CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

DATE OF MEETING: 12/11/97

CENTER FOR DRUG EVALUATION AND RESEARCH

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DATE OF MEETING: 12/11/97

SLIDES (BRIEFING PACKAGE)

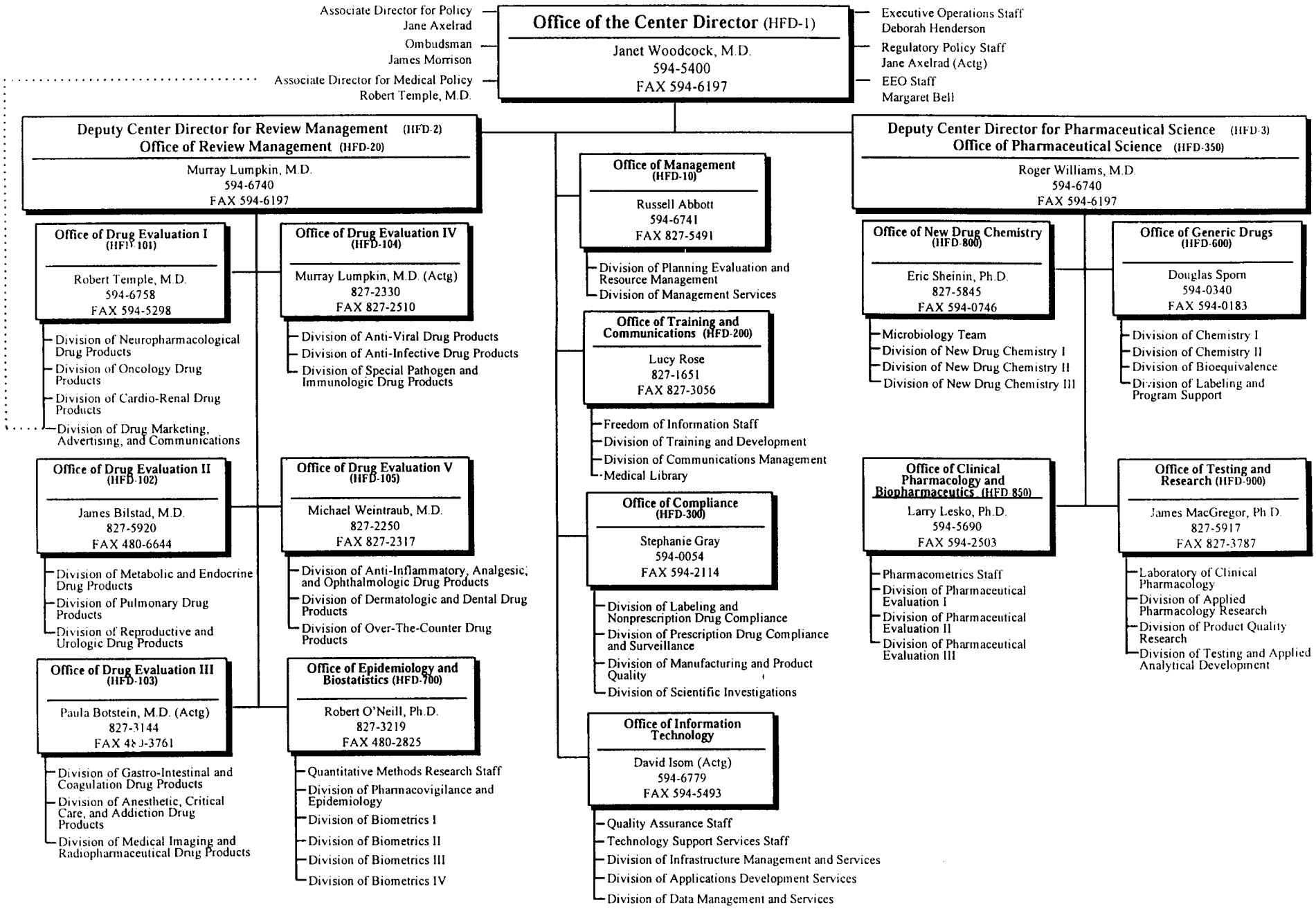
Advisory Committee for Pharmaceutical Science
Quality Hotel
Colesville Road, Silver Spring
December 11, 1997

Overview and Objectives

ROGER L. WILLIAMS, M.D.
DEPUTY CENTER DIRECTOR FOR PHARMACEUTICAL SCIENCE
CENTER FOR DRUG EVALUATION AND RESEARCH
FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

AS OF 10/29/97



Deputy Center Director for Pharmaceutical Science

Coordinating Committees

2. Pharmacology/Toxicology
3. Chemistry, Manufacturing, Controls
4. Biopharmaceutics
5. Compliance
6. Project Management
7. Information Technology
8. Research
9. Administrative Management
10. International Affairs
11. Reviewer Affairs

