration (FDA). FDA approval is necessary before a drug can be marketed in the United States. The ID found that expediting the FDA approval process was not the sole reason for respondents' copying, but reached no conclusion as to whether copying was a consideration supporting or refuting obviousness. 61/

Respondents argue that their copying should be accorded no weight in the obviousness determination because it is done solely to facilitate FDA

60/ See Under Sea Industries, Inc. v. Dacor Corp., 833 F.2d 1551, 1559 (Fed. Cir. 1987).

61/ See ID at 65.

approval. 62/ We cannot accept this argument. As the ID acknowledged, the fact the Bouzard monohydrate has already received FDA approval has affected respondents' decision to market that form of cefadroxil. Nevertheless, we believe that other factors influenced that decision as well. It is reasonable to infer that the proven demand for the Bouzard monohydrate, as well as its superior density and stability properties discussed above, led respondents to believe that they could obtain better acceptance in the marketplace for a cefadroxil product that copied the Bouzard monohydrate than for one that did not.

We therefore cannot agree that copying should be accorded no weight whatsoever. We instead find, pursuant to Federal Circuit precedent, that respondents' copying of a claimed invention, rather than one in the public domain, constitutes evidence of nonobviousness. 63/ 64/

Unexpected Properties. The ID states that Bristol no longer contends that the Bouzard monohydrate is unexpectedly superior to prior art forms of cefadroxil. 65/ Bristol asserts that it has not abandoned this argument and

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62/ Biocraft Response at 37; Gema Reply at 44-45; Kalipharma Response at 52.

63/ Specialty Composites v. Cabot Corp., 845 F.2d 981, 991 (Fed. Cir. 1988); Windsurfing International, Inc. v. AMF, Inc., 782 F.2d 995, 1000 (Fed. Cir.), cert. denied, 477 U.S. 905 (1986).

64/ Commissioner Rohr believes that the evidence in the record with regard to the reasons for copying is very inconclusive and does not rely on copying as evidence of obviousness or nonobviousness.

65/ See ID at 65-66.

contends that the Bouzard monohydrate's "accidental" discovery is proof of unexpected properties. 66/

The record supports a finding of no unexpected properties. As the ID found, the clinical effectiveness of the Bouzard monohydrate was precisely the same as that of prior art forms of cefadroxil. 67/ There is no evidence that the superiority of the bulk density and solubility of the Bouzard monohydrate over prior cefadroxil forms was unexpected. 68/ Finally, the "accidental" nature of the discovery of the Bouzard monohydrate is entirely irrelevant to the question whether it possesses unexpected properties. Consequently, we believe that the "unexpected properties" factor neither supports nor refutes a conclusion of obviousness.

Industry Acquiescence. The ID concluded that there is no evidence that the industry as a whole accepts the '657 patent as valid. 69/ Clearly, respondents do not accept the patent as valid. The ID also noted that a non-respondent foreign manufacturer of cefadroxil, Dobfar Industria Chimica Farmaceutica S.p.A. of Milan, Italy, was planning to import cefadroxil into the United States. 70/ Neither Bristol nor any other party has contested the ID's findings on acquiescence.

Conclusion. Three of the relevant objective criteria -- commercial success, long-felt need, and copying -- support a conclusion of non-

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66/ Bristol Petition for Review at 13 n.*, 62.

67/ Biocraft/Gema Exs. 7, 28.

68/ See TEO Tr. 348 (Bouzard).

69/ ID at 66.

70/ ID at 66. See also section III.A.3. below.

obviousness. We believe that examination of the objective criteria lends further support to the conclusion of nonobviousness reached by comparing the '657 patent with the prior art pursuant to the standard of Bristol-Myers.

C. Conclusion

Because we believe that both comparison of the '657 patent with the prior art and examination of the objective criteria of obviousness support the conclusion that the '657 patent is not obvious, we reverse the ID and conclude that the '657 patent is not invalid as obvious under 35 U.S.C. § 103. 71/ Because those portions of the ID that the Commission determined not to review (1) found that Bristol had established all elements of a section 337 violation except for patent validity and (2) rejected respondents' remaining arguments that the '657 patent is invalid or unenforceable, we also conclude that each of the respondents has violated section 337 in the importation and/or sale of crystalline cefadroxil monohydrate infringing the '657 patent.

71/ Before the ALJ, Bristol had argued that if the '657 patent was obvious in light of Garbrecht, modification of Garbrecht could succeed in producing the Bouzard monohydrate only because of the effects of crystal seeding. Bristol has argued that tiny crystals, or "seeds," of the Bouzard monohydrate in the atmosphere will transform the product that otherwise would have been produced by Garbrecht into the Bouzard monohydrate. Because the ID found the '657 patent to be prima facie obvious in light of Garbrecht, it considered Bristol's affirmative defense of seeding, as well as respondents' counterdefenses thereto. See ID at 14-34.

Because we do not find the patent to be prima facie obvious, we believe that consideration of Bristol's seeding defense and respondents' counterdefenses is unnecessary. We therefore take no position with respect to the seeding issue. We note that Bristol had requested Commission consideration of its seeding defense only if the Commission upheld the ID's conclusion that the '657 patent is prima facie obvious. Bristol Petition at 5 n.*.

III. REMEDY

A. Exclusion Order

1. Authority to Issue Limited Exclusion Orders

As a threshold matter, we examine whether we have the discretion to issue a limited exclusion order. Bristol contends that we do not. It states that section 337(d) mandates that the Commission issue a general exclusion order unless the public interest dictates otherwise. According to Bristol, "[t]he literal meaning of the statutory language 'shall' is mandatory in its execution; it does not permit any exclusion remedy short of excluding all the articles from entry into the United States." 72/

Bristol's "literal meaning" argument fails on a number of grounds. The 1935 Supreme Court case of Escoe v. Zerbst, which Bristol cites as holding that the word "shall" is the language of mandate, actually states that use of "shall" is "not controlling" as to whether a statute has a mandatory effect. 73/ Subsequent precedent similarly indicates that statutes providing that the government "shall" take certain action do not

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72/ Bristol Remedy Brief at 19 (footnotes omitted).

73/ 295 U.S. 490, 493 (1935). Escoe in turn cites Richbourg Motor Co. v. United States, 281 U.S. 528, 534 (1930), which holds that "'shall' is sometimes the equivalent of 'may' when used in a statute prospectively affecting government action."

automatically divest the government of discretion. 74/ We therefore cannot accept Bristol's argument that use of the word "shall" is controlling. 75/

Indeed, the Commission has construed section 337(d) as providing it with the discretion to issue limited exclusion orders for over eight years. 76/ Under the frequently-cited Supreme Court holding in Chevron U.S.A. Inc. v. Natural Resources Defense Council, 77/ the Commission's construction must be deemed correct unless clearly contrary to Congressional intent. Bristol has not cited, and we cannot locate, any material in the legislative history of section 337 evidencing a Congressional intent to limit the Commission's discretion in selecting the appropriate form of exclusion

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74/ United States v. Reeb, 433 F.2d 381, 383 (9th Cir. 1970), cert. denied, 402 U.S. 912 (1971):

> "[S]hall" may sometimes be directory only, just as "may" may be mandatory. [Citation omitted.] The interpretation of these words depends upon the background, circumstance, and context in which they are used and the intention of the legislative body or administrative agency which used them.

75/ Even assuming arguendo that Bristol is correct in arguing that the word "shall" is the language of command, its "plain meaning" argument still fails. It is an axiom of statutory construction that statutes are to be construed as a whole and statutory phrases are not to be read in isolation. E.g., United States v. Morton, 467 U.S. 822, 828 & n.8 (1984); In re Nantucket, Inc., 677 F.2d 95, 98 (C.C.P.A. 1982). Any reading of section 337(d) as requiring the Commission to issue a general exclusion order unless the public interest deems otherwise cannot be reconciled with language in section 337(f) that the Commission may issue cease and desist orders "[i]n addition to, or in lieu of, taking action under subsection (d). . . ." Thus the statute does not compel use of a specific remedy, as Bristol contends, but explicitly gives the Commission a choice of remedies.

76/ The Commission first issued a limited exclusion order in Certain Headboxes, Inv. No. 337-TA-82A, USITC Pub. 1197 (November 1981), an investigation in which the President had previously disapproved a general exclusion order for overbreadth.

77/ 467 U.S. 837 (1984).

orders. To the contrary, recent changes in the statute have increased, rather than restricted, the Commission's flexibility in determining the appropriate remedy for a section 337 violation. 78/ Moreover, although Congress amended the remedial provisions of section 337 as recently as 1988, it has not amended the statute to preclude the Commission from issuing limited exclusion orders. Such Congressional acquiescence to the Commission's practices further supports the proposition that the Commission's construction of section 337(d) is permissible. 79/ Federal Circuit precedent is in accord. That court, in upholding Commission issuance of a limited exclusion order, has determined that "under [section 337(d)] the Commission has broad discretion in selecting the form, scope, and extent of the remedy. . . ." 80/

The Commission's broad discretion to determine section 337 remedies includes the authority to issue either general or limited exclusion orders.

78/ In 1974, section 337 was amended to permit the Commission to consider public interest factors in fashioning the nature and type of relief. In 1988, the section was amended to expressly confirm the Commission's authority to issue both exclusion and cease and desist orders directed at the same unfair trade practice. Additionally, section 337(g)(1), added to the statute in 1988, expressly references the limited exclusion order as an appropriate remedy in default proceedings.

79/ See Zemel v. Rusk, 381 U.S. 1, 11-12 (1965); Abourezk v. Reagan, 785 F.2d 1043, 1055 (D.C. Cir. 1986), aff'd by an equally divided court, 484 U.S. 1 (1987).

80/ Viscofan, S.A. v. USITC, 787 F.2d 544, 548 (Fed. Cir. 1986). The party in Viscofan challenging issuance of the limited exclusion order did not contest, as does Bristol here, the Commission's authority to issue such orders. It instead argued that the Commission erred by issuing a limited exclusion order rather than a cease and desist order. The court affirmed the Commission's choice of remedy.

Nothing in the statutory language, legislative history, or court precedent supports Bristol's contrary view.

2. The Spray Pumps Criteria

In considering whether to issue a general exclusion order, we have traditionally balanced complainant's interest in obtaining complete relief against the public interest in avoiding the disruption of legitimate trade that such relief may cause. 81/ Thus, we determined in Certain Airless Paint Spray Pumps 82/ that a complainant seeking a general exclusion order must prove "both a widespread pattern of unauthorized use of its patented invention and certain business conditions from which one might reasonably infer that foreign manufacturers other than the respondents to the investigation may attempt to enter the U.S. market with infringing articles." Factors relevant to demonstrating whether there is a "widespread pattern of unauthorized use" include:

(a) a Commission determination of unauthorized importation into the United States of infringing articles by numerous foreign manufacturers;

(b) the pendency of foreign infringement suits based upon foreign patents which correspond to the domestic patent at issue;

81/ See, e.g., Certain Dynamic Random Access Memories, Inv. No. 337-TA-242, USITC Pub. 2034 at 84 (November 1987). Bristol argues that there is no need to engage in such balancing in this investigation because there is no possibility of "legitimate trade" in cefadroxil. We do not agree. The '657 patent at issue in this investigation covers only one specific form of cefadroxil, the Bouzard monohydrate. Even assuming arguendo the accuracy of Bristol's assertion that no other form of cefadroxil is currently marketed anywhere in the world, it is possible that forms of cefadroxil that do not infringe the '657 patent could be imported and marketed before expiration of that patent.

82/ Inv. No. 337-TA-90, USITC Pub. 1199 at 18 (May 1981).

(c) other evidence which demonstrates a history of unauthorized foreign use of the patented invention. 83/

Factors relevant to showing whether the "certain business conditions" exist include:

(a) an established market for the patented product in the U.S. market and conditions of the world market;

(b) the availability of marketing and distribution networks in the United States for potential foreign manufacturers;

(c) the cost to foreign entrepreneurs of building a facility capable of producing the patented article;

(d) the number of foreign manufacturers whose facilities could be retooled to produce the patented article; or

(e) the cost to foreign manufacturers of retooling their facility to produce the patented article. 84/

On the issue of "widespread pattern of unauthorized use," Bristol alleges that four companies manufacture bulk crystalline cefadroxil monohydrate powder that infringes the '657 patent. Two of these companies, IBI and Gema, are respondents. A third, Dobfar Industria Chimica Farmaceutica S.p.A. of Milan, Italy ("Dobfar"), is not a respondent but currently exports bulk cefadroxil to the United States. Dobfar-manufactured product is imported and marketed in the U.S. by non-respondent Zenith Laboratories, Inc. ("Zenith"). The fourth manufacturer, Dae Woong Pharmaceutical Co. of Seoul, Korea, ("Dae Woong") is not a respondent and does not currently export cefadroxil to the United States.

83/ Id. at 18-19.

84/ Id. at 19.

Bristol also alleges that extensive foreign marketing and distribution networks exist. 85/

On the issue of whether business conditions exist that would make new foreign entrants into the U.S. market likely, Bristol maintains that establishment of a manufacturing line for cefadroxil can be accomplished relatively easily by existing pharmaceutical companies. 86/ Bristol, a large company that operates pharmaceutical production facilities and presumably employs people knowledgeable about their operation, provides only an undocumented one-paragraph assertion of an in-house patent attorney on this point. Nonetheless, we still view the assertion as probative. A recent Commission report in an antidumping investigation concerning the cephalosporin antibiotic cephalexin reached a similar conclusion. 87/ Bristol does not, however, attempt to tabulate or estimate the number of pharmaceutical manufacturers that might be likely candidates to initiate cefadroxil production. It merely states that such manufacturers exist.

85/ We note, however, that non-respondent manufacturer Dae Woong and a number of the marketers and distributors are based in the Republic of Korea, where Bristol's cefadroxil patent has been found to be invalid. See Kalipharma exs. 128-130.

86/ Almula Declaration, par. 5F.

87/ See Generic Cephalexin Capsules from Canada, Inv. No. 731-TA-423 (Final), USITC Pub. 2211 at A-6 (August 1989) (finding that equipment used for producing cephalexin could be used for producing other cephalosporins, including cefadroxil, after a cleaning and sterilization process).
Commissioner Rohr notes that there was also evidence in that investigation indicating that as a general matter plants tended to specialize in particular products and that companies would not often switch a plant from one product to another not in the same family. Nevertheless he concurs with his colleagues that new cefadroxil lines could be established "relatively" easily.

Bristol acknowledges the existence of significant barriers to entry. It concedes that "the cost of setting up such facilities [for the production of antibiotics] from scratch is significant." 88/ Bristol spent $20 million to construct its own cefadroxil manufacturing facility, 89/ and has submitted a press report stating that Biocraft intends to spend between $25 million and $30 million for completion of a new antibiotic manufacturing facility in Missouri. 90/ Additionally, any new foreign manufacturer's product must receive approval from the FDA before it is marketed in the United States. Although Bristol (through its lawyers rather than sworn experts) contends that such approval is easier and faster for an existing drug than for a new one, it does not contend that the approval process is easy or fast in absolute terms. To the contrary, Bristol acknowledged in its complaint that, even for generic drugs, "[t]he FDA approval process is expensive. . . ." 91/ The record further indicates that the speed of the FDA approval process varied considerably among respondents. 92/

The record indicates that four firms currently manufacture bulk cefadroxil, that an unknown number of existing pharmaceutical firms could relatively easily convert their manufacturing processes to cefadroxil

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88/ Bristol Remedy Brief at 17.

89/ See TEO ID at 9.

90/ Bristol Remedy Brief, Ex. C.

91/ Complaint, par. 48.

92/ For Gema, the approval process took less than two months, Staff Ex. 6(C) at 13; for Purepac, seven months, Bristol Complaint, ex. D; for IBI, nine months, Bristol Complaint, ex. C; for Biocraft, [ ], Staff Ex. 5(C) at 16.

production but would need to undergo an expensive and potentially time-consuming FDA approval process before they could market their product in the United States, and that any firm wishing to begin a cefadroxil production operation from scratch would need to surmount the twin barriers of high start-up costs and the FDA approval process. Although Bristol's showing of conditions supporting issuance of a general exclusion order is better than the one it made in the temporary relief proceeding, it is still weak. Cases in which the Commission has issued general exclusion orders have generally involved greater numbers of manufacturers and/or much easier conditions of market entry. 93/ 94/ Because Bristol has not satisfied the Spray Pumps criteria, we will not issue a general exclusion order.

93/ See Certain Strip Lights, Inv. No. 337-TA-287, Commission Opinion at 5 (October 3, 1989) (unpublished opinion) (eight foreign factories produced infringing goods in addition to the one owned by named respondent; production start-up costs minimal); Certain Reclosable Plastic Bags and Tubing, Inv. No. 337-TA-266, USITC Pub. 2171 (March 1989) (infringement by 10 foreign respondent manufacturers and at least one foreign non-respondent manufacturer); Certain Plastic Light Duty Screw Anchors, Inv. No. 337-TA-279, Commission Opinion at 5 (January 30, 1989) (unpublished opinion) (ten foreign distributors, including four respondents, had imported infringing goods into the United States; only modest capital investment necessary to acquire machinery to produce infringing articles); Certain Apparatus for Installing Electrical Lines, Inv. No. 337-TA-196, USITC Pub. 1858 at 14 (May 1986) (although existence of only three foreign manufacturers established, new foreign entrants into the market likely because virtually any machine shop having a drill grinder and induction welding equipment could produce infringing goods).

94/ Vice Chairman Cass regards the number of importing firms as not having independent significance to the propriety of a general exclusion order. Rather, he believes that this evidence is at best a source of inferences regarding the ease of entry into the market for arguably infringing imports. Direct evidence on that point, discussed above, amply demonstrates the absence of a basis for issuance of a general exclusion order in this investigation.

3. The Issue of "Complete Relief"

We next consider whether we should attempt to structure relief in a manner that would exclude all cefadroxil currently imported into the United States that Bristol alleges infringes the '657 patent, notwithstanding Bristol's failure to satisfy the Spray Pumps criteria for issuance of a general exclusion order. 95/ Non-respondent Dobfar currently exports to the United States bulk cefadroxil powder that it manufactures; non-respondent Zenith has FDA approval to market Dobfar-manufactured cefadroxil in the United States and currently engages in such marketing. Issuance of a limited exclusion order directed at infringing products of the three named foreign respondents -- Gema, IBI, and IBSA -- will not exclude the cefadroxil manufactured by Dobfar and marketed by Zenith. 96/ We examine whether such a result would be so inequitable to Bristol as to warrant deviating from the criteria of Spray Pumps concerning when the Commission may issue relief affecting non-respondents. As explained below, we conclude that because Bristol could have named Zenith and Dobfar as proposed respondents before institution of or at a very early stage in this investigation, no inequity exists in issuing a limited exclusion order directed only at the infringing products of named respondents.

95/ This consideration is sua sponte. Despite an invitation by one Commissioner to do so, see Temporary Relief Opinion at 5 n.10 (footnote of Commissioner Newquist), Bristol did not request, even in the alternative, any relief narrower in scope than a general exclusion order.

96/ Although the product exported by Gema, IBI, and IBSA has been found to (or been conceded to) infringe the '657 patent, no such finding has been made with respect to the product exported by Dobfar and marketed by Zenith.

We do not believe that we should deviate from Spray Pumps when the complainant has requested that relief be directed against a specific entity that could have been, but was not, proposed as a respondent in the complaint or at an early stage in the investigation. Any contrary practice would subvert our policy of "encourag[ing] complainants to include in an investigation all those foreign manufacturers which it believes have entered, or are on the verge of entering, the domestic market with infringing articles." 97/ Moreover, if complainants had the assurance that, even if they did not satisfy the requirements for a general exclusion order, they would still receive relief against non-respondent entities then engaging in importation or marketing of the infringing imported goods, they would actually have an incentive not to name such entities that could raise strong defenses to allegations of section 337 violations as respondents, or to file only against likely defaulters.

Bristol, in its reply brief on remedy, offers the following explanation for its failure to name Dobfar and Zenith as respondents:

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97/ Spray Pumps, Commission Opinion at 18 n.1.

98/ [ ]

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A complete examination of the record reveals that Bristol's explanation is at best incomplete.