= Biopharmaceutics
= Clinical Pharmacology
= Development and Testing
= Pharm/Tox
= CMC

International Activities Coordinating Committee

1. ICH
2. Bilateral: EU/EC and US/FDA
3. Trilateral: Canada/HPB and US/FDA
4. WHO
5. Foreign Visitors

Office of Pharmaceutical Science
Director
Deputy Director

- Compendial Operations Staff
- Training Staff
- Quality Assurance
- Quality Implementation Staff
- Operations Staff
  - Info Tech
  - Admin Staff
  - Eval Staff

Office of Testing and Research

- Regulatory Research and Analysis Staff
- Division of Product Quality Research
- Laboratory of Clinical Pharmacology
- Division of Testing and Applied Analytical Development
- Division of Applied Pharmacology Research

Office of New Drug Chemistry

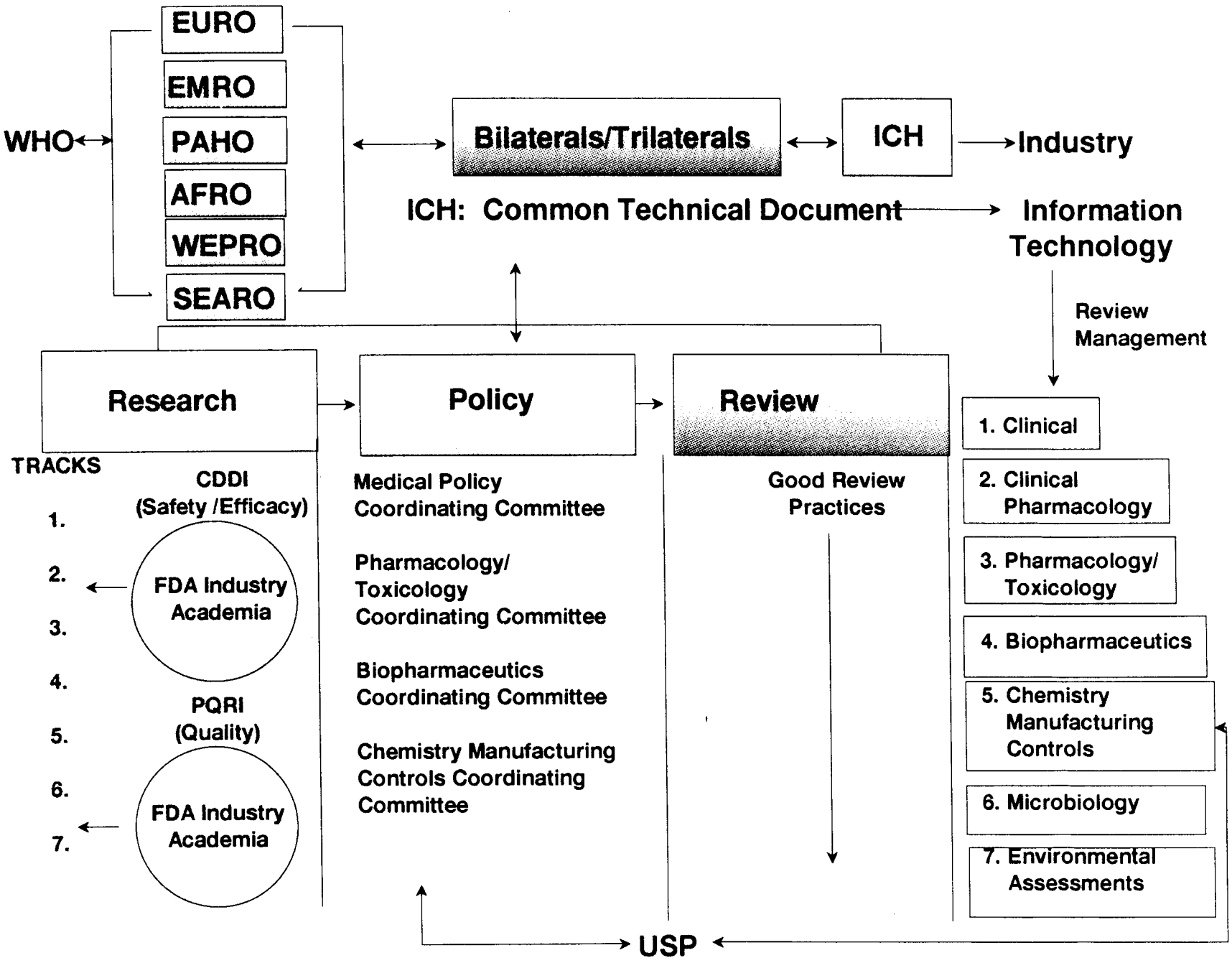
- EA
- Microbiology Staff
- ODE I — Division of Chemistry 1: Neuropharm; Cardio-Renal; Oncology
- ODE II — Division of Chemistry 2: Metabolic/Endocrine; Pulmonary; Reproductive and Urologic
- ODE III — GI and Coagulation; Imaging/Radiopharm; Anest/Critical Care/Addiction
- ODE IV — Division of Chemistry 3: Anti-Infective; Anti-Viral
- ODE V — Derm/Dental; Anti-Inflam/Anal/ Ophthal; OTC

Office of Generic Drugs

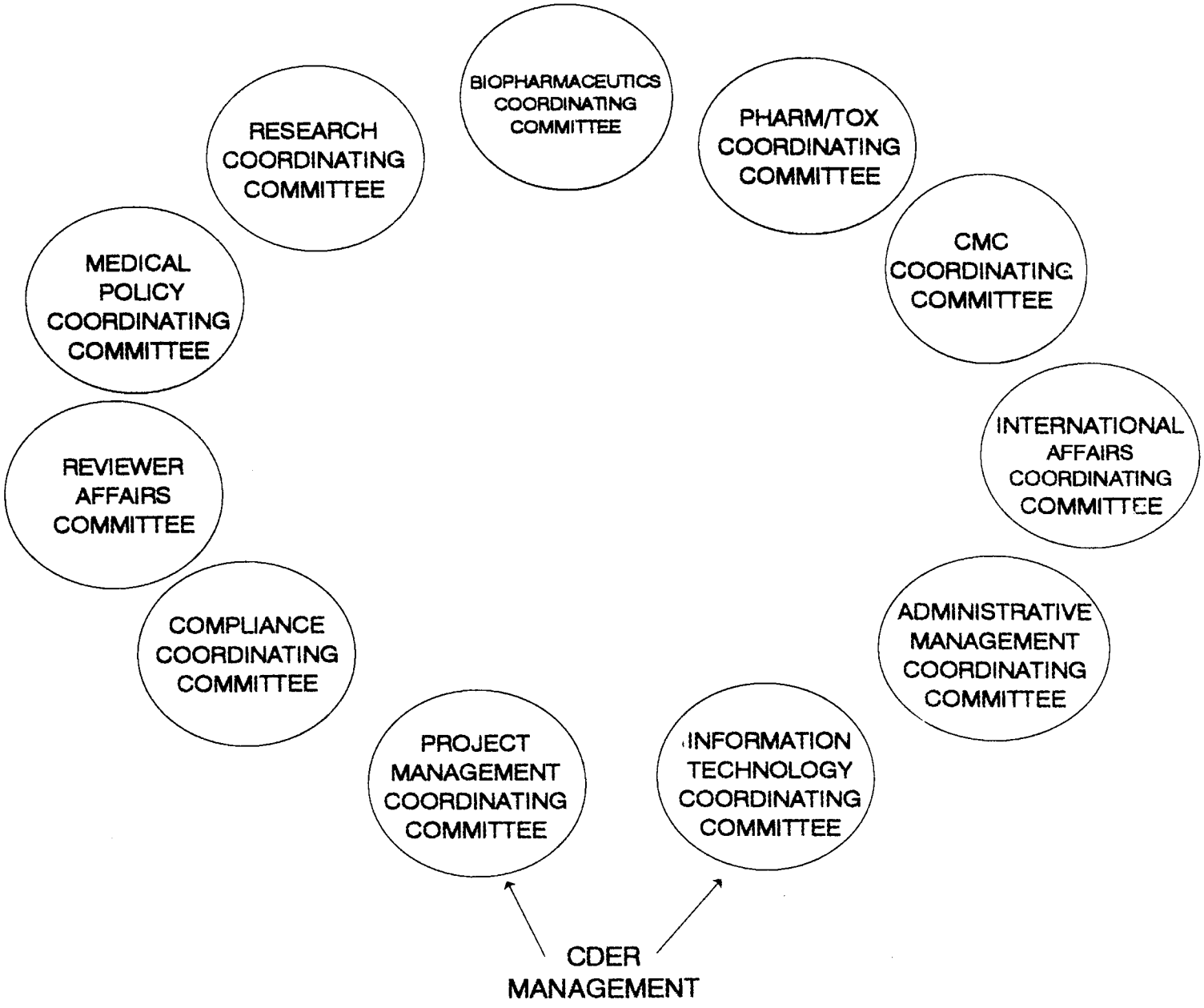
- Division of Chemistry 1
- Division of Chemistry 2
- Division of Bioequivalence
- Division of Labeling & Program Support