Bristol filed a complaint with the Commission on February 1, 1989, in which it proposed six respondents -- the same six firms that are currently respondents. At the time the complaint was filed, none of the proposed respondents were actually marketing crystalline cefadroxil monohydrate in the United States. Two of the proposed respondents -- Biocraft and Gema -- had not yet received FDA approval to market crystalline cefadroxil monohydrate. 100/

Bristol was aware, however, that Biocraft and Gema were not the only parties with pending FDA applications to market cefadroxil. On January 17, 1989 -- approximately two weeks before the complaint was filed -- Zenith sent Bristol a letter indicating its intention to market cefadroxil in the United States upon receiving approval from the FDA. 101/ Under the terms of

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99/ Bristol Reply Submission to the Commission on Remedy, the Public Interest, and Bonding at 19-20.

100/ Gema's FDA approval came on February 2, 1989. Staff ex. 6(C) at 13. Biocraft's approval came on February 10, 1989. Staff ex. 5(C) at 16.

101/ Kalipharma ex. 112, ex. C. Although the letter does not expressly state that the cefadroxil that Zenith intended to market would be manufactured by Dobfar, Bristol was aware that Dobfar was the manufacturer whose bulk cefadroxil Zenith had used in a prior attempt to market cefadroxil. Kalipharma ex. 65. Moreover, Bristol knew less than two weeks after initiation of this proceeding, at the latest, [

] See Staff Ex. 6(C) at 6; Staff Ex. 7(C) at 5-6.

a 1987 consent order concluding patent infringement litigation initiated against it by Bristol relating to the '657 patent, Zenith was required to provide Bristol with 50 days advance notice if Zenith intended to market cefadroxil in the United States. 102/ Bristol made written submissions to the FDA in February 1989 concerning the Zenith application. 103/ Bristol also had at least one telephone contact with FDA officials. A Bristol inter-office memorandum of a February 28, 1989, telephone conversation with the FDA indicated that the Zenith application was discussed; additionally, Bristol was informed that Dobfar had an outstanding application for cefadroxil on file with the FDA. 104/

Although neither Bristol's complaint nor the supplement thereto contains any reference to Zenith, Dobfar, or their pending FDA applications for cefadroxil, the Commission was nonetheless apprised of Zenith's existence prior to instituting this investigation. On February 24, 1989, the United States District Court for the District of New Jersey granted a preliminary injunction (shortly thereafter vacated) in patent infringement litigation between Biocraft and Bristol. The ruling identified Zenith as a company preparing to enter the U.S. cefadroxil market.

Upon receipt of the New Jersey ruling, the IA then assigned to this investigation requested information from Bristol concerning Zenith. Bristol's counsel wrote virtually identical letters to the IA and the Commission discussing the consent order, the representation therein that

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102/ Kalipharma ex. 112, ex. A.

103/ Kalipharma ex. 157.

104/ Kalipharma ex. 113.

Zenith "had no present intention or imminent ability to manufacture, use or sell in the United States crystalline cefadroxil monohydrate which was within the scope of the claim of the '657 patent," and the 50-day notification requirement. 105/ Bristol did not mention in either letter (1) that Zenith then had a present intention of marketing cefadroxil in the United States; (2) that Zenith had in fact communicated this intention to Bristol pursuant to the 50-day notification requirement; and (3) that Bristol was aware Zenith and Dobfar then had applications to market cefadroxil pending with the FDA. Bristol's remedy submissions to the Commission similarly omit any reference to that company's pre-institution knowledge of Zenith and Dobfar's intention to market cefadroxil in the United States.

Bristol's assertion in its remedy papers that Zenith and Dobfar suddenly thrust themselves onto the U.S. market after the TEO ID is inaccurate. 106/ In fact, Bristol knew of their intention to enter the market before the investigation was initiated. 107/ Even so, it did not name Zenith and

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105/ Letter from James Galbraith, Kenyon & Kenyon, to Cheri Taylor, OUII (March 3, 1989); Letter from James Galbraith to Kenneth R. Mason, Commission Secretary (March 6, 1989).

106/ Bristol's repeated assertions that Zenith and Dobfar did not commence importation until after issuance of the TEO ID, even if technically accurate, are misleading. In fact, Zenith submitted a second notification to Bristol, indicating its intention to market Dobfar-manufactured cefadroxil, on May 11, 1989. Kalipharma ex. 112, ex. E. This was twelve days before the TEO ID was issued, and thirteen days before it was served. Far from being tendered "when this Investigation was very far along," as characterized by Bristol, the notice was provided less than two months after the investigation was initiated.

107/ Bristol relies heavily on [

(continued...)

Dobfar as proposed respondents although it did name as proposed respondents other firms which sought to enter the market and which had FDA applications pending.

Assuming arguendo that the Commission would consider issuing a remedy reaching non-respondents, despite failure to meet the Commission's often-articulated Spray Pumps criteria, circumstances warranting such action are absent here. Accordingly, we have issued a limited exclusion order directed solely at the imports of the named foreign respondents -- Gema, IBI, and IBSA. 108/

107/(...continued)

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108/ To the extent such a limited exclusion order does not provide Bristol with complete relief against all current allegedly infringing imports, the cause lies not in section 337 or the Commission, but in Bristol's own litigation strategy. Moreover, Bristol has a forum for its dispute against Zenith and Dobfar. Bristol elected to file suit against those two firms in the United States District Court for the District of New Jersey, and has a hearing on its request for a preliminary injunction scheduled to occur on March 27, 1990. If Bristol succeeds in its preliminary injunction request, it will receive relief, at least on a temporary basis, equivalent to that it would have received had the Commission issued an exclusion order covering Dobfar. If Bristol does not succeed in its preliminary injunction request, it may seek to commence a second section 337 proceeding before the Commission naming Dobfar and Zenith as respondents.

B. Cease and Desist Orders

1. Against Domestic Respondents

Bristol requests that cease and desist orders be issued against the three domestic respondents (Biocraft, Kalipharma, and Purepac). This request is opposed by Biocraft, the Kalipharma respondents, and the IA. They argue that issuance of cease and desist orders is inappropriate because there is no evidence of "stockpiling," which they construe to mean above-average inventory levels.

Respondents and the IA cite Commission decisions such as Certain Compound Action Metal Cutting Snips 109/ in support of their view that above-average inventory accumulations are a prerequisite to issuance of a cease and desist order. In Snips the Commission issued cease and desist orders on the basis of a finding that "there have been importation of a large number of infringing metal cutting snips, which have yet to be sold." 110/ Snips, however, premised the grant of cease and desist orders upon the finding that significant inventories existed, not that inventories were in excess of normal or historical levels. Similarly, the cease and desist order issued in Certain High Intensity Retroreflective Sheeting 111/ was premised on the basis that the respondent had inventories of infringing goods; the Commission made no finding concerning the level of inventories relative to historic or industry norms. A unanimous Commission unequivocally indicated that information as to the level of inventories is

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109/ Inv. No. 337-TA-197, USITC Pub. 1831 (March 1986).

110/ Id., Commission Opinion at 9.

111/ Inv. No. 337-TA-268, USITC Pub. 2121 at 9 (September 1988).

immaterial to the issuance of a cease and desist order in Certain Erasable Programmable Read-Only Memories ("EPROMs"), where we issued cease and desist orders notwithstanding the record's lack of authoritative information as to inventory levels: 112/

> The Commission has in the past required evidence of significant inventories in the United States as a basis for an order to cease and desist selling in the United States. [Citation to Snips.] The precise extent of any inventories in the United States [in this investigation] is unknown, and is disputed by the parties. However, the evidence concerning [respondents'] production processes, which involve testing in the United States prior to sale, suggest that there are inventories of work in progress. On the record of this investigation, we determine this is sufficient to justify cease and desist orders directed at sales activities.

The Commission's holdings that issuance of a cease and desist order is appropriate if evidence exists of "significant" inventory levels, as opposed to inventories in excess of some historic level, are justified on a number of grounds. First, as a practical matter, a complainant will not be afforded complete relief so long as a respondent is allowed to sell without bond any commercially significant level of product in its inventory. If a respondent is permitted to sell without bond a "customary" inventory equal to, for example, two weeks' worth of sales, then the complainant still will be confronted with that amount of unfair import competition after issuance of an exclusion order. The adverse effect upon the complainant may be less than if the respondent had inventory equal to four weeks' worth of sales, but it is not insignificant or non-existent. Indeed, the recent cases that have denied requests for cease and desist orders have done so not because the respondents' inventories were not in excess of some historic level, but

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112/ Inv. No. 337-TA-276, USITC Pub. 2196 at 130-31 (May 1989).

because the record indicated that inventories did not exist or were de minimis. 113/

Additionally, records in section 337 investigations are no longer likely to contain information about inventory levels. Prior to 1988, section 337(a) required a complainant to demonstrate that unfair practices in the import trade had "the effect or tendency . . . to destroy or substantially injure an industry . . . in the United States." One factor the Commission considered in determining whether "injury" existed was the volume of imports of infringing goods. 114/ Because information about the volume of inventories was probative as to the amount of imports (or could easily be derived from subtracting U.S. sales from total imports) and thereby indicative of whether the section 337(a) "injury" requirement was satisfied, 115/ the volume of inventories was an issue on which the parties were likely to develop evidence in the proceedings before the ALJ. 116/

113/ See Certain Strip Lights, Inv. No. 337-TA-287 (October 3, 1989) (unpublished opinion) (cease and desist order inappropriate when record indicated that respondent had returned inventories to the foreign manufacturer, or at most, maintained a de minimis inventory); Certain Nonwoven Gas Filter Elements, Inv. No. 337-TA-275, USITC Pub. 2129 (September 1988) (cease and desist order denied when complainant conceded that respondent's inventory levels were not commercially significant).

114/ See, e.g., Certain Vertical Milling Machines, Inv. No. 337-TA-133, USITC Pub. 1512 (March 1984).

115/ This is indicative from the Snips case itself, where the Commission found that the inventories were a potential cause of substantial injury to the domestic industry.

116/ Nevertheless, as previously discussed, the Commission did not require proof of inventories beyond normal or historic levels as a prerequisite for issuing cease and desist orders in Snips and Retroreflective Sheeting, which were both decided prior to the recent amendments to section 337 that eliminated the "injury" requirement in patent-based cases.

The Omnibus Trade and Competitiveness Act of 1988 ("OTCA") amended section 337 to eliminate the "injury" requirement. 117/ Because the question of inventory levels is no longer relevant to the question of whether a section 337 violation exists, the Commission is now less likely to have available reliable information about inventory levels than it had in pre-OTCA section 337 investigations. This was the situation the Commission confronted in EPROMs and it is also the situation in this investigation.

Under EPROMs, respondents' assertions that they have not been "stockpiling" inventories, in the sense of hoarding them, are irrelevant even if true. 118/ The question is whether the domestic respondents maintain a commercially significant level of inventories. 119/

117/ The legislative history of OTCA addresses cease and desist orders only to make clear Congress' intent that the Commission may issue both a cease and desist order and an exclusion order to remedy the same unfair act when the public interest warrants. It gives an example of one instance in which issuance of a cease and desist order is appropriate -- that of inventory stockpiling -- but does not purport to address the scope of the Commission's authority in this regard. See S. Rep. 71, 100th Cong., 1st Sess. 131 (1987); H. Rep. 40, 100th Cong., 1st Sess. 159-60 (1987).

118/ Moreover, we do not find the assertions probative. Respondents' affidavits provide merely conclusory assertions, and are devoid of data or proof concerning inventory levels.

119/ Chairman Brunsdale and Vice Chairman Cass question whether the Commission should move toward issuing cease and desist orders whenever the Commission finds evidence that respondents hold commercially significant inventories. They believe that this practice could cause respondents to curtail their standard patterns of inventory stocking during the pendency of the proceeding in order to avoid the eventuality of being unable to sell this merchandise at a profit, or at all, should the Commission rule against them, thus unduly disrupting the normal business operations of respondents and their customers before a final determination of violation and imposing substantial hardship even on respondents not found in violation of section 337.

Whether the Commission uses evidence of stockpiling or only of

(continued...)

We believe that they do. The affidavit of Dirk Dames, Kalipharma's Vice-President, Business Planning and Control, submitted by the Kalipharma respondents, effectively concedes as much by stating that Kalipharma/Purepac inventories are at "normal" levels. 120/ The record additionally contains evidence that Biocraft has maintained substantial inventories. Biocraft has posted bonds with the Commission pursuant to the temporary cease and desist order issued against the firm, that, according to its accompanying calculations of entered value, will permit it to sell a substantial volume of cefadroxil. It is reasonable to infer, in the absence of any additional information from Biocraft, that some of this amount represents inventory.

We believe that this material constitutes the "more specific information" that the Commission indicated in its temporary relief opinion would be necessary to justify the issuance of permanent cease and desist orders. 121/ Moreover, to the extent that the Commission does not have

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119/(...continued)
commercially significant inventories as the standard for issuance of cease and desist orders, Chairman Brunsdale and Vice Chairman Cass reject the use of speculation by the Commission regarding the likely levels of respondents' inventories as the basis for conclusions with respect to either standard. In order to ensure that the Commission has the evidence that it requires to make informed decisions, they urge the Commission to amend its rules to require the ALJ to take this and other evidence relating to the appropriate remedy and bond from the parties. They agree that cease and desist orders are appropriate here in light of further developments in the record since the final determination in the related proceeding regarding temporary relief.

120/ Affidavit of Dirk Dames, par. 4.

121/ Temporary Relief Opinion at 8. By contrast, the temporary relief opinion indicated that the Commission majority was issuing temporary cease and desist orders on the basis of an evidentiary presumption that respondents had maintained significant inventory levels. Chairman

(continued...)

precise information on inventory levels, this is the fault of respondents, who have refused to provide such information -- which is clearly in their control -- despite numerous opportunities and requests to do so. 122/ Consequently, we have issued cease and desist orders to the domestic respondents, i.e., to Biocraft, Kalipharma, and Purepac.

2. Against Non-respondents

Bristol additionally seeks issuance of cease and desist orders against eight non-respondents, not including Zenith, who it asserts are domestic distributors of infringing cefadroxil. The sole factual support for this request that Bristol presents is the affidavit of Bruce Ross, the president of its U.S. pharmaceutical group. That affidavit, executed December 15, 1989, states as follows:

> I believe therefore that the other United States companies that are selling and distributing the infringing cefadroxil obtained such cefadroxil from [Biocraft, Kalipharma/Purepac, and/or Zenith]. Information provided to Bristol-Myers, which I believe to be accurate, that identifies such other United States companies, and they are: Best Generics, North Miami Beach, Florida; Bioline Labs, Inc., Brooklyn, New York; Goldline Laboratories, Inc., Fort Lauderdale, Florida; Major Pharmaceutical Corp., Chicago, Illinois; H.L. Moore Drug Exchange Inc., New Britain, Connecticut; Parmed Pharmaceuticals, Inc., Niagara Falls,

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121/(...continued)
Brunsdale and Vice Chairman Cass dissented from the use of a presumption.

122/ In its opinion on temporary relief, the Commission majority noted its dissatisfaction with the information in the record concerning the inventory levels of respondents. See Temporary Relief Opinion at 6. Nevertheless, respondents failed to provide any information quantifying their inventories in requesting reconsideration of the temporary relief orders, in their opening briefs on remedy, or in their reply briefs.

Moreover, Bristol, after issuance of the temporary relief opinion, requested that Biocraft, Kalipharma, and Purepac provide it with information concerning inventory levels. Bristol Remedy Brief, Exs. E, F. Biocraft, Kalipharma, and Purepac refused to respond to the requests. Id., Exs. I, J.

New York; Rugby Labs, Inc., Rockville Centre, New York, and Warner-Lambert, Morris Plains, New Jersey. 123/

The eight firms named in the affidavit are the non-respondents against which Bristol requests issuance of cease and desist orders.

Neither Bristol, nor its affiant, has provided (1) any further explanation of the information on which Mr. Ross bases his allegations; (2) any documentary evidence corroborating Mr. Ross's allegations; (3) any information as to whether these firms' alleged activities have continued since either the issuance of the Federal Circuit Bristol-Myers decision holding that the '657 patent is likely valid or the issuance of the January 10, 1990, temporary relief orders; 124/ (4) any allegation, much less information, as to the likelihood of these firms maintaining current inventories of infringing cefadroxil; or even (5) sufficient identification of the firms to permit service of a cease and desist order.

Assuming arguendo that the Commission has authority to issue cease and desist orders against non-respondents -- an issue we need not address -- we can see no basis for doing so here. We do not believe that the objective of providing complete relief to a successful section 337 complainant requires the Commission to issue a cease and desist order against an entity simply because a complainant alleges that the entity is marketing or distributing goods imported in violation of section 337. This is essentially what Bristol seeks; the "proof" that it offers in support of

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123/ Bristol-Myers Comments on Temporary Relief, Aff. of Bruce R. Ross, ex. 12 (footnotes omitted).

124/ The Ross affidavit was executed only one week after issuance of the Bristol-Myers decision and well before the Commission ordered temporary relief.

its request fails the most lenient tests of specificity, comprehensiveness, and documentation. We therefore have denied Bristol's request for issuance of cease and desist orders against non-respondents.

IV. PUBLIC INTEREST

Section 337 instructs the Commission to consider the effect of any remedy "upon the public health and welfare, competitive conditions in the United States economy, the production of like or directly competitive articles in the United States, and United States consumers." 125/ The Commission has declined to grant relief on public interest grounds in only three cases. In those cases, it found both (1) that a strong public interest existed in maintaining an adequate supply of the goods under investigation and (2) either that the domestic industry could not maintain an adequate supply of the goods or that the domestic users of the goods could not obtain a sufficient substitute. 126/

125/ 19 U.S.C. § 1337(d),(f). The legislative history of this provision, added to section 337 by the Trade Act of 1974, indicates that "[s]hould the Commission find that issuing an exclusion order would have a greater adverse effect on the public [interest] . . . than would be gained by protecting the patent holder (within the context of the U.S. patent laws), then . . . such exclusion order should not be issued." S. Rep. 1298, 93d Cong., 2d Sess. 197 (1974).

126/ See Certain Fluidized Supporting Apparatus, Inv. No. 337-TA-182/188, USITC Pub. 1667 (October 1984) (temporary relief denied when domestic industry could not provide adequate supply of medical product useful to public health); Certain Inclined-Field Acceleration Tubes, Inv. No. 337-TA-67, USITC Pub. 1119 (December 1980) (relief denied when exclusion order would have stifled nuclear structure research programs in public interest); Certain Automatic Crankpin Grinders, Inv. No. 337-TA-60, USITC Pub. 1022 (December 1979) (relief denied when domestic industry could not provide adequate supply of product needed for automobiles to satisfy federal energy efficiency requirements).

In this case, Biocraft and the Kalipharma respondents argue that the public interest in maintaining access to low-priced generic drugs militates against granting permanent relief. However, the very statute that respondents cite in favor of their public interest argument disavows the proposition that public policy supports an overriding right to access to generic drugs.

The legislative history of that statute, the Drug Price Competition and Patent Term Restoration Act ("the Drug Price Act"), 127/ indicates that it had two purposes. The first was to accelerate the process of obtaining FDA approval for generic drugs to allow marketing of drugs quickly after any patent or statutory period of market exclusivity expired. Congress intended not to restrict the rights of patent holders, but merely to ensure that their monopoly position did not extend beyond the expiration of the patent. 128/ The second purpose was to extend the patent term of certain pharmaceuticals beyond the statutory 17-year period to assure a minimum period of exclusive marketing. (Congress found that because the FDA approval process for a new drug is so lengthy, it could consume a large portion of the 17-year patent period.) In so doing, the legislative history indicates that Congress realized the public interest in granting patent rights to pharmaceutical companies. 129/

127/ Pub. L. 98-417, 98 Stat. 1585 (1984).

128/ See H. Rep. 877, Part II, 98th Cong., 2d Sess. 4 (1984), reprinted in 1984 U.S. Code Cong. & Ad. News 2647, 2688.

129/ H. Rep. 877, Part I, 98th Cong., 2d Sess. 17 (1984), reprinted in 1984 U.S. Code & Cong. News 2647, 2650:

> Patents are designed to promote innovation by providing the right to

(continued...)

Thus the public policy evidenced by the Drug Price Act is one of promoting access to generic pharmaceuticals, but only in a manner that does not unduly restrict the rights of pharmaceutical patent holders. Such a policy does not militate against granting relief in this case.

There is, of course, an additional public interest in maintaining an adequate supply of pharmaceuticals for U.S. consumers. This interest also does not bar relief. Bristol has sufficient capacity and resources to satisfy all domestic demand for cefadroxil, as it had until respondents entered the market in March 1989. 130/ Moreover, the availability of other cephalosporins will not be affected by the issuance of relief. The record indicates that Bristol perceives a number of these cephalosporins to be competitive with cefadroxil; that at least one of the competitive cephalosporins, cephalexin, is available in generic form; and that, even if generic cefadroxil were unavailable, [

]. 131/ The record consequently refutes respondents' contention that granting relief will somehow deprive the ill and indigent of necessary medication.

The only remaining argument respondents make is that granting relief

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129/(...continued)
exclude others from making, using, or selling an invention. They enable innovators to obtain greater profits than could have been obtained if direct competition existed. These profits act as incentives for innovative activities.

130/ TEO Tr. at 198-99 (Ross).

131/ Staff ex. 12 ("Duricef Marketing Plan -- 1988").

will raise prices to consumers. The Commission has previously held that this alone is not sufficient grounds for denying relief. 132/

We believe that respondents' public interest arguments lack merit. Consequently, we conclude that the public interest does not preclude granting relief determined to be otherwise appropriate.

V. BONDING

The parties have presented highly divergent proposals on the appropriate respondents' bond during the Presidential review period. The Kalipharma respondents request that any bond not exceed 5 percent of entered value. Biocraft expresses satisfaction at the respondents' bond of 68 percent of entered value that the Commission imposed on temporary relief. Bristol requests that the bond be established at 428 percent of entered value for cefadroxil capsules and 646 percent of entered value for bulk cefadroxil powder. The IA proposes that the bond be established at 520 percent of entered value for all cefadroxil imports.

The Kalipharma respondents' argument that a de minimis bond is sufficient to offset competitive disadvantages due to peculiarities in the generic drug market may be disposed of quickly. The argument was addressed

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132/ Acceleration Tubes, USITC Pub. 1119, Commission Opinion at 26:

> The increase in costs resulting from an exclusion order is an important consideration, but insufficient in itself to outweigh the patent owner's rights. One purpose of the patent monopoly is to enable the inventor to charge enough to recover research and development expense and provide financial reward for the innovation.

and rejected in the temporary relief opinion, 133/ and we see no reason to deviate from that conclusion here.

Bristol's argument, the essence of which has been adopted by the IA, is also one that we have seen before. Bristol suggests computation of a bond by (1) determining the difference between its and respondents' selling prices for cefadroxil; (2) imputing the entered value of respondents' imports based on its own entered value; and (3) calculating the percentage by which the entered value must be increased to eliminate the difference in selling prices. Bristol submitted nearly the same argument in its submission on temporary relief and precisely the same argument in its petition for reconsideration of the respondents' bond on temporary relief.

We did not adopt Bristol's proposal previously and will not do so here. The proposal remains fundamentally flawed. It compares respondents' cost of imported cefadroxil with its own selling prices. Even if Bristol's assumption that respondents' cost of imported cefadroxil is equal to Bristol's entered value were correct, which it is not, 134/ the comparison is still inapposite. Bristol assumes that the only cost respondents face is that of imported product. But druggists do not acquire pharmaceuticals at the dock. Between the time of importation and the time of sale,

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133/ See Temporary Relief Opinion at 8: "Contrary to respondents' assertion, the record indicates that their importation of cefadroxil provides them with a competitive advantage, viz., respondents are able to offer cefadroxil at a lower price because they, unlike Bristol-Myers, have not incurred research and development costs."

134/ Bristol estimates the entered value of the amount of cefadroxil powder necessary to make one hundred 500 mg capsules of cefadroxil at [ ]. Bristol Remedy Brief at 45 n.26. The record indicates that Biocraft actually paid Gema in 1988 an average of approximately [ ] for an equivalent amount of powder. See Staff Ex. 6(C) at 8.

respondents must incur transportation and distribution costs and, for importers of bulk powder, costs of manufacturing the product in capsule form. Bristol's bonding proposal simply ignores the existence of such costs.

Bristol maintains that there is a huge difference between respondents' entered value and selling prices for cefadroxil, yet its own gap is much larger. This large differential may be because of substantial distribution and processing costs, Bristol's research and development expenses, or because both Bristol and respondents maintain extremely high profit margins for cefadroxil. Some of these factors would be relevant to a bonding determination, but others might not. Nonetheless, Bristol provides no information purporting to explain the reasons for this differential and does no more than highlight its existence. Such a line of argument furnishes no information on which the Commission can base a bonding determination. 135/

Consequently, the record contains no information pertaining to respondents' bond beyond that available when the Commission decided temporary relief. We agree with Biocraft that no basis exists for deviating from the bonding determination on temporary relief.

The Commission, in its temporary relief opinion, set respondents' bond at 68 percent of entered value for both cefadroxil capsules and bulk

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135/ In the temporary relief opinion, one Commissioner specifically asked parties in future submissions to "more critically address the appropriate measure of respondents' bond and offer evidence to assist the Commission on setting the bond." Temporary Relief Opinion at 10 n.26 (footnote of Vice Chairman Cass). Nevertheless, no party has presented any new evidence pertaining to the bonding issue.

cefadroxil. This computation, based on the difference between respondents' and Bristol's prices for cefadroxil monohydrate, is based on a method that we have utilized in prior proceedings. 136/ 137/ In the absence of information that could permit application of a different calculation method, we will again calculate the bond based on the difference in prices. Therefore, we have established respondents' bond during the presidential review period at 68 percent of entered value for both cefadroxil capsules and bulk cefadroxil.

136/ See Certain High Intensity Retroreflective Sheeting, Inv. No. 337-TA-268, USITC Pub. 2121 at 12 (September 1988); Certain Foam Earplugs, Inv. No. 337-TA-184, USITC Pub. 1671 at 4 (March 1985).

137/ Vice Chairman Cass recognizes that this means of setting respondents' bond is in line with Commission practice. However, he believes that price differences are likely to reflect many things, only one of which might be differential investments in research and development. In future cases he would ask that parties more critically address the appropriate measure of respondents' bond and offer evidence to assist the Commission on setting that bond.

CERTAIN CRYSTALLINE
CEFADROXIL MONOHYDRATE

337-TA-293

CERTIFICATE OF SERVICE

I, Kenneth R. Mason, hereby certify that the attached NOTICE OF COMMISSION DECISION was served upon Mark Bernstein, Esq. and upon the following parties via first class mail, and air mail where necessary, on March 15, 1990.

Kenneth R. Mason, Secretary
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CERTIFICATE OF SERVICE Pg.2

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

In the Matter of	)	
CERTAIN CRYSTALLINE CEFADROXIL MONOHYDRATE	)	Investigation No. 337-TA-293

NOTICE OF DECISION TO REVIEW
CERTAIN PORTIONS OF AN INITIAL DETERMINATION

AGENCY: U.S. International Trade Commission.

ACTION: Notice.

SUMMARY: Notice is hereby given that the U.S. International Trade Commission has determined to review certain portions of an initial determination (ID) issued on December 15, 1989, by the presiding administrative law judge (ALJ) in the above-captioned investigation.

FOR FURTHER INFORMATION CONTACT: Marc A. Bernstein, Office of the General Counsel, U.S. International Trade Commission, 500 E Street, S.W., Washington, D.C. 20436, telephone 202-252-1087.

SUPPLEMENTARY INFORMATION: On February 1, 1989, Bristol-Myers Company (since renamed Bristol-Myers Squibb Company) (Bristol) filed a complaint with the Commission alleging violations of section 337 of the Tariff Act of 1930 (19 U.S.C. 1337) in the importation and sale of certain crystalline cefadroxil monohydrate. The complaint alleged infringement of claim 1 of U.S. Letters Patent 4,504,657 owned by Bristol. The Commission instituted an investigation into the allegations of Bristol's complaint and published a notice of investigation in the Federal Register. 54 F.R. 10740 (March 15, 1989).

On December 15, 1989, the ALJ issued an ID finding no violation of section 337 in the investigation. Petitions for review of the ID were filed by Bristol, the Commission investigative attorney (IA), and respondents Gema, S.A., Kalipharma, Inc., Purepac Pharmaceutical Co., Istituto Biochimico Italiano Industria Giovanni Lorenzini S.p.A., and Institut Biochimique, S.A. Responses were filed by all parties that had filed petitions and by respondent Biocraft Laboratories, Inc. No government agency comments were received.

Having examined the record in the investigation, including the ID, the Commission has determined to review the ID's findings and conclusions concerning obviousness and ancillary issues. Such review encompasses the portion of the ID beginning at page 14, with the heading "Seeding," and ending at page 68, above the heading "Infringement." The Commission has determined not to review the remainder of the ID. The Commission has,

however, determined to strike the first two sentences of the final paragraph on page 11 of the ID. The final two sentences of that paragraph are to be inserted at the end of the first paragraph on page 12.

The Commission has determined that the parties' petitions for review and responses thereto have fully addressed the issues to be reviewed. Accordingly, the Commission does not request further briefing on these issues.

In connection with final disposition of this investigation, the Commission may issue (1) an order that could result in the exclusion of the subject articles from entry into the United States, and/or (2) a cease and desist order that could result in a respondent being required to cease and desist from engaging in unfair acts in the importation and sale of such articles. Accordingly, the Commission is interested in receiving written submissions that address the form of remedy, if any, that should be ordered.

If the Commission contemplates some form of remedy, it must consider the effects of that remedy upon the public interest. The factors that the Commission will consider include the effect that an exclusion order and/or cease and desist order have on (1) the public health and welfare, (2) competitive conditions in the U.S. economy, (3) U.S. production of articles that are like or directly competitive with those that are subject to investigation, and (4) U.S. consumers. The Commission is therefore interested in receiving written submissions that address the aforementioned public interest factors in the context of this investigation.

If the Commission orders some form of remedy, the President has 60 days to approve or disapprove the Commission's action. During this period, the subject articles would be entitled to enter the United States under a bond, in an amount determined by the Commission and prescribed by the Secretary of the Treasury. The Commission is therefore interested in receiving submissions concerning the amount of the bond that should be imposed.

Written Submissions

The parties to the investigation, interested government agencies, and any other persons are encouraged to file written submissions on remedy, the public interest, and bonding. Bristol and the IA are also requested to submit a proposed exclusion order and/or proposed cease and desist order(s) for the Commission's consideration. Written submissions, including any proposed orders, must be filed by February 14, 1990, and reply submissions must be filed by February 21, 1990.

Persons filing written submissions must file with the Office of the Secretary the original document and 14 copies thereof on or before the deadlines stated above. Any person desiring to submit a document (or portion thereof) to the Commission must request confidential treatment unless the information has already been granted such treatment during the proceedings. All such requests should be directed to the Secretary of the Commission and must include a full statement of the reasons why the

Commission should grant such treatment. See 19 C.F.R. 201.6. Documents for which confidential treatment is granted by the Commission will be treated accordingly. All nonconfidential written submissions will be available for public inspection at the Office of the Secretary.

Additional information

Copies of nonconfidential versions of the ID and all documents filed in connection with this investigation are 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 202-252-1000. Hearing-impaired persons are advised that information on this matter can be obtained by contacting the Commission's TDD terminal on 202-252-1810.

By order of the Commission.

Kenneth R. Mason
Secretary

Issued: January 25, 1990

P U B L I C V E R S I O N

UNITED STATES INTERNATIONAL TRADE COMMISSION
Washington, D.C.

In the Matter of	)	
	)	Investigation No. 337-TA-293
CERTAIN CRYSTALLINE CEFADROXIL MONOHYDRATE	)	

89 DEC 20 A9:28

INITIAL DETERMINATION

Bristol-Myers Co. filed a complaint and a motion for temporary relief with the U.S. International Trade Commission alleging violations of Section 337 of the Tariff Act of 1930 as amended (19 U.S.C. § 1337). The Commission issued a notice of investigation that was published in the Federal Register on March 15, 1989. (54 Fed. Reg. 10740.) The notice instituted an investigation to determine:

> whether there is a violation of subsection (a)(1)(B) of section 337 in 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 certain crystalline cefadroxil monohydrate by reason of alleged direct or induced infringement of U.S. Letters Patent 4,504,657, and whether there exists an industry in the United States as required by subsection (a)(2) of section 337.

A hearing was held on the motion for temporary relief, and an initial determination denying temporary relief was issued on May 24, 1989. The Commission vacated part of the initial determination, but denied temporary relief. On December 8, 1989, the Federal Circuit reversed the determination on temporary relief, and concluded that it was likely that the patent ultimately would be found to be valid.

Meanwhile, this case had been assigned to an administrative law judge to hold a hearing under the Administrative Procedure Act (A.P.A., 5 U.S.C. § 557) and to issue an initial determination (a decision) on the issue of permanent relief.

Administrative law judges appointed under the A.P.A. are judges under Article 1 of the Constitution. Although their decisions are subject to review by the agency for which they work, neither the conduct of the hearings nor the decisions are under the control of the agency. The A.P.A. was the result of efforts by the private bar to get decisions in contested cases made by independent trial judges inside Federal agencies after a fair hearing. The perception of the administrative law judge as an employee who writes reports to the Commission makes it difficult for the administrative law judge to convince foreign parties in Section 337 cases that he is independent and will give a fair hearing to all the parties, even though he works for a Federal agency. Foreign parties may doubt that there is independence within the administration of a government. There is in ours.

A hearing on permanent relief has been held, and all parties actively participated in the trial. The Commission has jurisdiction over the subject matter of this case under Section 337 of the Tariff Act as amended, and the parties consented to the Commission's personal jurisdiction.

Complainant is Bristol-Myers Company. The respondents are Istituto Biochimico Italiano Industria Giovanni Lorenzini S.p.A., Kalipharma, Inc., Purepac Pharmaceutical Co., an unincorporated division of Kalipharma that should not have been named as a separate respondent, Biocraft Laboratories, Inc., Institut Biochimique, S.A., and Gema S.A.

Respondents either have imported into or exported to the United States the product in issue. From the beginning of March 1989 through the middle of April 1989, respondents had gross sales of about $6.7 million of imported crystalline cefadroxil monohydrate. (Staff Phys. Ex. F.)

The record in the hearing on permanent relief is far more extensive than the record in the hearing on temporary relief. The 6 day hearing in the first case was followed by a much longer hearing in the second case. The last briefs were received in the TEO proceeding on May 15, and the decision had to be issued on May 24. Although I would have no qualms about changing my mind, the conclusions reached in the TEO initial determination generally were confirmed by the evidentiary record in the permanent hearing.

THE '657 PATENT

The '657 patent, U.S. Patent Number 4,504,657, was issued on March 12, 1985. The single claim of the '657 patent claims a chemical product, a specific cefadroxil monohydrate described herein as the Bouzard monohydrate. The Bouzard monohydrate consists of:

> "crystalline 7-[D-a-amino-a(p-hydroxyphenyl) acetamido]-3-methyl-3-cephem-4-carboxylic acid monohydrate"

exhibiting essentially the X-ray diffraction properties listed in a chart that is made part of the claim. (The complete claim is set forth in Appendix A.) The Bouzard monohydrate is described in column 2 of the patent as a novel crystalline monohydrate of cefadroxil.

The date of the invention for the purposes of determining what is prior art to the '657 patent is deemed to be April 27, 1976, the foreign priority date for British Patent Application No. 17028/76. (Bristol-Myers Ex. 20.) An applicant may rely upon a foreign priority date as a

constructive reduction to practice to avoid a potential prior art reference. (35 U.S.C. § 119.)

The most pertinent prior art references, the Garbrecht and Crast patents, both were cited by the patent examiner in the prosecution history of the '657 patent.

In the late 1960s, Leonard Crast, working for complainant Bristol-Myers (Bristol), first made cefadroxil. This product was patented in United States Patent No. 3,489,752, issued on January 13, 1970. Although the product disclosed in the '752 patent contained impurities and was not marketed, Bristol later developed purifying procedures and produced marketable cefadroxil. The '752 patent protected Bristol' DURICEF and ULTRACEF products until the patent expired in 1987. After this patent expired, foreign importers began to import products that would compete with these products. Bristol is now trying to protect these products under another patent, the much narrower '657 patent here in suit.

In 1972, while Bristol and others were trying to make cefadroxil in a marketable form, Bristol developed a purification process in which crude cefadroxil was dissolved in dimethylformamide (DMF). The resulting DMF solvate or complex contained purified cefadroxil, but it also contained toxic DMF. Bristol scientists then tried various ways to remove the DMF from the cefadroxil. In one of these efforts, Bristol scientists Crast and Gottstein used various slurrying procedures to remove the DMF from solvate, and they obtained the Gottstein/Misco or Gottstein cefadroxil monohydrate. A slurrying procedure something like the procedures actually used by Gottstein and Misco was later disclosed in the Crast '741 patent, one of the two principal prior art patents relied upon by the respondents.

The Crast '741 patent, U.S. Patent No. 3,985,741, was not issued until Oct. 12, 1976, but it was granted on a division of an application filed on September 15, 1972. (Biocraft/Gema Ex. 10.) Crast claims a process and a solvate. The patent described improved purification processes for certain types of products; the purpose of these processes was to obtain higher yields for commercial production and to reduce the cost of production. (Id., Col. 2, lines 29-41.)

The slurrying process described in the Crast patent, if followed literally, does not produce the new Bouzard monohydrate of the '657 patent in issue. If certain modifications are made, the Crast process produces the Bouzard monohydrate.

Another group of Bristol chemists also was working on a method for producing a marketable cefadroxil product. The Bouzard '657 patent grew out of the work of this group that included Daniel Bouzard, Abraham Weber and Jacques Stemer. While working on this project, Dr. Weber first produced what is sometimes described as Bristol's "old monohydrate." Then, after making a slight change in the process that produced the old Bristol monohydrate, Weber produced a new trihydrate. (TEO Tr. 300-301.) From this trihydrate, a new cefadroxil monohydrate appeared. This was the Bouzard monohydrate later claimed in the '657 patent. Dr. Bouzard testified that after the new monohydrate had been formed, Bristol no longer could obtain the trihydrate, even using identical procedures to those that produced the trihydrate the first time. (TEO Tr. 306-307.)

When the patent application was filed, the patent examiner repeatedly rejected the claim of the '657 patent over the prior art Garbrecht patent. Although the patent examiner did not reject the Bouzard claim as obvious,

he found that a skilled chemist would have obtained the Bouzard monohydrate by following the teachings of the Garbrecht patent. To overcome this rejection, Bristol had additional testing done by Dr. Micetich.

Before these experiments were made, Bristol discussed a protocol for proposed tests with the patent examiner in September 1983. In the third experiment, additional hydrochloric acid would have been added to the initial mixture in Example 1 to provide a pH in the range of 1.0-1.5 for several hours. (Biocraft/Gema Ex. 73, p. 7.) Adding this amount of hydrochloric acid would not have produced the Bouzard monohydrate, but if more hydrochloric acid had been added at room temperature or somewhat warmer, the Bouzard monohydrate would have been obtained.

Bristol did not ask Dr. Micetich to make the third test. After making the first two experiments requested by Bristol, modifying Garbrecht Example 7, Dr. Micetich produced a crystalline cefadroxil product that was not the Bouzard monohydrate. When Bristol advised the patent examiner that the first two experiments in the protocol did not produce the new Bouzard monohydrate, the patent examiner withdrew his objection to the claim. Only then was the '657 patent issued.

Bristol takes the position that the '657 patent claims a nonobvious form of the antibiotic cefadroxil. The crystalline form of the Bouzard cefadroxil monohydrate is identified in the patent by its X-ray powder diffraction pattern. An X-ray powder diffraction pattern is like a fingerprint of the product, although it does not disclose the three-dimensional shape of the crystal. A totally different material can produce a powder pattern whose lines match precisely in position but not in intensity the pattern of the Bouzard material. (Tr. 2397.) The Bouzard

powder pattern distinguishes the Bouzard monohydrate from all other crystalline forms of cefadroxil monohydrate, if line intensities and positions are considered.

VALIDITY OF THE '657 PATENT

Bristol contends that the Bouzard monohydrate was unknown prior to its accidental and unpredictable invention by Bristol scientists in 1974.

Respondents argue that this form of cefadroxil monohydrate was anticipated under Section 102 and obvious under Section 103 of the Patent Act.

The Commission's trial attorney supported the position of the respondents that the patent was invalid, but supported the position of complainant on all other issues.

There is a statutory presumption in the Patent Act (35 U.S.C. § 282) that the '657 patent is valid. Respondents must prove by clear and convincing evidence that the patent is invalid.