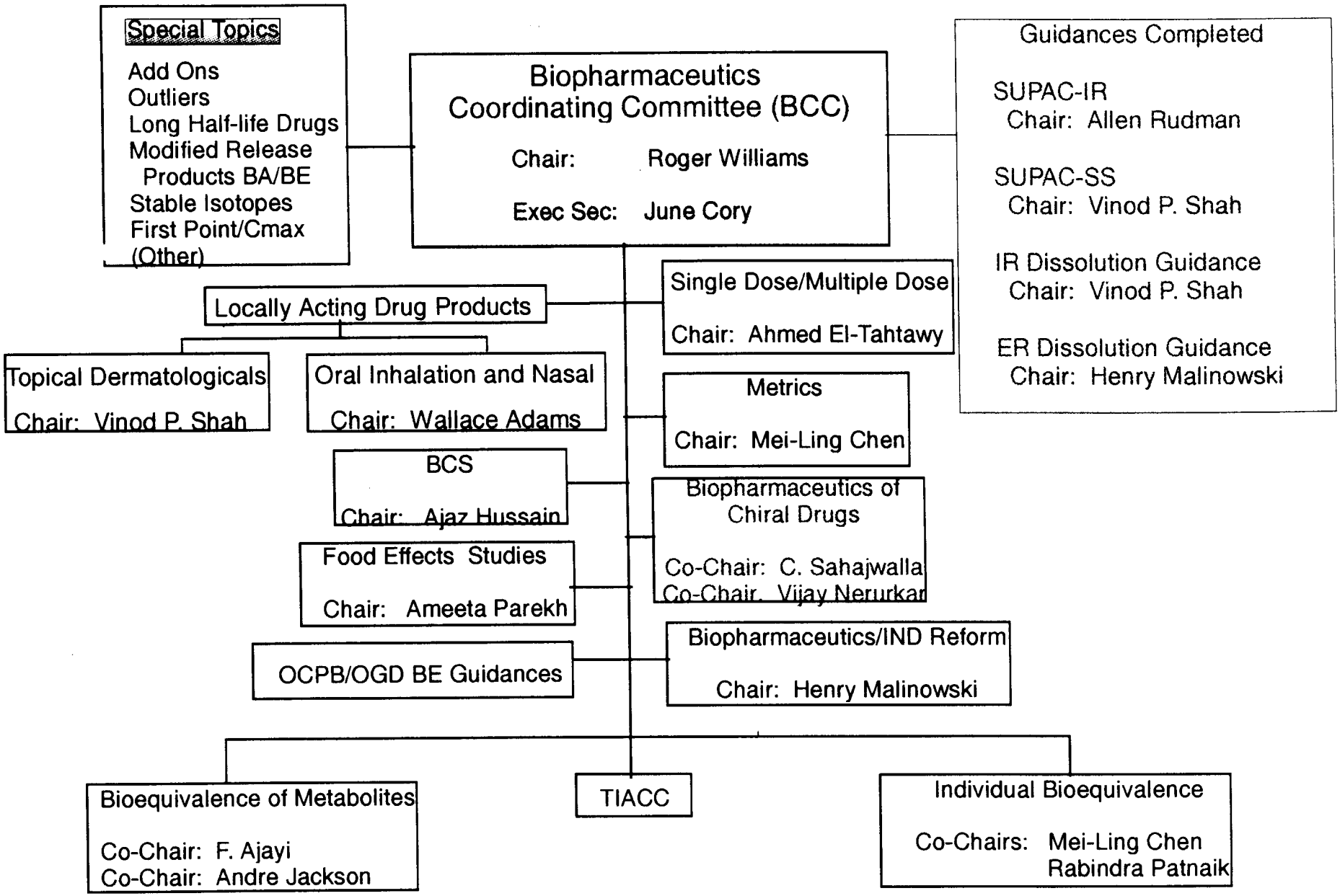
Office of Clinical Pharmacology and Biopharmaceutics

- Pharmacometrics Staff
- ODE I — Division of Pharmaceutical Evaluation 1: Neuropharm; Cardio-Renal; Oncology
- ODE II — Division of Pharmaceutical Evaluation 2: Metabolic/Endocrine; Pulmonary; Reproductive and Urologic
- ODE III — GI and Coagulation; Imaging/Radiopharm; Anest/Critical Care/Addiction
- ODE IV — Division of Pharmaceutical Evaluation 3: Anti-Infective; Anti-Viral
- ODE V — Derm/Dental; Anti-Inflam/Anal/ Ophthal; OTC