ANTICIPATION UNDER SECTION 102

Under Section 102(b) of the Patent Act, a person shall not be entitled to a patent if the invention was patented in this country more than one year prior to the date of the application for patent in the United States.

The application for the '657 patent in the United States was filed on March 16, 1982.

Respondents contend that the Garbrecht '282 patent (U.S. Patent No. 3,781,282, issued on December 25, 1973) fully anticipates the '657 patent.

To anticipate, the prior art reference need not teach what the anticipated patent teaches. Kalman v. Kimberly-Clark Corp., 713 F.2d 760, 772, 218 U.S.P.Q. 781, 789, cert. denied, 465 U.S. 1026 (1984), overruled on other grounds, SRI International v. Matsushita Electric Corp. of

America, 775 F.2d 1107, 227 U.S.P.Q. 577 (Fed. Cir. 1985). Every element of the claim must be described in a single prior art reference either literally or inherently. Kloster Speedsteel AB v. Crucible Inc., 793 F.2d 1565, 1571, 230 U.S.P.Q. 81, 84 (Fed. Cir. 1986); Corning Glass Works v. Sumitomo Electric USA Inc., 868 F.2d 1251, 9 U.S.P.Q.2d 1962, 1965 (Fed. Cir. 1989).

1. The Bouzard monohydrate is not literally described in the Garbrecht patent. The '657 patent claims a form of crystallized cefadroxil monohydrate that has a particular X-ray diffraction profile. This form of crystallized cefadroxil monohydrate is not expressly claimed or literally described in the Garbrecht patent. (Biocraft/Gema Ex. 13.)

Respondents argue that the Garbrecht patent as a whole describes this form of crystallized cefadroxil monohydrate (the Bouzard monohydrate). If the Garbrecht patent adequately described the Bouzard monohydrate, then the product would have the three-dimensional shape of the Bouzard monohydrate crystal and its X-ray fingerprint as one of its attributes.

Complainant argues that the Bouzard monohydrate is not described in the Garbrecht patent because the patent does not describe the form of cefadroxil that would be obtained, and this form could not be predicted. It is found that the form of cefadroxil could not be predicted accurately until the experiment was made. Dr. Garbrecht expected that the cefadroxil-DMF solvate produced by his '282 patent process would be crystalline, and that the final product of the aqueous crystallization procedure would be a solid, but he had no expectations about the nature of its crystallinity or its hydration. (Tr. 342-344.) Dr. Baldwin agreed with Dr. Garbrecht, and

testified that no chemist could predict the form of hydration that a cefadroxil crystal would take. (Tr. 228.)

By inference, the Garbrecht patent describes a cefadroxil monohydrate, even though this may have been unintentional. The patent describes cephalosporin solvates and the cephalosporin products of the Garbrecht process as crystalline. (Columns 1, 6 and 7). Column 1, the abstract of the disclosure, discloses that cephalosporin antibiotic, e.g., cephalexin, can be recovered from purified cephalosporin-DMF complex by dissolution in acidified water, heating the solution to 40° to 70°C. to form the monohydrate, and treating the solution with base to raise the pH to the isoelectric point of the antibiotic in that solvent system. Cefadroxil is a cephalosporin. (Tr. 211-217.) A chemist would know that cefadroxil is a cephalosporin antibiotic, and that cefadroxil monohydrate would be a form of cephalosporin hydrate. With respect to its hydration, Example 5 explicitly describes a cephalexin monohydrate. Cefadroxil is a cephalexin, so it would be reasonable to assume that the cefadroxil would be a monohydrate. The patent also describes an aqueous crystallization of cephalexin hydrate. (Col. 7.) The prosecution history refers to "the final aqueous crystallization of the cephalosporin antibiotic." (Bristol Ex. 107, Amendment dated October 11, 1972, page 2.) The patent examiner in the '657 prosecution history, who was a chemist, interpreted Example 7 of Garbrecht as describing the preparation of cefadroxil/DMF complex, and he noted that under the treatment described in Example 5, a monohydrate would be obtained. (Bristol Ex. 45 at 211-212.)

Dr. Ludescher testified that a chemist could have predicted from the information in Column 1, lines 16-22, and Example 7, column 10, that

Example 7 would produce a crystalline cefadroxil monohydrate, even though the Garbrecht patent contains no explicit reference to a crystalline cefadroxil monohydrate. (TEO Tr. 580-83, 662-664.)

Dr. Kosak testified that the Example 7 of the Garbrecht patent disclosed diprotected cefadroxil, and that the Garbrecht patent disclosed a method for preparing diprotected cefadroxil, its conversion to a DMF solvate, and the processing of the DMF solvate to form the cefadroxil monohydrate. (Kalipharma Ex. 79(a) at 9-12.)

Although the Garbrecht patent does not explicitly refer to a crystalline cefadroxil monohydrate, one can be inferred from reading the patent as a whole. But not every crystalline cefadroxil monohydrate is the Bouzard monohydrate. The Gottstein monohydrate and the old Bristol monohydrate are different from the Bouzard monohydrate. Following Garbrecht examples Examples 5 or 7 sometimes produces a cefadroxil monohydrate that is not the Bouzard monohydrate. Garbrecht describes a cefadroxil monohydrate, but it does not describe only the Bouzard monohydrate.

2. Under the doctrine of inherency, a prior art patent may anticipate a claimed product if the process described in the prior art reference necessarily and invariably produces the product claimed.

Respondents offered evidence that Dr. Micetich, when he followed Garbrecht Example 7, obtained a combination of the Bouzard monohydrate and something else. The expert witnesses who analyzed the X-ray evidence disagreed with one another on this point. The product itself is not available, and the X-ray evidence is of poor quality. At the time that the product was made, Bristol advised the PTO that the product was not the

Bouzard monohydrate. Respondents rely in part on the X-ray of a product made by Dr. Farina, identified as PF 19/89. This product was made by following the Micetich procedure with minor modifications. The solution then was seeded with the Bouzard monohydrate. The X-ray analysis of the resulting product, PF 19/89, does not support a finding that by following the Micetich procedure one will get the Bouzard monohydrate plus impurities. The Bouzard monohydrate was found in this product along with the Micetich material because the solution had been seeded with about 1% of Bouzard monohydrate crystals. (TEO Tr. 808-809.) It is found that the procedure followed by Dr. Micetich does not produce a mixture of the Bouzard product and impurities. (Tr. 3218.)

If Garbrecht Example 7 is followed in a reasonable manner, the Bouzard monohydrate may or may not be obtained. The bench chemist must make certain decisions as to how to carry out the experiments, and the way in which the experiments are carried out determines the outcome.

If Garbrecht Example 5 is followed without first going through the steps of Example 7 and Example 1, it would be extremely difficult for a bench chemist, starting with a relatively pure DMF solvate, not to obtain the Bouzard monohydrate. Almost everyone who followed Example 5 literally got the Bouzard monohydrate unless the solution was chilled before it precipitated. Chilling to induce precipitation was not taught in Example 5, although it is a common technique and was not expressly prohibited. Even Garbrecht Example 5 does not describe the process of getting the Bouzard monohydrate in enough detail so that one following Example 5 in any reasonable manner would be sure to get the Bouzard monohydrate.

Example 5 describes a large scale process in which a cephalexin-bis (DMF) complex or solvate is dissolved in acid and water, heated to 55°C, and then neutralized with a base, causing the precipitation of a cephalexin monohydrate. The abstract of the Garbrecht patent summarizes what happens in Example 5 as follows: A cephalosporin antibiotic, e.g., cephalexin, can be recovered from purified cephalosporin-DMF complex by dissolution in acidified water, heating the solution to 40° to 70°C. to form the monohydrate, and treating the solution with base to raise the pH to the isoelectric point of the antibiotic in that solvent system. A crystalline cephalexin monohydrate eventually will precipitate, if one has done things right. Precipitation may or may not take a long time, depending on factors such as product purity, temperature, concentration, seeding, and whether precipitation is induced.

The DMF solvate can be made by following Example 7 and then Example 1 or Example 6. If one is successful in getting a relatively pure DMF solvate, then the process of Example 5 will yield the Bouzard monohydrate. If one fails to get a good DMF solvate following the other examples, Example 5 will not produce the Bouzard monohydrate.

Respondents contend that if you skip the other examples, and follow Example 5 using any DMF solvate made by any process, (various methods of preparing cefadroxil DMF solvate were available in 1976, Tr. 654-655), one invariably will obtain the Bouzard monohydrate. If this were true, Example 5 would anticipate the product of the '657 patent because the Bouzard monohydrate claimed in the '657 patent would be inherently described in Garbrecht Example 5.

Kalipharma asserts that every chemist who processed a DMF solvate in accordance with Example 5 in this case obtained the Bouzard monohydrate, citing experiments made by Drs. Baldwin, Schofield, Crouch, Farina, Cainelli, Ludescher, Guazzi and Biffi. But Kalipharma excluded experiments where the product was crystallized at temperatures below room temperature.

The first Crouch experiments in which Example 5 was followed resulted in the Bouzard monohydrate when crystallization began at or above room temperature in a seeded room. The Bouzard monohydrate was not obtained when the product was chilled before precipitation.

Line 16 of Garbrecht Example 5 calls for chilling the filtrate, as the first step of making the second crop. The material left in the filter would be the first crop. This suggests that precipitation of the first crop had occurred while the product was still warm. Nevertheless, the record will not support a finding that any DMF solvate processed in accordance with Example 5 invariably would produce the Bouzard monohydrate. Example 5 tells one to heat the starting material to 55°, and the patent abstract tells one to heat the starting material to above 40°, but neither the abstract nor Example 5 explicitly states the temperature at which the product should precipitate. Nothing expressly states that the temperature at the time of precipitation is important.

In practicing Garbrecht Example 5, as the temperature falls, it is not clear at what temperature the first crop must be precipitated out of solution. Many of the chemists making experiments under the Garbrecht patent had trouble getting the material to precipitate quickly. When chilling was used to speed precipitation, the Bouzard monohydrate was not

obtained. Garbrecht Example 5 does not clearly state that one cannot induce precipitation by chilling.

Even if crystallization occurred at the right temperature, Example 5 might not produce the Bouzard monohydrate if the DMF solvate contained too many impurities. A cephalexin-bis (DMF) complex is necessary to start Example 5. Dr. Dunitz testified that precipitation could be affected by concentration, temperature and impurities. (TEO Tr. 618-619.) The lack of purity of the DMF solvates used in other experiments has been raised by the parties repeatedly as an explanation of why an experiment might not have been successful.

In Farina's experiment PF19 (Kalipharma Ex. 5, at 5-3), an old monohydrate (not Bouzard) precipitated at 20° C, at the lower end of room temperature range. This experiment was not a test of Garbrecht Example 5, because the solution never was heated above 20° C.

Respondents have demonstrated that all relatively pure DMF solvates processed in accordance with Example 5, where precipitation has occurred at a warm temperature, have produced the Bouzard monohydrate. While this is evidence that the Bouzard monohydrate of the '657 patent is obvious, because commercial DMF solvates were available in 1976, respondents have not proved that any DMF solvate, regardless of its impurities, would produce the Bouzard monohydrate invariably if processed in accordance with Example 5. The product claimed in the '657 patent was not anticipated.

SEEDING

Before the issue of obviousness can be decided, the issue of seeding must be considered. If seeding by the Bouzard monohydrate is the only source of the Bouzard monohydrate, as Bristol argues, the product of the

'657 patent could not have been obvious in 1976 under Section 103 in view of the Garbrecht and Crast prior art patents.

A seed can be either a very small particle or a crystal. (TEO Tr. 610, 225.) A crystal has molecules in a definite arrangement. (TEO Tr. 617.) A crystal that acts as a seed is capable of seeding a solution and forming crystals that replicate its own shape. Dr. Dunitz guessed that each seed might be about one micron in size. (TEO Tr. 633-634.)

Seeding may be intentional. A chemist may add crystals of a particular form to a solution in the hope that the solution will crystallize in that particular form. As defined by Professor Lipscomb, intentional seeding is the addition of known material of a known structure or a known composition to a solution or to other crystals in order that the crystals be transformed. (TEO Tr. 1295.)

Seeding may be unexpected, when crystals in the environment contaminate a solution, or induce crystallization in an unexpected form. (TEO Tr. 262-263, 610-611.)

The term seeding is also used to describe the use of any material that is added to a solution to induce precipitation or faster precipitation of crystals out of solution without affecting the shape of the crystals that are formed. Such a seeding material may or may not be crystalline. Although it may not appear in the crystals precipitating out of solution, it can help precipitate crystals out of solution. For example, scratching the side of a glass container separates tiny pieces of glass that can help precipitate crystals out of solution, but it has no effect on the shape of the crystals formed. (Tr. 3227.)

When a new cefadroxil monohydrate crystal is formed for the first time, the evidence in this record does not show how the first seed gathered around it a group of molecules in a new arrangement. Perhaps some internal instructions went awry. But after the first crystal is formed, it can reproduce crystals identical to itself.

As described by Professor Baldwin, a cefadroxil solvate or complex is a type of crystal that packs together a number of cephalosporin molecules and a number of solvent molecules in a regular fashion. When the solvent molecule is water, the crystal is a hydrate. The hydrates or solvates are formed with a regular composition. (TEO Tr. 226-228.) The solvent molecules fill in the spaces between the cephalosporin molecules, as Professor Baldwin surmised perhaps because nature abhors a vacuum. Some crystals are dominant over others. These dominant or stable crystals appear to be the crystals with more regular arrangement of molecules. Perhaps nature also abhors groups carelessly arranged molecules. These are called stable crystals. Now and then new crystal forms appear which have different arrangements of molecules. This record does not show that new crystal forms always have more regular arrangements of molecules than the forms they replaced. Perhaps crystals with less regular arrangements of molecules are formed, like the Bristol trihydrate, but they fail to survive. The crystals with more regular arrangements of molecules are the stable ones that on rare occasions may displace other crystals. The Bouzard cefadroxil monohydrate crystal, which is very regular and stable, may be dominant over some of its close relatives, other forms of cefadroxil crystals or polyforms. These crystals may have a less regular arrangement, and may be less stable than the Bouzard monohydrate.

When seeding from the surrounding atmosphere occurs under the right conditions, the crystals precipitating out of solution may follow the form of the seed. A seed from the surrounding atmosphere may be dominant over the crystal that otherwise would form from a precipitating solution. When this occurs, the seeding crystal may displace the crystal that otherwise would have formed, and the form of the dominant crystal would be repeated as the solution precipitates.

As described by Dr. Keizer, when two different crystal modifications of a particular compound exist, such as the old and the new cefadroxil monohydrate, there are instances in which the two different forms (polymorphs) can coexist together. One does not displace the other. When one seeds the solution from which the other is crystallizing, neither is displaced by the other. In rare cases, one of the polymorphs may take over the other, perhaps because it is a more stable form of the compound. It would act as a contamination seed and provide a foreign nucleus around which the crystal could form. (TEO Tr. 265-266.)

The evidence in this record suggests that under some conditions the seed of the Bouzard monohydrate forms some crystals like itself, while different polymorph crystals of another cefadroxil monohydrate precipitate out of solution either at the same time or at a later time at a lower temperature. Some experiments suggest that the Bouzard monohydrate may displace some but not all of the other cefadroxil monohydrate crystals, and that sometimes the Bouzard monohydrate continues to transform the other crystals after they have precipitated out of solution. Factors that affect whether more than one crystal is formed in the same experiment may include the number of seeds in the air around the experiment that are available for

seeding by the Bouzard monohydrate, and the speed at which the other cefadroxil monohydrate crystals are precipitating out of solution. (TEO Tr. 615.)

At the time that its original application for the '657 patent was considered by the Patent and Trademark Office, Bristol's theory of seeding was that the whole world's atmosphere is seeded with the Bouzard monohydrate. Bristol had abandoned this seeding theory by the time that this Section 337 proceeding began.

In the hearing on temporary relief (the TEO hearing), Professor Lipscomb, Professor Dunitz and Professor Keizer agreed that atmospheric seeding occurs only across small distances and that universal seeding of the whole atmosphere by the new Bouzard monohydrate was implausible. (TEO Tr. 266-267, 610-613, 1295-1296.)

At first, there was a question as to whether the old Bristol monohydrate had been displaced by the Bouzard monohydrate. After the new monohydrate had been formed for the first time, Dr. Bouzard no longer could make the old monohydrate or the trihydrate from which it had been formed. (Tr. 306-307.) This could have been the result of an extremely unusual type of seeding where a crystal is so dominant that it displaced an extremely unstable crystal form and prevented its formation ever again. Professor Lipscomb testified that a few extremely unstable crystals have existed in the past that no longer can be made at all, because they have been replaced forever by a more stable form. (TEO Tr. 1320-1321; Bristol Ex. 45 at 137-139.) He had found in the literature only 20 to 30 examples of this type of seeding among about six million organic compounds. (Tr. 3336, TEO Tr. 1293.)

Experiments made by Dr. Ludescher and Dr. Schofield showed that the old monohydrate still can be made. Professor Lipscomb thought that the Bouzard monohydrate, which is very stable, might have displaced the unstable trihydrate, but not the old monohydrate. (TEO Tr. 1293-1298, 1320-1324.) Dr. Ludescher and Dr. Schofield demonstrated that the new Bouzard monohydrate had not displaced the old monohydrate, and that the old monohydrate can be produced in the same room a day or two after the new monohydrate was produced and had seeded the atmosphere in the room. Dr. Ludescher showed that the old monohydrate and the Bouzard monohydrate could be crystallized at the same time in the same dish. In a single experiment he crystallized a mixture of the old monohydrate and the Bouzard monohydrate. (TEO Tr. 543; Biocraft/Gema Ex. 148.) A crystal of the old monohydrate and a crystal of the Bouzard monohydrate were growing together. (TEO Tr. 676; Biocraft/Gema Ex. 151 at G 282-3, 301-305.) Dr. Keizer testified that when two polymorph crystals appeared together, neither was dominant over the other, and that no seeding had taken place in the sense of a dominant crystal replacing another crystal. (TEO Tr. 275.)

The evidence in this case suggests that seeding by a stable crystal (the Bouzard monohydrate) may occur, where the Bouzard monohydrate replaces some but not all of the other cefadroxil monohydrates crystallizing out of the same solution. (TEO Tr. 616.) After both types of crystals have been formed, the Bouzard monohydrate may continue slowly to displace the other form of cefadroxil crystal. (See Ludescher experiment.)

Bristol's current seeding theory

Bristol contends that the Bouzard monohydrate is dominant over other forms of cefadroxil crystals, and that the only source of the Bouzard

monohydrate today is from local seeding by the Bouzard monohydrate of an appropriate solution. If Bristol's seeding theory is accepted, then the Bouzard monohydrate claimed in the '657 patent cannot be obvious under Section 103.

This seeding theory must be dealt with before the question of obviousness is reached. Otherwise, seeding can be used as a possible explanation of every appearance of the Bouzard monohydrate, and no headway can be made on the issue of obviousness. Until the role of seeding is determined, Bristol's seeding theory can undermine the analysis of any experiment. It poisons the well.

Bristol's seeding theory is this: Nobody could have produced the Bouzard monohydrate for the first time without the production of the intermediate trihydrate from which the Bouzard monohydrate appeared. That process was accidental, unpredictable and not obvious. Up to now, no one has been able to reproduce the trihydrate. Without the trihydrate, nobody in any part of the world has been able to produce the Bouzard monohydrate since 1976 without the presence of the Bouzard monohydrate in the surrounding atmosphere (or in undissolved ingredients in the mixture) to seed the solution that is crystallizing.

Professor Lipscomb testified that seeding of the environment in a distant place could occur when someone inadvertently carries or sends seeds of the new monohydrate to a place where those seeds were not present before. The seeds spread like a virus. (TEO Tr. 1296-1297.)

Bristol argues that now, wherever scientists are able to make the Bouzard monohydrate using modifications in the Crast and Garbrecht patents, they are able to obtain the Bouzard monohydrate only because the seed is

present in the surrounding atmosphere. No one could have produced the Bouzard monohydrate from the teachings of the Crast or Garbrecht patents until Bristol scientists had produced the Bouzard monohydrate accidentally the first time. After that first time, the Bouzard monohydrate seeds always have been present whenever the Bouzard monohydrate has been obtained. The seeds may have come from making the Bouzard monohydrate previously in the same location, or the seeds may have been brought in inadvertently from other places. So goes Bristol's second seeding theory.