EURO
EMRO
PAHO
AFRO
WEPRO
SEARO
WHO
Bilaterals/Trilaterals
ICH
Industry
ICH: Common Technical Document
Information Technology
Review Management
Research
Policy
Review
TRACKS
CDDI (Safety /Efficacy)
1.
2.
3.
4.
PQRI (Quality)
5.
6.
7.
FDA Industry Academia
FDA Industry Academia
Medical Policy Coordinating Committee
Pharmacology/ Toxicology Coordinating Committee
Biopharmaceutics Coordinating Committee
Chemistry Manufacturing Controls Coordinating Committee
Good Review Practices
1. Clinical
2. Clinical Pharmacology
3. Pharmacology/ Toxicology
4. Biopharmaceutics
5. Chemistry Manufacturing Controls
6. Microbiology
7. Environmental Assessments
USP

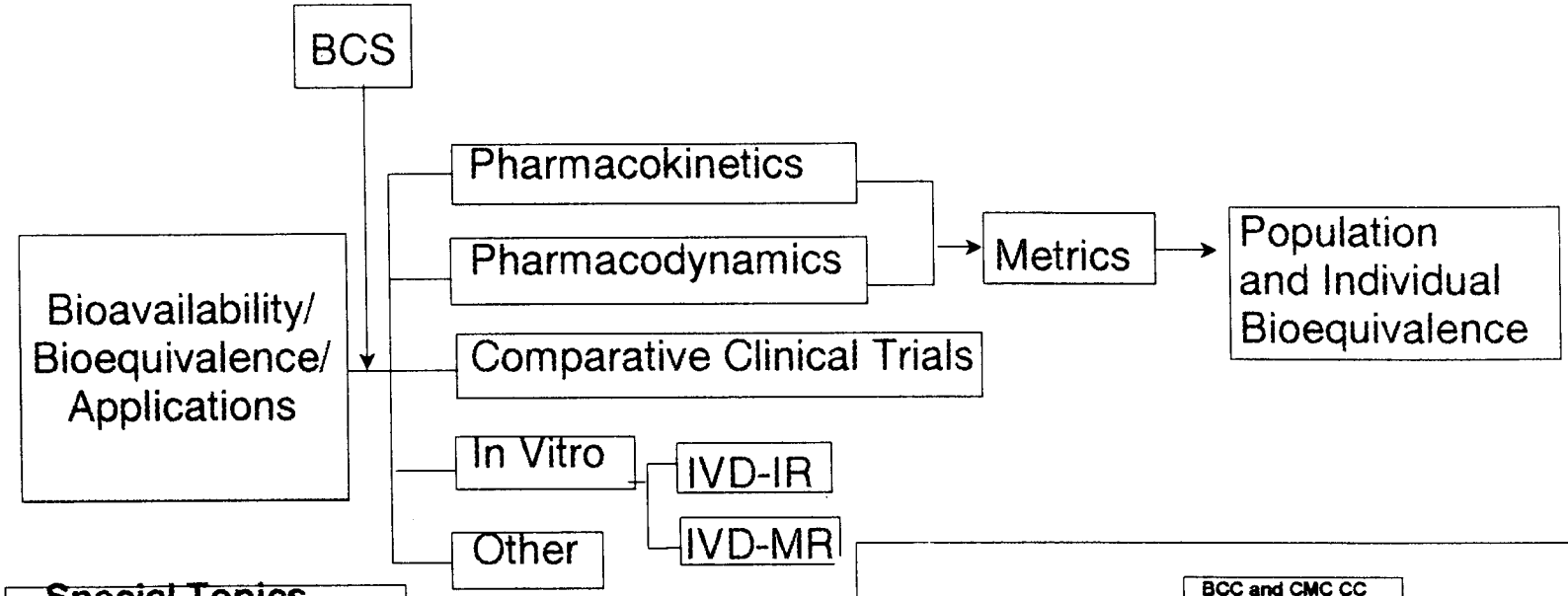
CDER COORDINATING COMMITTEES




Special Topics
Add Ons
Outliers
Long Half-life Drugs
Modified Release Products BA/BE
Stable Isotopes
First Point/Cmax
(Other)
Biopharmaceutics Coordinating Committee (BCC)
Chair: Roger Williams
Exec Sec: June Cory
Guidances Completed
SUPAC-IR
Chair: Allen Rudman
SUPAC-SS
Chair: Vinod P. Shah
IR Dissolution Guidance
Chair: Vinod P. Shah
ER Dissolution Guidance
Chair: Henry Malinowski
Locally Acting Drug Products
Topical Dermatologicals
Chair: Vinod P. Shah
Oral Inhalation and Nasal
Chair: Wallace Adams
Single Dose/Multiple Dose
Chair: Ahmed El-Tahtawy
Metrics
Chair: Mei-Ling Chen
BCS
Chair: Ajaz Hussain
Biopharmaceutics of Chiral Drugs
Co-Chair: C. Sahajwalla
Co-Chair: Vijay Nerurkar
Food Effects Studies
Chair: Ameeta Parekh
OCPB/OGD BE Guidances
Biopharmaceutics/IND Reform
Chair: Henry Malinowski
Bioequivalence of Metabolites
Co-Chair: F. Ajayi
Co-Chair: Andre Jackson
TIACC
Individual Bioequivalence
Co-Chairs: Mei-Ling Chen
Rabindra Patnaik