The evidence established that atmospheric seeding can cause the Bouzard monohydrate to be formed. When the new Bouzard monohydrate is seeded into a solution made by a process that otherwise would produce the old monohydrate, the new monohydrate appears in the same dish with the old monohydrate, as was shown by Dr. Ludescher. The Bouzard monohydrate did not necessarily come from atmospheric seeding; theoretically, it could have come from the solution itself. But this is unlikely because this process in the absence of seeding produced only the old monohydrate, not a mixture of the new and old monohydrate.

Bristol's seeding theory fails because respondents have proved that the Bouzard monohydrate can be obtained <u>without</u> seeding.

1. <u>The Crast patent</u>

One obstacle to Bristol's second seeding theory is the group of experiments made by chemists who modified the teachings of the Crast patent and obtained the Bouzard monohydrate in a seed-free atmosphere.

After Professor Just made his first three experiments, in which he followed Crast 6B, more or less, and did not get the Bouzard monohydrate, he made a fourth experiment in which he obtained Bouzard. In his fourth

experiment, Professor Just added water before he added methanol. This was a departure from the process set forth in Crast Example 6B. Professor Just's laboratory was not seeded.

Dr. Schofield repeated Professor Just's fourth experiment in a seeded environment (Tr. 3358-3359), and obtained the Bouzard monohydrate. Following Crast 6B literally, he did not obtain Bouzard. When he used the Just modification to the slurrying procedure of Crast Example 6B, he produced the Bouzard monohydrate. (TEO Tr. 1139; Biocraft/Gema Ex. 76.) When he used the slurrying procedure of Crast Example 6B, he produced an old cefadroxil monohydrate identical to that produced by Gottstein and Misco in 1972. (TEO Tr. 1138; Biocraft/Gema Ex. 76.) Later, Dr. Schofield again followed Professor Just's modification of Crast, and again produced the Bouzard monohydrate. When he made his own modifications to Crast 6B, he produced the old Gottstein monohydrate. (Tr. 1670; Bristol Ex. 215B; Biocraft/Gema Ex. 242.)

When Professor Just's experiments in an unseeded laboratory were repeated by Dr. Crouch in a seeded laboratory, the results were the same. Seeding alone did not determine whether the Bouzard monohydrate was obtained when following Crast.

Dr. Schofield proved that one following the Crast teachings today, with some modifications, could produce either the old Gottstein monohydrate or the new Bouzard monohydrate, depending on changes in the way in which the slurrying procedure is carried out in Example 6B. Dr. Schofield's experiments proved that seeding has no effect when Crast Example 6B is followed literally; they do not prove that seeding causes the formation of the Bouzard monohydrate when the Just modification is used.

If Crast Example 6B is followed literally, seeding by Bouzard does not occur. (Tr. 3271.) When Crast Example 6B is modified by adding water before the methanol is added, the Bouzard monohydrate is obtained, with or without seeds in the atmosphere.

Professor Baldwin realized that seeding did not work when Crast 6B was followed literally. He thought that because Professor Just in his fourth experiment first slurried the DMF solvate in water prior to adding methanol (rather than slurrying it directly in 90% methanol), the addition of water before the methanol may have made it possible for seeding by the Bouzard monohydrate to occur. (Tr. 3274-3276.)

Dr. Ludescher's experiments throw doubt upon Professor Baldwin's explanation that the modified Crast procedure produces the Bouzard monohydrate because of seeding. Dr. Ludescher tried slurrying the DMF solvates in water in a seeded atmosphere (TEO Tr. 539-541; Biocraft/Gema Ex. 148), but he produced the old monohydrate. Seeding did not occur when he slurried the solvates in water, or at least it did not produce the Bouzard monohydrate. (TEO Tr. 541-542; Biocraft/Gema Ex. 148.)

In Professor Just's experiments following the Crast teachings, the Bouzard monohydrate could not have been obtained from the intermediate trihydrate from which Bristol originally obtained the Bouzard monohydrate because the Crast patent does not produce the trihydrate. (TEO Tr. 1368.)

The Bouzard monohydrate obtained in Just's fourth experiment could not have come from seeding. Professor Just's laboratory was seed-free. When Professor Just made the fourth experiment, no cefadroxil had been made in his laboratory previously. There was no evidence that Professor Just used ingredients that could have been contaminated with the Bouzard monohydrate.

His first four experiments were likely to be seed-free because he had no known previous contact with the Bouzard monohydrate. (TEO Tr. 389.)

The Bouzard monohydrate was produced by the modification of the Crast process made by Professor Just, rather than by seeding.

2. The Garbrecht patent

Some experiments relevant to this issue were made in artificially constructed seed-free environments. They showed that the Bouzard monohydrate could be produced in a seed-free environment following the Garbrecht examples.

In addition to the naturally seed-free environments in which some experiments were made, both Bristol and the respondents tried to create a seed-free environment in which experiments could be carried out. There is no way for respondents or complainant to prove that any experiments were absolutely free of the Bouzard monohydrate seeds, but both sides did a good job in creating seed-free environments. Respondents' apparatus is more complicated than that of complainant. Once the tubes and needles are connected to respondents' container, respondents flushed the system three times with argon and a vacuum, cleaned the system with hydrochloric acid, stirred the acid for hours, and then removed the acid. Any seeds remaining in the container before the acid was added should have been dissolved and removed with the acid. Then respondents maintained a constant overpressure throughout the experiments. (Tr. 2190, 2785.) A mercury valve was used to keep the pressure high. Later, this seed-free equipment was moved into a sterile bacteriological room under the filtration of a laminar flow cap, where some of the experiments were made. (Tr. 2814-2819.) It is extremely unlikely that any outside atmosphere remained in the container or reached

the contents of the container after it was cleaned. After the container was prepared, nothing else was inserted into the container except through a filter. (Tr. 2791-2809.)

Respondents used a filter that would let larger particles through it than complainant's filter would. Complainant used a 0.20 micron filter. (Tr. 1934.) No one is sure of the size of the Bouzard seed that both parties were trying to exclude. (TEO Tr. 633.) The seed might have been too large to get through either filter or too small to be excluded by either. No one is certain of the precise size of a seed that would be capable of seeding a solution and forming crystals that replicate its own shape, but Dr. Dunitz guessed that each might be about one micron in size. (TEO Tr. 633-634.) No other expert even hazarded a guess.

Other precautions were taken by respondents to make it unlikely that seeds would have been in the ingredients that were introduced through the filters, such as the use of special clean rooms.

Complainant's flasks were simpler than respondents' seed-free equipment. They too were likely to be seed-free. Dr. Crouch used a smaller filter size through which material was introduced into the flasks, but in his apparatus, there was the possibility that a seed would be carried into the container on the head of a needle, as it was inserted through the rubber stopper into the container. (Tr. 1913-24, 2156, 2058.)

It is found that both respondents' and complainant's seed-free experiments were seed-free most of the time.

Under conditions in which Bouzard seeds were surely present, chemists were able to produce the old cefadroxil monohydrates known in the prior art as well as the Bouzard monohydrate. Under conditions that were seed-free

most of the time, the Bouzard monohydrate has been produced repeatedly by modifying the Crast procedure or by following the Garbrecht procedure.

Complainant has proved, primarily through the experiments of Dr. Crouch and Dr. Ludescher, that seeding sometimes determines whether the Bouzard monohydrate is obtained.

The experiments of Dr. Crouch tend to prove that seeding is not always the cause when the Bouzard monohydrate is obtained. Considered as a whole, the experiments made by Dr. Crouch and others prove that the Bouzard monohydrate can be obtained without the presence of Bouzard seeds in the surrounding atmosphere.

The Crouch experiments prove that seeding is an important factor in obtaining the Bouzard monohydrate, or in increasing the speed with which it is obtained, when precipitation of a solution made by following Garbrecht Example 5 occurs at a certain temperature. Three of his experiments tend to prove that the Bouzard monohydrate can be formed by following Garbrecht Example 5 in the absence of seeding.

Dr. Crouch made about 50 experiments in all. (Bristol Ex. 227, Tr. 2101-2137.) He started with 18 experiments in his laboratory where he knew the atmosphere was seeded with the Bouzard monohydrate. Dr. Crouch used a commercial DMF solvate in the majority of the experiments that he made. (Tr. 1989.)

Dr. Crouch treated the DMF solvate in accordance with Example 5 of Garbrecht, but varied certain factors in each experiment. First, he varied the pH from very low to very high, and in a seeded atmosphere he obtained the Bouzard monohydrate. Then he changed the concentration of cefadroxil, and obtained Bouzard in a seeded atmosphere. Dr. Crouch also varied the

scale on which the experiments were made, and it made no difference; he still obtained Bouzard in a seeded atmosphere.

Dr. Crouch made experiments in which the crystals formed at different temperatures. He obtained the Bouzard monohydrate only at room temperature and above. (Bristol argues that Dr. Crouch obtained the Bouzard monohydrate at 0°C. in Experiment E10, but in the three samples in which Bouzard crystals developed, crystallization definitely began at room temperature.) (Tr. 2732-2733.)

Dr. Crouch then made a second series of experiments in sealed seed-free flasks. Again following Garbrecht Example 5, he made 20 experiments. In 17 of these he did not obtain the Bouzard monohydrate. In one, he obtained a mixture of the Bouzard monohydrate and another crystal. In two he obtained the Bouzard monohydrate.

Bristol explains the times that Dr. Crouch obtained the Bouzard monohydrate in a sealed flask as being the result of seeds getting into the flask through a needle that was injected into the flask more frequently in these experiments than in the others. Bristol's explanation that whenever the Bouzard monohydrate was formed, the seed-free equipment must have failed is an example of Bristol trying to pull itself up by its own bootstraps. The explanation just as easily could be that the Bouzard monohydrate can be obtained in the absence of seeding.

In Dr. Farina's experiment where he intentionally seeded a solution with the Bouzard monohydrate, he obtained the old and the new monohydrate together at the low end of the range of room temperature. In that experiment, which did not follow Example 5, it is likely that the Bouzard crystals came from seeding and the other crystals precipitated out of the

solution independently. The experiment shows that the Bouzard monohydrate can come from seeding.

In the sealed flask where Dr. Crouch obtained the Bouzard monohydrate and another crystal, the results would look the same whether seeding created the Bouzard crystals or the Bouzard crystals formed out of the solution. Seeding may have formed the Bouzard crystals, or they may have precipitated out of the solution at a warm temperature, while different crystals precipitated out of the same solution as the temperature fell.

When the two sealed flasks produced only the Bouzard monohydrate, either the temperature or seeding could have caused its formation.

In Experiments E23 and E24, Dr. Crouch made identical side-by-side experiments in sealed flasks following Garbrecht Example 5. He then moved both flasks to his seeded laboratory and opened the E23 flask. He left both flasks overnight at room temperature. The next day, he observed crystals growing down from the surface in the opened flask. This suggests that seeding from the surrounding atmosphere was occurring. Dr. Crouch observed no crystals forming in the closed flask. Without waiting any longer, he cooled the sealed flask in an ice bath to induce crystallization. Two days later he determined that he had obtained the Bouzard monohydrate from the open flask but a different crystal from the closed flask which had been chilled.

Dr. Crouch proved that the formation of Bouzard monohydrate crystals sometimes can be affected by seeding. The Bouzard crystal may form more quickly in a seeded atmosphere, although it may form anyway if left alone at room temperature. Dr. Crouch found Bouzard crystals in the open flask at room temperature in a seeded room, while the sealed flask had no

crystals at all. By the time Bouzard crystals might have formed in the sealed flask, if it had been left at room temperature, Dr. Crouch already had cooled the flask down to a temperature at which the Bouzard crystal would not appear. Seeding with the Bouzard monohydrate at room temperature probably increased the speed at which Bouzard crystals formed.

The experiment of Dr. Crouch did not show whether the sealed flask would have produced the Bouzard crystals if precipitation had been induced by other means before the temperature had been lowered. (He could have added another material to the solution by a needle through the cap to induce precipitation, or he could have waited a couple of days more to see if the crystals would form at room temperature.)

Dr. Crouch demonstrated that seeding either causes the formation of the Bouzard monohydrate in an appropriate solution at room temperature, or it speeds up the formation of the Bouzard crystals that would have formed anyway at room temperature. It may do both.

When Dr. Crouch followed Garbrecht Example 5, and did not obtain Bouzard, the temperature at which the crystals precipitated out of solution never was between room temperature and 55°. (Tr. 2082.)

The record shows the importance of temperature in determining whether the Bouzard monohydrate is obtained with or without the presence of seeds. Bristol's experiments showed that seeding is an important factor in forming Bouzard quickly at room temperature at least when following Garbrecht Example 5, but Bristol has not eliminated temperature as a factor that determines whether the Bouzard monohydrate can be obtained at all when following Garbrecht Example 5.

Although it is impossible to know with absolute certainty whether there are Bouzard seeds in the atmosphere surrounding an experiment, it has been proved beyond any reasonable doubt that at least some of the experiments made in this case where the Bouzard monohydrate was produced were made in a seed-free environment.

Professor Just's Crast experiments were seed-free. Some of Dr. Crouch's experiments were seed-free. Some of Dr. Farina's and Dr. Biffi's experiments also were seed-free.

In July, 1987, Dr. Farina made a series of experiments modifying Garbrecht Example 7. While generally following Example 7, he realized that he had to remove two protecting groups, instead of one. He added much more hydrochloric acid than the amount recommended in Example 1 to remove one protecting group, and then carried out Example 5. (Dr. Farina added more hydrochloric acid than had been suggested in Example 1 or 2 of Garbrecht or in the third experiment in Bristol's protocol that was discussed with the patent examiner.) He obtained the Bouzard monohydrate.

In March of 1989, Dr. Farina repeated his Example 7 experiment using his own special sterile equipment in a sterile laboratory, and he again obtained the Bouzard monohydrate. Dr. Biffi repeated the Farina experiment using the seed-free apparatus in a sterile laboratory, and obtained the Bouzard monohydrate. (Kalipharma Exs. 155, 155A, 202 and 203.)

When Dr. Farina and Dr. Biffi made these special efforts to keep their experiments seed-free, the experiments were seed-free beyond a reasonable doubt. They made the Bouzard monohydrate.

Dr. Nudelman followed Garbrecht Example 7 in an unseeded laboratory in Israel, and he obtained a cefadroxil monohydrate that was different from

the Bouzard monohydrate. (Tr. 1752-1757, 1764-1800.) When Bristol asked Dr. Nudelman to make his experiments, Bristol gave him instructions because Bristol wanted Dr. Nudelman to repeat the Micetich procedure in an unseeded environment. Dr. Nudelman used a crystallization procedure similar to that of Dr. Micetich. When crystallizing his product, Dr. Micetich had cooled the reaction mixture in a refrigerator after neutralization with triethylamine. He did not attempt to induce crystallization at room temperature or above. Dr. Nudelman placed the reaction mixture in an ice bath bringing the temperature down to about 0° C. (Tr. 1873-74.) Although he was aware of the technique of scratching to induce precipitation, he used scratching only after the temperature was reduced. (Tr. 1873-1874.) Dr. Nudelman obtained a cefadroxil monohydrate that was not the Bouzard monohydrate.

There was conflicting testimony as to what the product obtained by Dr. Micetich was. Dr. Glazer testified that Dr. Nudelman's cefadroxil monohydrate was identical to the product obtained by Dr. Micetich. (Tr. 2356-2571). Others disagreed. Because Dr. Micetich did not remove both protecting groups completely, and the product itself has been destroyed, and only copies of the old X-rays are available, it is not surprising that his product is hard to analyze. It is found that Dr. Micetich's product contained some cefadroxil monohydrate identical to that obtained by Dr. Nudelman.

Dr. Micetich probably would not have obtained much Bouzard monohydrate if he had induced precipitation before cooling because he obtained only a partial cleavage of the two blocking groups. Dr. Nudelman, however, was told to use the two-step procedure of Garbrecht and to remove both blocking

groups. He did. If Bristol's seeding theory is set aside, the failure of Dr. Nudelman to get the Bouzard monohydrate can be attributed only to chilling the reaction mixture before crystallization was induced. The experiments of Dr. Micetich and Dr. Nudelman show the importance of the temperature at which precipitation occurs.

In determining whether seeding is possible at the moment of crystallization, the temperature at which crystallization occurs appears to critical. Seeding may be possible only at a temperature somewhere in the range between a low to normal room temperature and 55°C. Based on the evidence in this case, at least, the Bouzard monohydrate is obtained only when precipitation occurs at a temperature that is not too low, although temperature is not the only critical factor in obtaining the Bouzard monohydrate.

The Bouzard monohydrate can be obtained following Garbrecht Example 5 in a seeded room at room temperature. It can be produced when the Crast patent teachings are modified, even when the room is not seeded. Seeding does not always cause the Bouzard monohydrate to be formed even when the temperature is conducive to its formation. (In a warm seeded atmosphere, the Bouzard monohydrate is not obtained when the literal instructions in the Crast Example 6B are followed.) It is only obtained when certain obvious modifications are made, and it is not made when different obvious modifications are made.

If Bouzard could be formed only in a seeded atmosphere, one could conclude that the Just modification of the Crast process simply made seeding possible, while in the Crast process followed literally, seeding was impossible. One could conclude that seeding in the Crouch seeded

experiments caused the formation of the Bouzard monohydrate, but all experiments in which Bouzard was obtained in a sealed flask were the result of a failure to exclude seeds. This would not explain how Bouzard can be obtained repeatedly in laboratories where there should be no seeds present in the atmosphere or in the ingredients being used. A far more reasonable explanation is that when a process would produce Bouzard anyway (assuming that crystallization occurs at a warm temperature), seeding may cause the Bouzard monohydrate to be formed faster. (See Tr. 615) If the temperature is falling, forming the Bouzard monohydrate faster might be critical to obtaining it at all.

After looking at the results of complainant's and respondents' experiments, it is found that either an old form of cefadroxil monohydrate or the Bouzard monohydrate can be obtained in a seeded atmosphere or in an atmosphere that is seed-free. The Bouzard monohydrate can be obtained without seeding.

If it were found that the Bouzard monohydrate could not be obtained without seeding, it would be found that the '657 patent would be invalid under Section 112. If the patent in issue could be practiced only if the product is seeded with the Bouzard monohydrate, the '657 patent would not be enabling under Section 112 of the Patent Act because the necessity of seeding the product is not mentioned in the patent.

Because the Bouzard monohydrate can be obtained without seeding and without the trihydrate, someone could have produced the Bouzard monohydrate in 1976 without the discovery of Dr. Weber's cefadroxil trihydrate. The Bouzard monohydrate could have been made from a modification of the Crast patent teachings or Garbrecht teachings, and this could have occurred in a

seed-free atmosphere. It is therefore necessary to go back to the traditional analysis under Section 103 to determine whether the product of the '657 patent is obvious.

OBVIOUSNESS UNDER SECTION 103

The issue under Section 103 is whether the product claimed in the '657 patent would have been obvious to one with ordinary skill in the art in April, 1976, the constructive date of the invention.

In Graham v. John Deere Co., 383 U.S. 1, 17-18, 148 U.S.P.Q. 459, 467 (1966), the Supreme Court required that certain factual inquiries be made before a determination of obviousness is made:

> Under Section 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 inquiries may have relevancy.

The level of ordinary skill in the pertinent art

The pertinent art (for the purposes of defining ordinary skill in the art under Section 103) will be defined as chemistry, with a specialty in the field of cephalosporins.

Ordinary skill in the art as used herein will refer to ordinary skill in the art as of April 27, 1976, the constructive reduction to practice. Many chemists working in the field of cephalosporins in April 1976 were highly skilled and had a Ph.D. degree in chemistry and a year or so of experience in the field of cephalosporins. (See Tr. 992-95, 1037-1038.)

The hypothetical person with ordinary skill in the art at that time would have been a skilled and experienced chemist with at least an undergraduate degree in chemistry and some experience in the field of cephalosporins, even if that experience were simply what he had learned in the last experiment that he had made. Such a person would have had enough experience with cephalosporins to understand the conditions under which they would be stable. (Tr. 992.) He would have been aware that the beta-lactam ring, which was critical to the performance of the antibiotic, might be destroyed by hydrochloric acid, but he would not have known how much hydrochloric acid would be needed to destroy it. (Tr. 247-50.)

The scope and content of the prior art

The principal prior art references relied upon by respondents are the Garbrecht '282 patent and the Crast '741 patent.

The prior art also includes Bristol's Crast '752 patent, which now has expired after 17 years. The '752 patent covered cefadroxil in any form. As long as the '752 patent was in effect, Bristol-Myers had a monopoly on the sale of cefadroxil in any form. Now, to protect the sale of its cefadroxil monohydrate, Bristol needs the much narrower '657 patent in issue here.

The differences between the prior art and the claim

The Garbrecht patent

The Garbrecht '282 patent discloses a process for making purified cephalosporins (Biocraft/Gema Ex. 13), while the '657 patent discloses a specific cefadroxil monohydrate. Cefadroxil is a cephalosporin and a cephalexin. (Tr. 211-217.) The Garbrecht patent discloses ways to make a cephalexin monohydrate, including a cefadroxil monohydrate.

The Garbrecht patent makes the product of the '657 patent obvious both because of Example 7 (read in the context of the rest of the patent) and because of the teachings of Example 5 alone.

Example 7

Example 7 of the Garbrecht patent describes a process by which a cefadroxil monohydrate crystal can be recovered from a cephalosporin DMF solvate. In Example 7, an intermediate product is produced from a cephalosporin and dimethylformamide (DMF). (Biocraft/Gema Ex. 13; Tr. 663-664.) Example 7 teaches that this intermediate product can be treated as in Example 1 until the compound precipitates as its DMF complex. It then teaches that the complex should be treated as in Example 5 to produce a cephalexin monohydrate. From reading the whole patent, a bench chemist would know that if one follows Example 7, then Example 1 (or Example 6), and then Example 5, he should be able to get a crystallized cefadroxil product. (See TEO Tr. 227-228, 546-551.)

After the initial application for the '657 patent had been rejected by the patent examiner because of the Garbrecht patent teachings, Bristol wanted to make some experiments to prove to the examiner that a chemist with ordinary skill would not get the Bouzard monohydrate if he followed the teachings of the Garbrecht patent. Bristol drafted a protocol outlining four proposed experiments. In the third experiment, more hydrochloric acid would be added to the initial mixture of Garbrecht Example 1 to provide a pH in the range of 1.0-1.5 for several hours. (Biocraft/Gema Ex. 73 at 7.) By adding more hydrochloric acid to Garbrecht Example 1, one could try to remove two blocking groups identified in

Example 7 in one step. Example 1 taught how to remove only one blocking group with hydrochloric acid.

The patent examiner discussed with Bristol whether this third experiment should be made. Bristol scientists were aware at that time that hydrochloric acid could be used to remove t-BOC. (See Tr. 301, 383-385). The Garbrecht patent itself taught that hydrochloric acid could be used to remove the t-BOC group. Other literature in the prior art taught the use of additional hydrochloric acid to remove the t-BOC group. (Biocraft/Gema Exs. 72 and 73.) Still, after the discussion, the examiner did not request that the third experiment be made.

Only the first two experiments were made. Dr. Micetich made a few modifications in what the Garbrecht patent described, and these were either suggested or approved by Bristol before the experiments were made. Dr. Micetich did not get the Bouzard monohydrate.

After Dr. Micetich failed to obtain the Bouzard monohydrate in his first two experiments, Bristol reported this failure to the patent examiner, who then allowed the claim. If the patent examiner had been told that there had been a partial cleavage of the second protecting group even without any additional hydrochloric acid, and if he had been told that adding hydrochloric acid was a known way to remove the t-BOC group, it is likely that the examiner would have wanted the third test to be made to see if adding more hydrochloric acid would remove both protecting groups.

It is found that one with ordinary skill in the art would have known that some amount of hydrochloric acid would remove the t-BOC group, but he would not have known how much was needed. If he experimented, he could have removed both protective groups in the one-step process.

The one-step deblocking process

One with ordinary skill in the art in April 1976 would have known from the description of the starting material in Garbrecht Example 7 that the protected cefadroxil had two protecting groups. He would have known that the two protecting groups were amino-nitrogen protecting groups.

The Garbrecht patent teaches both one-step and two-step deblocking procedures. The two-step deblocking procedure refers to the process by which the t-BOC and paranitrobenzyl blocking groups are removed sequentially from the diprotected cefadroxil. In the one-step process, both protecting groups are removed at the same time, as in Example 1. Following Example 1 while using the right amount of acid to deblock both protecting groups required some experimentation.

Example 7 refers the reader to Example 1 where he learns a one-step process in which the starting material is treated with zinc and hydrochloric acid. There the reader learns that one of the protecting groups in Example 7 (para-nitrobenzyl) can be removed by the use of hydrochloric acid and zinc. (Biocraft/Gema Ex. 13, col. 7, 8.) He would have recognized that Example 1 does not suggest the use of enough hydrochloric acid to remove both protecting groups in Example 7 completely. (Tr. 811 and 1176.) Or he could have learned this in his first experiment following Example 1 as written. Then he would have realized that he should try to add more hydrochloric acid to remove both protecting groups. The Garbrecht patent itself at Col. 6, lines 40-42 would have taught him that enough hydrochloric acid would remove both protecting groups, the t-BOC and paranitrobenzyl groups, from diprotected cefadroxil:

> ... hydrochloric acid is preferred. Such acid treatment also removes certain amino nitrogen

protecting groups if such groups were not removed earlier in the process.

Even if this had not been taught in the Garbrecht patent, the reader already would have known that hydrochloric acid alone would be enough to remove the second protecting group (the t-BOC group). (Tr. 811, 1185.) Or he would have learned this in his first experiment following Example 1 as written. He would have known that if enough hydrochloric acid remained after the zinc had reacted with it and absorbed as much as it could, both protecting groups would be stripped away. (Tr. 798-99, 811, 1190.) Example 7 then tells him to process the resulting DMF solvate as described in Example 5.

Dr. Farina, using the one-step process of Example 1, added about three times as much hydrochloric acid as suggested in Garbrecht Example 1, and more than was suggested in Example 2. (TEO Tr. 824-25.) He obtained the Bouzard monohydrate. After a few experiments, one would be likely to get Bouzard following the teaching of Example 7, then going to Example 1, and then to Example 5.

The addition of more hydrochloric acid to remove both the first and the second protecting groups in a one-step procedure had been taught in basic chemistry courses well before 1976. (Tr. 902-903.)

Bristol argues that a person of ordinary skill in the art would not have tried this because he would have known that hydrochloric acid could destroy the beta-lactam ring. One with ordinary skill in the art in 1976 would have known this (Tr. 1160, 1167), but without some experimentation, he would not have known how much hydrochloric acid was needed to destroy the beta-lactam ring. It would not have been unusual in 1976 to experiment with various amounts of hydrochloric acid to determine what would happen to

the beta-lactam ring. (See Tr. 861-862, Tr. 1166.) Only a few simple experiments would have been required to determine whether enough hydrochloric acid could be used to remove a protecting group without destroying the beta-lactam ring. Any bench chemist does a little experimentation every time he tries to reproduce the experiment of another chemist. (See Tr. 383-385.)

The Garbrecht patent itself suggests that one could add more hydrochloric acid than is taught in Example 1 without destroying the beta-lactam ring. It teaches using acid at a pH of 1-2 on the solvate form of cephalexin and heating it to 40° to 70°C. (Biocraft/Gema Ex. 13, Col. 7.)

Dr. Ludescher and Dr. Kosak thought that if one followed Garbrecht Example 1 literally and failed to remove both blocking groups, the closest way to follow Example 1 would be to add more hydrochloric acid. (TEO Tr. 564 and 589.)

Bristol argued that adding more hydrochloric acid was not an obvious modification because the method of choice for removing t-BOC groups in 1976 was adding trifluoroacetic acid, and when that acid was used, the Bouzard monohydrate was not obtained. But Dr. Guazzi used a two-step deblocking process using trifluoroacetic acid, treated the resulting product in accordance with Example 5, and obtained the Bouzard monohydrate. (Kalipharma Exs. 210-213, Tr. 2835-2837, 2929-2930.)

Trifluoroacetic acid may have been the most common acid used to remove t-BOC groups in cephalosporin chemistry in 1976. Even if it did prevent the formation of the Bouzard monohydrate, the bench chemist knew that hydrochloric acid could be used to remove t-BOC groups and the prior art literature frequently disclosed the use of hydrochloric acid for this

purpose. (See the article in The Journal of the American Chemical Society by Dr. Louis Carpino, Biocraft/Gema Ex. 146, TEO Tr. 572, the 1970 article in Helvetica Chimica Acta, Biocraft/Gema Ex. 161, Tr. 572, and British patent 1265315, the Glaxo patent, Biocraft/Gema Ex. 173.) A person with ordinary skill in the art is deemed to have known both methods. Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc., 796 F.2d 443, 230 USPQ 416 (Fed.Cir. 1986), cert. denied, 108 S.Ct. 85 (1987).

The two-step deblocking process

Garbrecht Example 6 discloses a two-step deblocking process in which para-toluenesulfonic acid is used to remove the para-nitrobenzyl group from the cephalosporin molecule, after which zinc and hydrochloric acid are added to remove the t-BOC group. (Tr. 511.) Two-step procedures to remove the t-BOC and para-nitrobenzyl groups were known well before 1976. (Tr. 334.) A chemist with ordinary skill reading Example 6 would have understood that this two-step procedure could be used for removing the blocking groups in Example 7. (Tr. 647.)

If this two-step deblocking process had been used in following Example 7, a reasonably pure cefadroxil DMF solvate would have been obtained without the problems inherent in using a one-step process to get rid of two protecting groups following Example 1. (Tr. 648.) Then, Example 5 would have yielded the Bouzard monohydrate, if the product precipitated at room temperature or above.

Dr. Farina made a two-step deblocking experiment in which he treated diprotected cefadroxil for 24 hours with hydrochloric and para-toluenesulfonic acid before adding zinc. (Kalipharma Ex. 6 at 6-2.) He obtained a cefadroxil bis-DMF solvate. (Tr. 510; Biocraft/Gema Ex. 202.)

Professor Baldwin repeated the experiment with the same result. (Id.) From this cefadroxil bis-DMF solvate, using Garbrecht Example 5, a Bouzard monohydrate could have been obtained, if precipitation occurred at room temperature or above. The DMF solvate of Example 5 could be obtained from any source, as long as the solvate was relatively pure. (Kalipharma Ex. 79(a) at 13; Tr. 653-654.)

Dr. Guazzi used a two-step deblocking process using trifluoroacetic acid to obtain a DMF solvate. He treated the resulting product in accordance with Example 5, and obtained the Bouzard monohydrate. (Kalipharma Exs. 210-213.)

Dr. Nudelman used a two-step procedure in an unseeded laboratory in Israel, he removed both blocking groups, and he obtained a cefadroxil monohydrate that was not the Bouzard monohydrate. Before crystallization, Dr. Nudelman placed the reaction mixture in an ice bath bringing the temperature down to about 0°C. (Tr. 1873-74.) He used scratching to induce precipitation only after the temperature was reduced. (Tr. 1873-1874.) The failure of Dr. Nudelman to get the Bouzard monohydrate was the result of chilling before crystallization was induced.

Example 5

In addition to the one-step and two-step deblocking processes, Garbrecht teaches a third and simpler way to make the Bouzard monohydrate.

Example 5 teaches that if one starts with a cephalexin-bis (DMF) complex or solvate and dissolves it in an acidified solution, heats it to 55°C, neutralizes it and then crystallizes it, one can obtain a crystalline cephalexin monohydrate. Based on the experiments in evidence here, what almost always is obtained when Example 5 is followed is the Bouzard

cefadroxil monohydrate. (TEO Tr. 551 and passim.) Heating the product to 55°C is an important step in this procedure. Example 5 requires heat. It also suggests that the first crop precipitates and is filtered out before the filtrate of the second crop is chilled.

Any relatively pure DMF solvate processed in accordance with Example 5 usually produces the Bouzard monohydrate, if the product crystallizes at room temperature or above. (See Kalipharma Exs. 1-V, 1-W, 1-X, 53, 55, 195, 201, 202, 204, 210-213, 79(a) at 85, Biocraft/Gema Ex. 148, TEO Tr. 551, and Bristol Ex. 227.) Dr. Ludescher obtained the Bouzard monohydrate using the Crast DMF solvate and the Bouzard DMF solvate. Dr. Farina used another DMF solvate, and Dr. Crouch used a commercial DMF solvate. All produced the Bouzard monohydrate following Garbrecht Example 5. One with ordinary skill in the art reading Example 5 would recognize that any DMF solvate could be treated as taught in Example 5, regardless of whether the DMF solvate had been made in accordance with Example 7 or Example 1. (Kalipharma Ex. 79(a) at 13, Tr. 653.)

If one treated any commercial or relatively pure DMF solvate in accordance with Example 5, which teaches heating the product to 55° and suggests that the first crop precipitates out and is filtered before the filtrate is chilled for the second crop, the chances would be good that he would get the Bouzard monohydrate on his first try. Unless he tried to induce precipitation by chilling, which is not taught by Example 5, he would get Bouzard following Example 5 literally. It might take a long time for the material to precipitate, or crystallize out of solution, unless the process were helped along. He would not get the Bouzard monohydrate if he induced crystallization by chilling. A bench chemist might have tried any

of a number of ways to induce crystallization without chilling, for example, shaking the vessel, stirring, scratching, adding a material in which the precipitate was known to be less soluble, or waiting longer for precipitation to occur. All of these were and are familiar procedures to the bench chemist. Only cooling might have prevented him from obtaining the Bouzard monohydrate. Chilling is a customary way to induce crystallization, but it is not the only customary way or the most common way to induce crystallization.

Example 5 suggests chilling after precipitation, not before. If this suggestion were followed, the Bouzard monohydrate would have been obtained in the first crop. If nothing were done to induce crystallization, in time the Bouzard monohydrate would have precipitated out of solution. Example 5 of Garbrecht comes very close to anticipating the '163 patent.

To show that the modifications in the Garbrecht process that resulted in the Bouzard monohydrate were not obvious, Bristol relies upon the failure of Dr. Micetich, Professor Nudelman, and Dr. Marsili to make the Bouzard monohydrate when they followed Garbrecht.

Dr. Micetich was hired by Bristol to make certain tests following Bristol's instructions, so that Bristol could get the patent examiner to issue the '657 patent. There is no evidence that Dr. Micetich made less than his best effort to do the work he was instructed to do, but he did no more than what Bristol asked him to do. This is not a reliable measure of what one with ordinary skill in the art in 1976 would have done without limiting instructions.

Dr. Nudelman's experiments were made in an unseeded laboratory in Israel. As requested by Bristol, Dr. Nudelman prepared a diprotected

cefadroxil. He then removed the two blocking groups sequentially, the first with zinc and hydrochloric acid, and the second with TFA. Then he isolated the cefadroxil as a DMF solvate and finally converted the DMF solvate to a cefadroxil hydrate. He did not produce the new Bouzard monohydrate. Dr. Nudelman did not obtain the Bouzard monohydrate because he chilled the reaction mixture before he induced precipitation. It is unlikely that the absence of seeds had much to do with the product he obtained, although if he had been in a heavily seeded atmosphere, precipitation might have begun before he chilled the mixture.

Dr. Nudelman, like Dr. Micetich, was asked to follow Bristol's instructions. He was not handed the Garbrecht patent and asked to make the examples work. He was not asked to try Example 5 alone. If he had been allowed to follow the examples in his own way, it might be some evidence of what one with ordinary skill in the art might have done to make the Garbrecht examples work. Those who were not given Bristol's detailed instructions usually obtained the Bouzard monohydrate with ease in a very few tries.

As for Dr. Marsili, he worked for Dobfar, and Dobfar wanted to export the new monohydrate to the United States. But about six months before he tried to reproduce Garbrecht Example 7, Dr. Marsili successfully made the Bouzard monohydrate following Example 5. (Bristol-Myers Exhibit 99, at 86-88.) When Dr. Marsili repeated Example 7, he wanted to make the Garbrecht solvate, but he already knew that he could get the Bouzard monohydrate from Example 5. In following Example 7, he did not use enough hydrochloric acid to remove both protecting groups because he feared he would destroy the beta-lactam ring. (Bristol-Myers Ex. 99 at 168.) He knew by experience

that hydrochloric acid could destroy the ring, and he did not want to experiment with this. Why he did not want to experiment is puzzling, because the Garbrecht patent itself taught that more hydrochloric acid could be used than was taught in Example 1 without destroying the beta lactam ring. In following Example 7, Dr. Marsili obtained some diprotected cefadroxil, but he failed to follow the other instructions in Example 7. He did not treat the diprotected cefadroxil with specific amounts of DMF, HCL and zinc as called for in Example 7. (Id. at 113-116, 127.) He also did not adjust the pH to 6.5 with triethylamine. If he had done these things, as taught in Example 7, he should have obtained at least some Bouzard monohydrate. But he had no incentive to do so. The work of Dr. Marsili does not support Bristol's position.

One with ordinary skill in the art in April 1976 could have made the Bouzard monohydrate if he had followed the general teachings of the Garbrecht patent, and if he had made only modifications that were not innovative in nature, or in the case of Example 5, if he had made no modifications at all.

The next question is whether one with ordinary skill would have had to combine more than one teaching in the prior art to get the Bouzard monohydrate, and if so, whether anything in the prior art suggested that he combine them.

In Garbrecht Example 5, he could have obtained the Bouzard monohydrate if he followed it literally, and used a relatively pure DMF solvate, and did not induce precipitation in one of a number of ways familiar to any bench chemist. There was no question as to whether the prior art suggested any modifications to him. No modifications were necessary. The only

problems would have been of his own making, if he tried to speed up precipitation by chilling the reaction mixture, a process that was not taught in Example 5.

When following Example 7, the procedures followed by each chemist would be slightly different. Examples 7, 6, and 1 do not spell out everything that one needs to do to get a good product. Each chemist would make his own variations to carry out the general teachings of the patent. In this case it is not so much a question of looking for specific prior art that suggests specific combinations in the prior art, but the particular choices that would be made by individual chemists in selecting from common laboratory procedures. All of the necessary tools to carry out the examples in the Garbrecht patent successfully would have been learned by the chemist in a basic chemistry course. He would have to want to try to get the patent examples to work. If the hypothetical person with ordinary skill in the art is deemed to have no interest in getting prior art chemical patent examples to work, then no prior art chemical patents can make a claimed invention obvious. Chemical patents do not tell one how to light the Bunsen burner or how to induce precipitation of crystals.

In 1976 there was a major incentive for a chemist working in the area of cephalosporins to find a form of crystalline cefadroxil that could be produced commercially. This meant finding a pure product with relatively high yield. When Garbrecht Example 1 was followed literally, a product of commercial quality cefadroxil was not obtained.

During the prosecution of the '657 Bouzard patent, the applicant stated:

> Old cefadroxil monohydrate and cefadroxil trihydrate of the Weber and Berman declarations are, nevertheless,

> believed to be representative of the prior art since their production represented contemporaneous best efforts of chemists and pharmacists skilled in cephalosporin and penicillin chemistry to produce a pharmaceutically acceptable form for commercial use.

(Biocraft/Gema Ex. 8, page 4, lines 19-24.)

The work done at Bristol that was not made public is not part of the prior art. The statement made by Bristol to the Patent and Trademark Office is significant because it admits that chemists at the time of the invention wanted to produce a pharmaceutically acceptable form of cefadroxil for commercial use. There was an enormous incentive for one with ordinary skill in the art in April, 1976 to find a pure form of cefadroxil, such as the Bouzard monohydrate, with the high yield necessary for commercial production.

If one who followed Garbrecht Example 5 by itself or Example 7 failed to get a pure cefadroxil of good yield on the first try, he would have had a strong incentive to try again. He would have been looking for a high-yield good quality cefadroxil suitable for commercial production.

Using Example 7, a chemist with ordinary skill in the art, trying to get rid of the two protecting groups using the one-step process of Example 1, would have made the Bouzard cefadroxil monohydrate at least after two or three tries, making only obvious modifications, and doing nothing surprising, unusual or innovative. If required, a third or fourth try would not have been uncommon for a chemist.

Using the two-step procedure, he should have been able to get the Bouzard monohydrate on his first or second try, if he did not chill the reaction solution before precipitation and obtain the cefadroxil monohydrate that Dr. Nudelman made before he obtained the Bouzard

monohydrate. It would be unfair to assume that Dr. Nudelman's product would have been made first. Most of the chemists working without instructions from Bristol obtained the Bouzard monohydrate first.

Using Example 5 alone it would have been hard not to get Bouzard on the first try. One would have to chill the reaction mixture before precipitation, and this was not taught by Example 5.