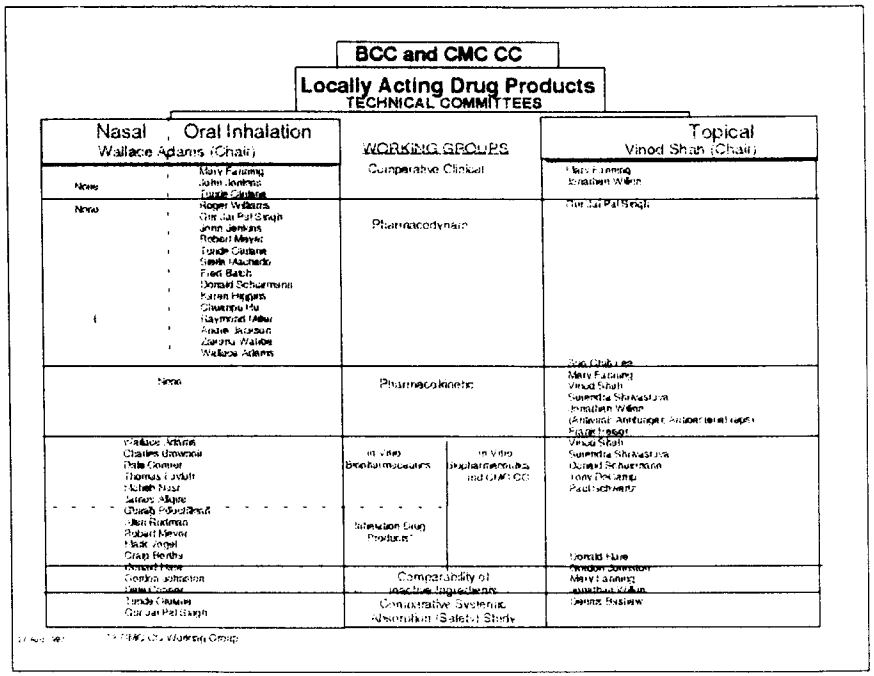
7/7/97

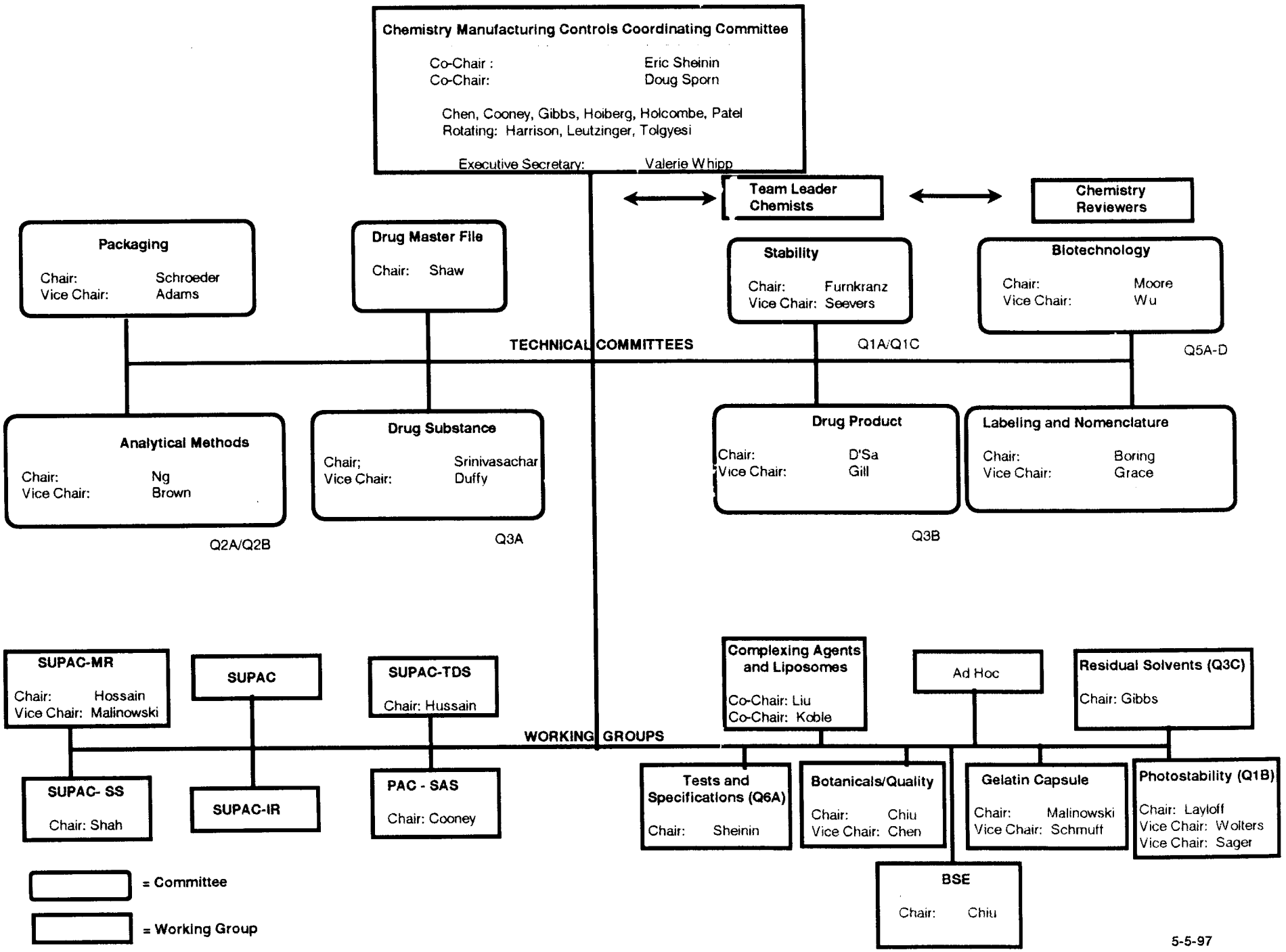
Biopharmaceutics Guidance Topics