One with ordinary skill in the art who had this compelling incentive to produce a good quality cefadroxil suitable for commercial production would have made minor adjustments to the procedures taught in Garbrecht and produced the Bouzard monohydrate. To get the other cefadroxil monohydrate first would have been unusual. If one followed Garbrecht Example 5 alone, starting with a pure DMF solvate, and not chilling to induce precipitation, he would have made the Bouzard monohydrate with no modifications at all.

The Crast patent

The Crast '741 patent was issued on Oct. 12, 1976. (Biocraft/Gema Ex. 10.) The patent described improved purification processes for certain types of products. The purpose of these purification processes was to obtain higher yields for commercial production and to reduce the cost of production. (Id., Col. 2, lines 29-41.) Crast claims a process and a solvate. Unlike the '657 patent, it does not claim a specific crystalline cefadroxil product that is identified by its X-ray profile.

The hypothetical person with ordinary skill in the art is deemed to be aware of all prior U.S. patents, including the Crast patent. It is assumed that such a person would try to practice the examples in the prior art chemical patents at least once. Such a person, in trying to practice Crast patent Example 6, is by definition a chemist, and a chemist would have

tried to modify the process explicitly taught in Crast to obtain a better product if he were completely dissatisfied with the first product he made.

By using what is taught in Example 6, and making minor variations consisting of procedures commonly known by any bench chemist, procedures that have been taught in undergraduate chemistry courses since at least the 1950's, he could have made the Bouzard monohydrate.

He would have had an incentive to do so, because in 1976 companies were trying to obtain a cefadroxil product that could be produced commercially, and this required a pure product made by a high yield process. The Crast patent promised a pure product in a high yield, but when followed literally, the Crast patent did not produce it.

Professor Just did a number of experiments for respondents to try to prepare a substantially pure crystalline cefadroxil following Crast Example 6. After making some modifications, he produced the Bouzard monohydrate. (TEO Prehearing Conf. Tr. 38-39.) His only instructions were to follow the process described in Crast Example 6 as closely as possible, and that he should perform the process on a relatively large scale. (TEO Tr. 390, 411.)

Cefadroxil had not been produced previously in Professor Just's laboratory in Montreal. He had no previous contact with cefadroxil. There were no Bouzard seeds in the surrounding atmosphere. (See TEO Tr. 389.)

In his first two attempts, Professor Just followed Example 6 literally. He failed to make a satisfactory DMF solvate following Example 6(A). In his first experiment Professor Just heated the mixture to 100°C, but the DMF solvate did not precipitate after cooling. He correctly concluded that the heating step had ruined the product. (TEO Tr. 413;

Bristol Ex. 80, p. 2.) Professor Just taught chemistry, was an experienced bench chemist, and he was capable of learning the characteristics of DMF solvate and cephalosporins from the experiments as he was making them.

In his second experiment Professor Just slurried the DMF solvate intermediates in 90% aqueous methanol. He made a product that contained a cefadroxil DMF solvate and a para-substituted aromatic compound contaminant. (TEO Tr. 413-414; Tr. 2603; Bristol Ex. 78, p. 2; Bristol Ex. 80, pp. 2-6.)

Although his first two experiments were unsuccessful, he learned something about cephalosporin products, even though the products of these experiments were discarded. (TEO Tr. 408-14.)

In his third experiment he tried to identify his own mistakes and any mistakes in Crast Example 6, and to determine what modifications should be made. (Tr. 2603-2604; Bristol Ex. 78, p. 2.) He referred to the third experiment as "an exploratory type of experiment to find out what I should do to get a proper product." (Tr. 2604.) In the third experiment, he made two crops. He produced no samples that he thought were good enough to send away for X-ray diffraction analysis.

Professor Just prepared the first crop of DMF solvate in his third experiment, but was unable to form a pure crystalline monohydrate by slurrying it in 90% methanol as called for in Crast. (TEO Tr. 422-423.) This process yielded "pretty good material containing 12-15 mole percent DMF." (TEO Tr. 422.) He did not think that this material (15YR) was pure, because he had determined by NMR (nuclear magnetic resonance) analysis that it contained 12-15 percent DMF. (Tr. 2604.) NMR analysis was available to the bench chemist in 1976. (Tr. 2623-2625.)

Professor Just did not request an X-ray diffraction analysis of product 15YR because sample 15YR was impure and had a substantial aromatic contaminant according to its NMR analysis. In making the first crop, Professor Just did not follow Crast Example 6 closely. The experiment in which 15YR was produced was a preliminary experiment. (Tr. 2604-2605.)

To purify this material further, Professor Just slurried it in 90% methanol for another hour. (TEO Tr. 422-423.) This second slurry, which was not described in Crast Example 6(B), yielded 2.2 grams of a crystalline product (15YRR) that Professor Just described in his notebook as DMF-free. (TEO Tr. 422-423.) The 15YRR product still contained a substantial amount of the aromatic compound contaminant para-hydroxyphenylglycine. (Tr. 2605; Bristol Ex. 78 at 4.)

Professor Just did not submit sample 15YRR for X-ray analysis because he had modified the Crast procedure and because the ratio of aromatic impurities was much higher than it should have been for a pure compound. (Tr. 2605.) Dr. Levy found that sample 15YRR, prepared by the slurry method of Crast, was barely more than half cefadroxil, and had approximately 35% of the aromatic impurity. (Tr. 2566.)

Professor Just then prepared a second crop of DMF solvate (15X). It still contained the aromatic contaminant. (Tr. 2606; Bristol Ex. 78, p. 4.) Then 11.5 grams of the second crop solvate were slurried in 90% methanol to form product 15XR. (Tr. 2606.) Sample 15XR is the only product obtained by Professor Just that did not result from changes in the procedure described in Crast Example 6. (Tr. 2615-2616.)

Professor Just thought that 15XR was a "very good material," but that the yield of crystals was much less than he expected from reading Crast.

(Tr. 2606; Biocraft/Gema Ex. 10, col. 11, lines 5-9.) This was the reason he gave for not sending 15XR out for X-ray analysis. (Tr. 2606.) He moved on to his fourth experiment.

None of the procedures in Professor Just's third set of experiments resulted in pure cefadroxil in the yield described in the Crast patent. (Tr. 2604-2606.)

Before the fourth experiment was made, Professor Just had determined that the DMF solvate crops he was getting by following Crast were relatively soluble in water and relatively insoluble in methanol. (TEO Tr. 425; Bristol Ex. 77, p. 12.) With this and the other information he had obtained in his first three experiments in hand, he modified his fourth experiment. He changed the proportions of ingredients, lowering the amount of the Dane salt reactant to eliminate the aromatic contaminant. (Bristol Ex. 78, p. 5, conclusion 3.) He washed the first DMF crop with acetone. He first dissolved the solvate in water, and then precipitated the cefadroxil by adding the methanol in which it was less soluble. (TEO Tr. 395-396; Tr. 2600; Bristol Ex. 80, pp. 7-8.)

The products of Professor Just's fourth experiment were crystalline cefadroxil monohydrates. They were found to be the Bouzard monohydrate. (Biocraft/Gema Ex. 64; TEO Tr. 1432-1433; Bristol Ex. 78, pp. 6-12; April 24, 1989 Pre-Hearing Conf. Tr. 38-39.)

In his successful fourth experiment Professor Just treated the DMF solvate with water first because he had found in a prior experiment that the solvate was relatively soluble in water (TEO Tr. 425) but relatively insoluble in methanol. The DMF solvate crops prepared in his fourth experiment did not totally dissolve in water but were partially slurried.

(Tr. 2599.) (In the slurrying technique described in Crast 6B, the product was slurried all at once in a 90% methanol.) From the part of the solvate that dissolved in the water he hoped to crystallize a cefadroxil product that was more pure and higher in yield than his previous products. Just recrystallized the product after treating the product first with water and then with methanol, and obtained the Bouzard monohydrate. (TEO Tr. 395, 424-425; Tr. 2599-2600.)

He had used this procedure before. Whenever he used solvents to crystallize a product he always tried to find a solvent in which the product readily dissolved. He would dissolve the product in this solvent before he added a solvent in which the product was less soluble. (TEO Tr. 395-98.) This was a standard practice in chemistry (TEO Tr. 415). Professor Just had been teaching it to his students since 1958. (TEO Tr. 398-399.) This was a common crystallization technique in 1952 when Professor Wolfe took his first laboratory course in organic chemistry. (TEO Tr. 984-985.) It was conventional to use co-solvents simultaneously or in sequence to precipitate products. (TEO Tr. 246-47.) Dr. Bouzard had used the technique of adding water first and then the other solvents. (TEO Tr. 321-324.) Both Professor Wolfe and Professor Dunitz thought that it was reasonable to dissolve the DMF solvate in water before adding the methanol solvate, and that it would have been the first thing they would have thought of doing. (TEO Tr. 627-630.)

Professor Baldwin pointed out that Crast Example 6 disclosed a slurry rather than a solution, and he saw no need to try to dissolve the solvate at all when reproducing Crast Example 6. But in at least three of the experiments upon which Crast Example 6 is based, Gottstein (one of the

inventors named in the Crast patent) had dissolved the DMF solvate in water before crystallization. (Biocraft/Gema Ex. 78 at 67-69, Biocraft/Gema Ex. 68 at 4-8.)

Professor Baldwin also noted that adding water and then methanol in sequence would have been unnecessary because slurrying as taught in Crast produced a pure product. It is reasonable to assume that one with ordinary skill would try first to follow the patent example literally. But slurrying as described in Crast did not always produce a pure product.

Anyone following the Crast example would have to add some steps not specifically spelled out in the patent. Depending on the steps that were added, different products would be obtained. Many chemists who tried to reproduce the Crast example as written got a bad product. Even if one obtained a pure product following Crast Example 6B as written, one with ordinary skill who was trying to get a pure cefadroxil with high yield, would not have liked the product. It had a very poor yield. He would be looking for a pure product with high yield, and he would have moved on to the next experiment.

It was reasonable for Professor Just to try three or four modifications of Crast, after he had followed the slurrying procedure taught in Crast Example 6 and did not like the sample he obtained. The patent law requires that a patent specification describe the invention in sufficient detail to enable one skilled in the pertinent art to make and use the invention (35 U.S.C. § 112), but there is no requirement that the invention be spelled out in such detail that someone without skill in the art can practice it.

The Crast procedure could have been modified by one with ordinary skill in the art to make the Bouzard monohydrate. The Federal Circuit has held that this does not make the modification obvious unless the prior art suggested the desirability of the modification. In re Gordon, 733 F.2d 900, 902, 221 U.S.P.Q. 1125, 1127 (Fed. Cir. 1984), In re Regel, 526 F.2d 1399, 1403 n.6, 188 U.S.P.Q. 136, 139 n.6 (C.C.P.A. 1975).

The modification made by Professor Just was so minor and obvious that it was suggested by any basic chemical course. He added water first, and then methanol. This modification was desirable because his earlier experiment following Crast as written had not produced a pure cefadroxil with high yield. He wanted the solvate to dissolve in the water before he added the methanol, and then he could recrystallize the product. He hoped to obtain a better cefadroxil product. Anyone with ordinary skill in the art could have made Crast Example 6(b) even for the first time either as written or by adding water first and later methanol. Neither way would have been an unusual way to follow the teachings of Crast. (Tr. 246-247, 627-630.)

The motivation to get a cefadroxil product that could be produced commercially was the same in 1976 for the chemist trying to follow Crast as it would have been for the chemist trying to follow Garbrecht. To get a product that could be produced commercially, yield was important. One getting a low yield product in 1976 would have tried the experiment again.

Bristol argues that if the Crast patent teachings are followed literally, a perfectly good crystalline cefadroxil monohydrate is produced that is not the Bouzard monohydrate, and that there would be no incentive to one with ordinary skill in the art to modify the Crast patent teachings

to obtain the Bouzard monohydrate. To support this argument, Bristol cites the experiments of Gottstein and Misco, Baldwin and Schofield, and Marsili, in addition to the third experiment of Professor Just.

Mr. Gottstein, a coinventor of the Crast patent, and his assistant Mr. Misco did the work on which Example 6 of the Crast patent is based. Example 6 is a composite description of more than half a dozen different experiments carried out in 1972 by Gottstein and Misco. Mr. Gottstein himself did not carry out Example 6 as specifically described in the patent. He had trouble crystallizing a pure cefadroxil monohydrate. In five different experiments he used four different techniques for purifying the DMF solvate. In three of these he first dissolved the DMF solvate in water prior to crystallizing it. (This was the same technique as that used by Professor Just.) (Biocraft/Gema Ex. 156 at 246, 276-277; Biocraft/Gema Ex. 78 at 23-70; Biocraft/Gema Ex. 68 at 3-8.)

The Gottstein product was then combined with three different samples prepared by Misco. The Misco samples were made by a different process, including a modification subsequently used by Professor Just, washing the first DMF crop with acetone. This modification was not described explicitly in Crast. Misco also slurried his DMF solvate products in twice the amount of solvent described in the Crast patent example. (Biocraft/Gema Ex. 29 at 295, 302-303; Biocraft/Gema Ex. 78 at 36-37; Biocraft/Gema Ex. 68 at 11; Biocraft/Gema Ex. 22 at 42.)

Gottstein and Misco, like Professor Just, modified the procedures described in Crast. The work of Gottstein and Misco supports respondents' position that literal teaching of Crast had to be modified to get a pure product with high yield.

In April, Dr. Schofield produced DMF solvates following Professor Just's modifications of Crast Example 6A. (TEO Tr. 1133-1134; Tr. 1405-1406, 1429; Biocraft/Gema Ex. 76, Notebook at 1-6, 11-13.) In one experiment under Crast 6B he used the Just procedure of adding the water first and then the methanol. He made the Bouzard monohydrate. In another experiment under Crast 6B he followed the Crast procedure of slurrying the methanol and the water at the same time. Here he obtained the Gottstein/Misco monohydrate. (TEO Tr. 1136-1139, Bristol Ex. 81.)

Dr. Schofield and Professor Baldwin proved that one could get the Gottstein/Misco monohydrate by following Crast with minor modifications, but one also could get the Bouzard monohydrate if the water was added before the methanol. Although this was not a major or innovative modification, it appears to be the critical modification that caused the Bouzard monohydrate to be formed.

Sample 15XR, the one sample of pretty good quality obtained from Just's third experiment and the one that he had made without modifying Crast Example 6, was found and given to Bristol for analysis in August, 1989. Dr. Schofield's analysis for Bristol shows that it is an "essentially pure Crast material as regards cefadroxil" and that it has less para-hydroxyphenylglycine impurity than the Bouzard material produced by Just's modification of the Crast procedure. (Tr. 1533-1534.)

In his August experiments Dr. Schofield modified the Crast reactant proportions in the same way as Professor Just (Tr. 1686), but he made other changes of his own. The Crast patent teaches the use of "dry acetone." (Biocraft/Gema Ex. 10, col. 6, line 19.) Dr. Schofield also dried the other reactants and the apparatus used in his experiments. (Tr. 1547,

1549-1551, 1556, 1560; Bristol Ex. 213 at 17-22.) Instead of air drying as described in Crast (Biocraft/Gema Ex. 10, col. 10, lines 35, 47), Dr. Schofield dried his solvate crops for a long time under vacuum. (Tr. 1575, 1582; Bristol Ex. 213 at 21-22.) He reacted the ethyl chloroformate and the Dane salt under dry argon, shook the mixture of the mixed anhydride and 7-ADCA, and then placed the mixture in an isopropanol bath at -10°C. (Tr. 1558, 1562-1566; Bristol Ex. 213 at 17-22.)

After forming the DMF solvate, Dr. Schofield washed his reaction flask with acetone to remove the product slurry. This further purified the first solvate crop. (Tr. 1573-1575.) He then took the two crops and treated them as in Crast Example 6B, using Professor Just's modifications on one sample from each crop, and using on another sample from each crop the Crast slurrying procedure in which he slurried in water and methanol at the same time. (Tr. 1508-1509.) When he used Professor Just's modification, he obtained the Bouzard monohydrate, and when he used his own process, he produced the Gottstein monohydrate. When he tested the products for purity, he found that the products of his procedure were of higher purity than the products obtained following Professor Just's sequential slurrying procedure. (Tr. 1511-1513.) He concluded that the Crast procedure (with his modifications) produced a substantially pure cefadroxil. (Tr. 1513.)

Dr. Baldwin and Dr. Schofield concluded that the unmodified Crast procedure produced a cefadroxil that was purer than the modified Crast procedure used by Professor Just in his fourth experiment that produced the Bouzard monohydrate, and therefore there would be no reason for one with ordinary skill in the art to make any modifications in the Crast process. A good product could be obtained following Crast literally.

Dr. Schofield's modifications, although they were not outside the ordinary skill in the art, departed from the Crast procedure far more than Professor Just's modification in which he added the water before the methanol. Moreover, Dr. Schofield found his product to be pure, but he did not state that it had a good yield.

It made little difference to Professor Just whether 15XR was relatively pure, because it had a low yield. He did not reject the product of the third experiment because it was not a good product; he rejected it because there was not much of it. This was reasonable because the Crast patent was about improving yield. Although the Crast patent indicates that Example 6 relates to purifying the product, the whole Crast patent is concerned with the improvement of yield so that a pure product can be produced commercially. Professor Just wanted to make another experiment that would have a higher yield. When he did, he not only had a higher yield, he had obtained the Bouzard monohydrate.

What he did after his third experiment was probably what anyone with ordinary skill in the art in 1976 who wanted to produce a commercial product would have done. He did not test the product with poor yield. He moved on to another experiment.

In 1986, Dr. Marsili of Dobfar made some experiments involving Example 6(B) of the Crast patent to test the validity of the '657 patent. Because Dobfar would benefit if the '657 patent were shown to be invalid, Dr. Marsili initially had an incentive to obtain the Bouzard monohydrate using the Crast process. (Biocraft/Gema Ex. 170 at 31-34.) Dr. Marsili did not use the procedure described in Exhibit 6A of the Crast '741 patent for preparing the DMF solvates. Instead, he used what he considered to be

a pure DMF solvate prepared by Dobfar's own procedures. He did not analyze the DMF solvate for purity. He followed Example 6(B) of the Crast patent to purify each of his solvate samples by slurrying them in 90% methanol. He did not modify the slurrying step, although he made minor modifications in the Crast process, nor did he analyze the materials produced in his experiments to determine whether they were relatively free of DMF. He obtained what he believed to be a pure crystalline cefadroxil, and it was not the Bouzard monohydrate. (Id. at 51-56, 68-80, 92-96, 169-170.)

Dr. Marsili apparently was satisfied with what he considered to be a pure crystalline cefadroxil that he had made by slurrying as described in Crast. Dr. Marsili was not present at the hearing in this case, and it is not clear whether yield was important to him in connection with this experiment. He did obtain the Bouzard monohydrate following Garbrecht Example 5 at about the same time that he made his Crast experiment. He may have had no reason to continue modifying Crast. (Bristol Exhibit 99, Deposition Exs. 5 and 7.)

Other chemists, like Professor Just and Dr. Schreiber, who literally followed the slurrying process described in Crast 6B, were not satisfied with the product they obtained.

When Dr. Schreiber first followed Crast Example 6 literally, he produced a product that was hardly crystalline. (Bristol Ex. 1 at 84-85 and Dep. Ex. 4 at 001677.) Later, after adopting modifications similar to those used by Professor Just, Dr. Schreiber produced the Bouzard monohydrate. (Bristol Ex. 1 at 89-91.) The work of Dr. Schreiber supports respondents' position. He did not obtain a satisfactory product when

following Crast literally, but when he tried again, he obtained the Bouzard monohydrate.

A chemist failing to get a pure product with high yield following Crast would have had an incentive in 1976 to make more experiments to obtain a commercial cefadroxil product.

Not everyone failed to get a pure product using the Crast 6B slurrying procedure. Dr. Schofield obtained a pure cefadroxil, but he made modifications in the Crast process directed towards drying the product out. Although the skills he used to dry the product out were not unusual, they were not as simple and ordinary to a bench chemist as adding water first, and then the methanol. His modification was called for by his prior unsuccessful efforts to obtain a pure cefadroxil of high yield from the Crast slurrying process.

It probably would have taken considerable luck in 1976 to get any pure crystalline cefadroxil by following the literal teachings of Crast 6B for the first time. Although one with ordinary skill in the art is deemed to know and understand all of the prior art, he is not necessarily endowed with luck.

From the experiences of Just, Gottstein and Schreiber, it is found that one with ordinary skill in the art in 1976 would have had difficulty in obtaining a pure product of good yield the first time that he used the Crast 6B slurrying process as written, and that he would have tried the experiment again, with obvious modifications familiar to any bench chemist. On his second or third attempt at getting a satisfactory product from the Crast teachings, it is more likely that he would have obtained the Bouzard

monohydrate than the Gottstein monohydrate because Just's modification was simpler than Schofield's.

Finally, Bristol argues that as a matter of law the Bouzard monohydrate cannot be prima facie obvious from prior cefadroxil monohydrate crystal forms having different X-ray powder diffraction patterns. In re Grose, 592 F.2d 1161, 201 U.S.P.Q. 57 (C.C.P.A. 1979). The Bouzard monohydrate has no unexpectedly superior properties in comparison with the Gottstein/Misco monohydrate or the old monohydrate. (A finding suggesting the contrary at page 39 of the initial determination on temporary relief was wrong. It would be correct to state that the new monohydrate can be given in doses that last longer than earlier-developed oral cephalosporins such as cephalexin, cephadrine and cefaclor. See Bristol Ex. 59 at 4-5. The corrected finding is of little interest, however.) The only thing that was unexpected about the Bouzard monohydrate was its X-ray powder diffraction pattern. This could not have been predicted.

Bristol takes the position that if the X-ray pattern of a new crystal form of a compound is unpredictable, that form cannot be obvious within the meaning of 35 U.S.C. § 103. One of its identifying characteristics, its powder diffraction pattern, could not have been predicted in advance. Yet all new crystalline compounds have different diffraction patterns, as well as other identifying characteristics, and a novel crystalline compound is not necessarily patentable.

In Grose, the C.C.P.A. held that on the record before it, a certain crystalline structure was not obvious under Section 103. The court expressly pointed out that the prior art did not disclose any method for producing the claimed crystalline structure. 592 F.2d at 1168, 201

U.S.P.Q. at 63. In footnote 8 the court noted that nothing in the record indicated that one skilled in the art would be able to prepare the claimed product. In contrast, the record here contains extensive evidence that one skilled in the art would be able to prepare the Bouzard monohydrate.

The Crast patent discloses a method for preparing a pure crystalline cefadroxil monohydrate. If one of ordinary skill in the art made minor modifications in Crast that were not innovative and were within his skills, and which he would be motivated to make, it is likely that he would have produced a crystalline cefadroxil monohydrate with an X-ray diffraction pattern like that later claimed in the Bouzard patent.

Secondary Considerations

Secondary considerations must be considered in the context of what one with ordinary skill in the art in 1976 would have known. If it is clear that one with ordinary skill in the art using the prior art would be likely to make the product in issue rather easily, in a number of different ways, then the secondary considerations or indirect objective evidence of obviousness may not be as important as they might otherwise be.

1. There is evidence of commercial success, long felt but unsolved needs, and failure of others to obtain a desired result.

Other scientists failed to find the Bouzard monohydrate earlier, although they had an incentive to do so. Before Dr. Weber, working with Dr. Bouzard, obtained the new Bouzard monohydrate from the trihydrate, other scientists had been trying to prepare commercial forms of cefadroxil, but they had been unsuccessful. (TEO Tr. 308-320; Biocraft/Gema Ex. 157.) Mr. Crast, the inventor of cefadroxil, did not obtain the new monohydrate. Mr. Gottstein, an experienced cephalosporin chemist, made a cefadroxil

hydrate, but not the new monohydrate. The inventors named in the '657 patent had been working for about two years with cefadroxil before Dr. Weber obtained a trihydrate that led to the Bouzard monohydrate. Although Bristol had a patent on cefadroxil that would cover the Bouzard monohydrate for 17 years, it was working hard to find a commercial form of cefadroxil. Skilled cephalosporin chemists did not make the Bouzard monohydrate despite an incentive to do so in 1976.

Respondents' use of the Bouzard monohydrate in their products amounts to copying, and copying is a sign of commercial success. Respondents are importing the Bouzard monohydrate, rather than some other form of cefadroxil monohydrate, although there are other forms of this monohydrate that are not covered by the '657 patent. It is easier and faster for respondents to get approval from the FDA if they import a formulation already approved by FDA than to obtain approval from FDA of a new formulation. Respondents are not importing the Bouzard monohydrate solely because it has had commercial success, but for other reasons as well. Nevertheless, the Bouzard monohydrate, which is sold by Bristol and the respondents, has had commercial success. The product claimed in the '657 patent is sold by Bristol today under the brand names DURICEF and ULTRACEF. (Staff Ex. 3 at 16.) Bristol is going to great expense to protect its exclusive right to sell these products, and respondents are incurring great expense to be able to continue to sell identical products.

2. Bristol argued that the Bouzard monohydrate had properties superior to those of other cefadroxil products, but in the prosecution history of the '657 patent Bristol had abandoned this same argument. In the Berman declaration in the prosecution history, Bristol admitted that

the extended half-life, allowing a reduction in dosage, was the result of the cefadroxil structure, and not the result of any unique feature of the Bouzard monohydrate. (See Biocraft Ex. 23 and Ex. 28.)

3. Finally, Bristol argued that the industry had accepted the patent as valid, relying upon Interchem's failure to import the Bouzard monohydrate as evidence of industry acceptance of the patent. (TEO Tr. 1111.) The record shows, however, that Dobfar, the Italian manufacturer of the product Interchem would have imported, is planning to sell cefadroxil to another firm in the United States as well as to Interchem. (Kalipharma Ex. 109-113.) Bristol has not proved any reluctance on the part of Dobfar to export the product to the United States to any willing buyer. There is no evidence that the industry as a whole accepts the patent as valid.

The indirect evidence supporting patent validity (failure of others to make the product and the commercial success of the product) is found to be inadequate to overcome the substantial direct evidence that the product claimed would have been obvious to one with ordinary skill in the art. The chemists who had an incentive before 1976 to find a form of cefadroxil that could be produced commercially and who could have made the Bouzard monohydrate by following the Garbrecht or Crast examples may have been following other leads. If they had tried to reproduce the Garbrecht Example 5, it would have been hard for them not to have obtained the Bouzard monohydrate. I assume that the hypothetical chemist with ordinary skill in the art would have tried to make all of the examples in prior art chemical patents work, regardless of whether any real chemist did so. Little weight is given to the argument that some chemists failed to make

the Bouzard monohydrate because of the ease and frequency with which other chemists have obtained the Bouzard monohydrate while making only minor modifications in the Crast patent or no modifications whatsoever in Garbrecht patent Example 5.

The '657 patent is obvious

Everyone looking at this problem at this time has hindsight. But to find that the respondents' experiments reproducing Garbrecht and Crast were the result of hindsight would be an oversimplification and it would be wrong. When this case started, no one knew what procedures would produce the old monohydrate, and what procedures would produce the new monohydrate. Hindsight was of little practical value here.

It would be unfair to overlook the careful steps taken by the respondents to avoid doing anything that would have been beyond the ordinary skill of the bench chemist in 1976 when following Garbrecht or Crast. Bristol gave detailed instructions to Dr. Micetich and to Professor Nudelman, although not to Dr. Baldwin and his associates. It is likely that Dr. Micetich and Dr. Nudelman would have followed different procedures if they had been left on their own. I understand that Dr. Nudelman was supposed to repeat the Micetich procedures in an unseeded atmosphere, and so he needed instructions, but complainant never proved that what Micetich had done was what someone with ordinary skill in the art would have done. In contrast, respondents did not give detailed instructions to the chemists who made their experiments. Most of the modifications that they made in the Garbrecht and Crast processes involved the use of common skills that had been familiar to bench chemists all over the world for over 30 years at least. They were not the gift of hindsight.

Respondents have proved by clear and convincing evidence that the '657 patent is invalid under Section 103.

INFRINGEMENT

Respondents Biocraft and Gema admitted infringement. (Conference Tr. 84.) The Kalipharma respondents contested infringement, but their own witness testified that their product infringes. (TEO Tr. 934.)

The evidence shows that the product now produced by respondents falls under claim 1 of the patent. All of the respondents (except Kalipharma, Purepac, IBI and IBSA) stipulated that their product was covered by the '657 patent claim. (March 21, 1989 Preliminary Conference Tr. 84.)

X-ray experts testified that the IBI product was identical to the product claimed in the '657 patent. (TEO Tr. 934, 961.) IBI manufactures bulk crystalline cefadroxil monohydrate in Italy and sells it to IBSA. (Staff Ex. 7.) IBSA processes the bulk cefadroxil into dosage form in Switzerland and exports the resulting capsules to Kalipharma in the United States. (Id.) Kalipharma, through its Purepac division, sells in the United States the infringing crystalline cefadroxil monohydrate. (Id.)

If the patent were found to be valid and enforceable, all the respondents would be found to infringe the patent directly or to induce its infringement.

ENFORCEABILITY

Respondents have not carried the burden of proving that the patent is unenforceable under the current precedent in the Federal Circuit because of inequitable conduct in the Patent and Trademark Office.

Respondents failed to prove by clear and convincing evidence that Bristol-Myers had an intent to deceive. More than gross negligence must be

proved. Inequitable conduct is the failure to disclose material information or the submission of false material information to the Patent and Trademark Office, with an intent to deceive. Both materiality and intent must be proven by clear and convincing evidence. Kingsdown Medical Consultants Ltd. v. Hollister Inc., 863 F.2d 867, 9 U.S.P.Q. 2d 1384, 1389 (Fed. Cir. 1988), cert. denied, 109 S.Ct. 2068 (1989). The failure to disclose part of what Dr. Micetich's experiments had shown was material, but there was no evidence of an intent to mislead.

Respondents allege that complainant acted inequitably on a number of occasions during the prosecution of the patent.

On August 7, 1978, Bristol filed a patent application for one product claim for crystalline cefadroxil monohydrate. The claim was rejected on May 4, 1979 and again on October 19, 1979 over the Garbrecht patent. The patent examiner suggested that the only way to show that the product is not that of Garbrecht would be to repeat Garbrecht's crystallization procedure. (Bristol Ex. 45 at 121-123.) Bristol appealed, and the Board of Appeals affirmed the rejection.

On March 16, 1982, Bristol filed another application claiming the crystalline cefadroxil monohydrate. It was in connection with this application that Dr. Micetich filed two declarations, one dated October 13, 1982, and one dated June 29, 1984. (Bristol Ex. 45 at 133-144.)

Respondents allege that Bristol's representations to the PTO relating to Dr. Micetich's two declarations and Bristol's failure to ask Dr. Micetich to make the third experiment in the protocol for the second group of experiments amounted to inequitable conduct.

1. In 1982 Bristol asked Dr. Micetich to make some experiments following Garbrecht Example 7 to determine whether the new monohydrate could be produced by using Example 7. On August 3, 1982, Dr. Micetich reported to Dr. Carnahan of Bristol that he had made five experiments attempting to follow Garbrecht Example 7. Dr. Micetich reported that the removal of the t-BOC group was "at best incomplete." (Biocraft/Gema Ex. 91.)

In reporting the results of Dr. Micetich's experiments to the patent examiner, Bristol failed to disclose that Dr. Micetich had removed part of the t-BOC group. In the first declaration of Dr. Micetich dated August 31, 1982, filed with the PTO (Bristol-Myers Ex. 45, '657 prosection history, at 92), he stated only that by repeating Garbrecht Example 7, he was unable to produce the monohydrate of what is now the '657 patent.

Bristol should have told the examiner that the removal of the t-BOC group was incomplete, not that it had failed. It would have been important for the patent examiner to know that a small amount of hydrochloric acid had removed part of the t-BOC group. Nevertheless, respondents fell short of proving that Bristol intended to mislead the patent examiner. After reading the first declaration of Dr. Micetich, the examiner rejected the application anyway. (Id. at 93.)

2. After this rejection of the claim over Garbrecht again, Bristol drafted a protocol proposing four experiments that could be made to determine whether the new monohydrate could have been made using the teaching of the Garbrecht patent and ordinary skill in the art. The third experiment described in the protocol would have added more hydrochloric

acid to the treatment of Example 1. The tests were discussed with the patent examiner on October 4, 1983.

In his report after he had discussed the proposed experiments with Bristol, the patent examiner stated:

> "In addition, if Zn/HCl is known to be able to remove t-BOC, then choice C is also a reasonable option." (Bristol Ex. 45 at 117.)

The examiner was an experienced chemist, he was capable of interpreting the Garbrecht patent for himself, and he could have done his own research on what the literature in the prior art taught about removing t-BOC with zinc and hydrochloric acid. Bristol scientists were aware that hydrochloric acid could be used to remove t-BOC. (See Tr. 301, 383-385). The Garbrecht patent itself taught that hydrochloric acid could be used to remove the t-BOC group. Other literature in the prior art taught the use of additional hydrochloric acid to remove the t-BOC group, (Biocraft/Gema Exs. 72 and 73).

Yet the examiner did not ask that the third test be made to see if both blocking groups could be removed in one step. It is not clear what happened at the conference between Bristol and the examiner on the subject of the proposed experiments. It is hard to believe that the patent examiner would have left it up to Bristol to decide whether to make the third test, but apparently he did. When the examiner reviewed the results of the first two experiments, he did not ask why the third test had not been made.

When the protocol was drafted, Bristol must have intended to try the third experiment, but Bristol did not ask Dr. Micetich to make it. Bristol's own chemists did not make this test (TEO Tr. 706) until Professor

Baldwin made it while preparing for trial in this case. When Professor Baldwin later used the amount of hydrochloric acid suggested in the third experiment in this protocol, he did not get complete cleavage of the t-BOC, but only about 10% cleavage. (Tr. 405-406.) It is reasonable to assume that one with skill in the art, knowing that a 10% cleavage had been achieved, would have tried adding more hydrochloric acid to get complete cleavage if he wanted to get rid of both protecting groups.

In his second declaration to the PTO dated June 29, 1984, (Id. at 133-144), Dr. Micetich indicated that with specified modifications to the examples of the Garbrecht patent, he was unable to produce the monohydrate of the '657 patent. He described the two tests that he had made. Dr. Micetich had not used enough hydrochloric acid to remove both protecting groups. Dr. Micetich knew that both protective groups had to be removed to get a cephalosporin, but he thought that he was supposed to do no more than repeat Garbrecht Example 7. (Biocraft/Gema Ex. 33 at 37.) He therefore used only the concentration of acid called for by Garbrecht Example 1. (Biocraft/Gema Ex. 33 at 71.)

Bristol argues that the first two tests made by Dr. Micetich already had produced a crystalline cefadroxil that was not the Bouzard monohydrate, so that there was no incentive to go on to the third test. (Kalipharma Ex. 33; TEO Tr. 1167-1170.) But the examiner was not told that there had been partial cleavage of the second blocking group even with the small amount of hydrochloric acid that Dr. Micetich had used. If the examiner had known this fact, it might have persuaded him to ask that the third test be made.

One with ordinary skill in the art (acting without instructions from Bristol) who was trying to make Example 7 work would have tried to use more

hydrochloric acid to remove the t-BOC group, after he found that literally following Garbrecht Example 7 would not remove the second blocking group completely.

Even if the amount of hydrochloric acid specified in the third test had been added to Example 1, it would not have resulted in complete cleavage of the t-BOC, (Tr. 405-6), but it would have given enough information to the chemist about partial cleavage to encourage him to add more hydrochloric acid.

There was no clear and convincing evidence of an intent to mislead. Bristol simply did not try very hard to make the Bouzard monohydrate following the teachings of Garbrecht. What happened was perhaps a predictable consequence of the ex parte conduct of patent prosecutions. One cannot expect a patent applicant to be enthusiastic about proving that his claimed invention can be found in the prior art.

If the '657 patent were found to be valid and infringed, the patent would be enforceable.

COMPLAINANT'S DUTY OF CANDOR AND VERIFICATION

Respondents charge that Bristol-Myers in its complaint and supplemental complaint misrepresented to the Commission the status of foreign counterparts to the '657 patent. Complainant failed to disclose that the South Korean equivalent of the '657 patent was found to be invalid on October 26, 1987.

Under Interim Rules 210.20(a)(1) and 210.5(b) the complainant had a duty of verification. In Certain Indomethacin, Inv. No. 337-TA-183, the Commission indicated that it was essential the someone investigate the allegations and stand behind the merits of the complaint. In this case,

someone did try to verify the facts on which the complaint was based, but the information about the South Korean patent being invalid had not yet been entered into the computer base on which the attorneys preparing the complaint had relied. (Tr. 1094-1095) There was no evidence of any intent to misrepresent any facts.

The Commission has held that there is a duty of candor on the part of a complainant, because the Commission acts upon the proposed complaints before any responses have been filed. In the present case, a mistake was made, but there was no evidence that it was intentional. If one considers materiality as well as intent, the information that the South Korean patent had been found to be invalid was certainly relevant to the issues in this case, but it is unlikely that the Commission would have declined to initiate an investigation of the possible infringement of a U.S. patent owned by a U.S. corporation solely on the grounds that a corresponding foreign patent had been found to be invalid in a foreign country. It is more likely that if the Commission had known about the South Korean patent, it would have wanted a full investigation in this country of the validity of the U.S. patent.

Complainant met its duty of verification and candor to the Commission.

THE DOMESTIC INDUSTRY

Respondents do not contest the fact that Bristol-Myers has a domestic industry engaged in the manufacture and sale in the United States of cefadroxil monohydrate that falls within claim 1 of the '657 patent.

Bristol practices the patent in its DURICEF and ULTRACEF products. Both products fall within the X-ray diffraction pattern claimed in the '657 patent. (TEO Tr. 922, 948, 961, Kali. Exs. 3, 58.)

Bristol imports the bulk form of cefadroxil from its subsidiary in Italy, and packages it in dosage amounts in Puerto Rico. (TEO Tr. 109.) The plant in Puerto Rico processes the product and performs quality control tests. Bristol has a substantial investment in engineering and research related to crystalline cefadroxil monohydrate. (TEO Tr. 51-52, 105.) Research and development for crystalline cefadroxil monohydrate is done only in the United States. (TEO Tr. 108.)

Bristol-Myers has a domestic industry engaged in the manufacture and sale in the United States of cefadroxil monohydrate that falls within claim 1 of the '657 patent.

CONCLUSIONS

Respondents failed to prove that the applicant for the '657 patent engaged in inequitable conduct at the U.S. Patent and Trademark Office, or that complainant failed to meet its duty of candor and verification at the Commission. Complainant proved that each respondent either exported to the United States or imported into the United States a cefadroxil product that would infringe claim 1 of the '657 patent if that patent were found to be valid. Complainant proved that it had a domestic industry that practiced the patent.

Respondents failed to prove that the '657 patent is anticipated under Section 102 of the Patent Act.

Respondents have offered clear and convincing evidence that the '657 patent is invalid under Section 103 of the Patent Act, overcoming the presumption of patent validity. Complainant therefore has failed to prove that Section 337 has been violated.

The evidentiary record in this proceeding consists of all exhibits identified in the following exhibit lists:

Bristol-Myers Ex. #294,
Biocraft/Gema Ex. #188 (documentary exhibits)
(except Exs. 83, 87, 121, 124, 125),
Biocraft/Gema Ex. #153 (physical exhibits),
Kalipharma Ex. #52,
Staff Ex. #1 and

Kalipharma Exs. 227, 228 and 229 which were admitted by Order No. 43.

The evidentiary record, which also includes the transcript of the testimony at the hearing, is hereby certified to the Commission.1/ The pleadings record also includes all papers and requests properly filed with the Secretary in this proceeding.

Janet D. Saxon

Janet D. Saxon
Chief Administrative Law Judge

Issued: December 15, 1989

1/ Pursuant to 19 C.F.R. § 210.53(h), this initial determination shall become the determination of the Commission unless a party files a petition for review of the initial determination pursuant to § 210.54, or the Commission pursuant to § 210.55 orders on its own a review of the initial determination or certain issues therein. For computation of time in which to file a petition for review, refer to §§ 210.54, 201.14, and 201.16(d).

CERTAIN CRYSTALLINE CEFADROXIL MONOHYDRATE PRODUCTS Inv. No. 337-TA-293

CERTIFICATE OF SERVICE

I, Kenneth R. Mason, hereby certify that the attached Public Version Initial Determination was served by hand upon George C. Summerfield, Esq., and upon the following parties via first class mail, and air mail where necessary, on December 20, 1989.

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