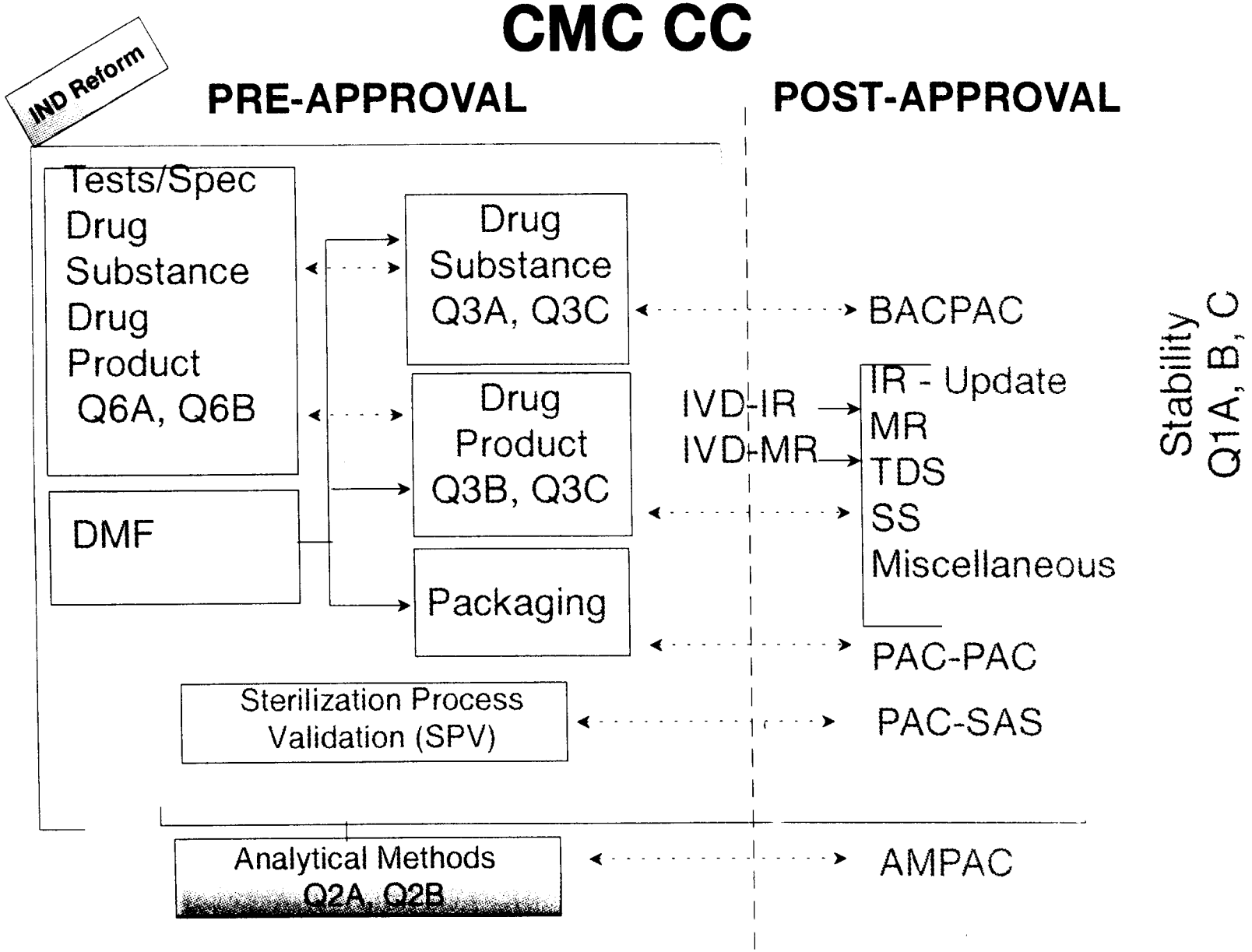
Special Topics

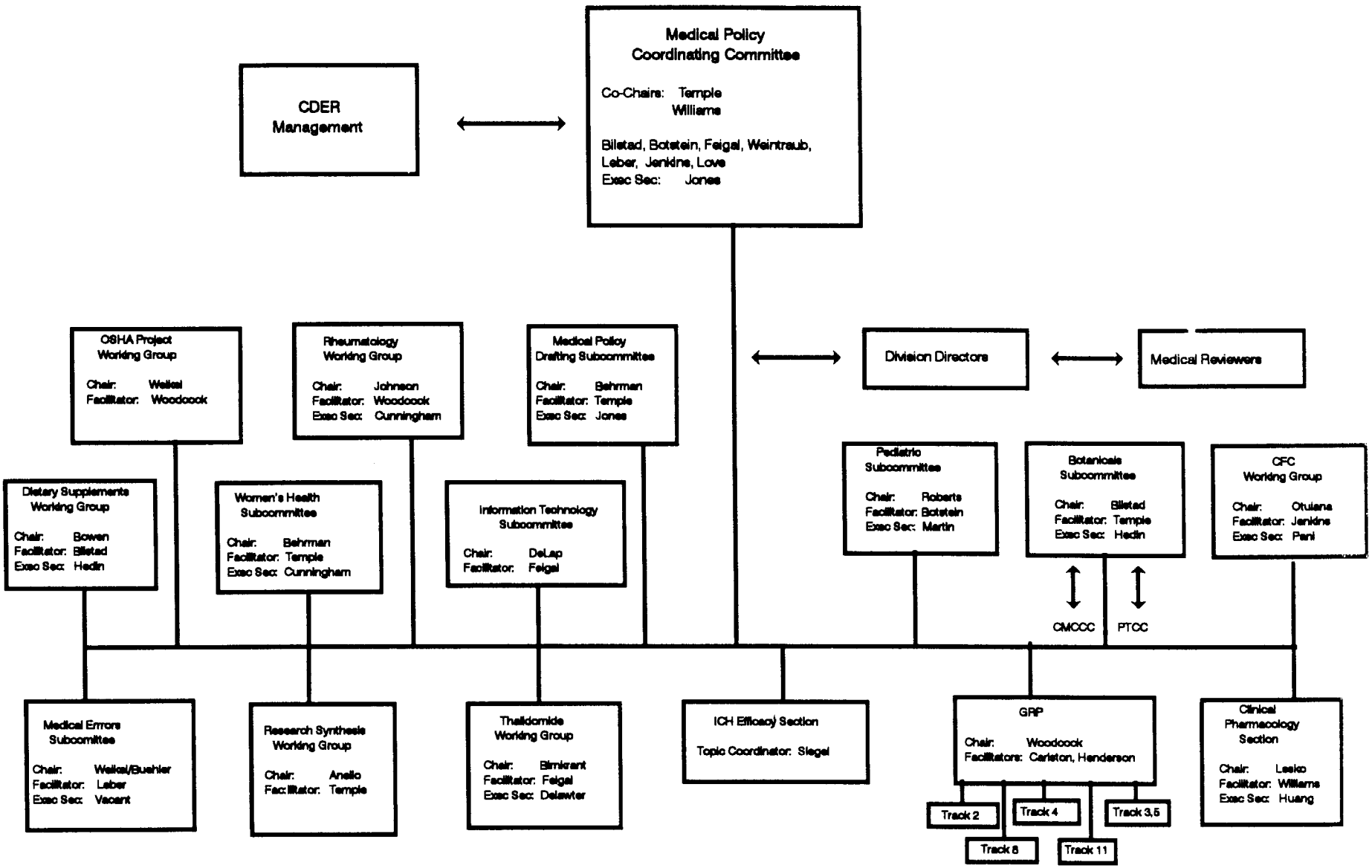
Add Ons
Outliers
Long Half-life Drugs
Modified Release Products BA/BE
Stable Isotopes
First Point/Cmax
Metabolite



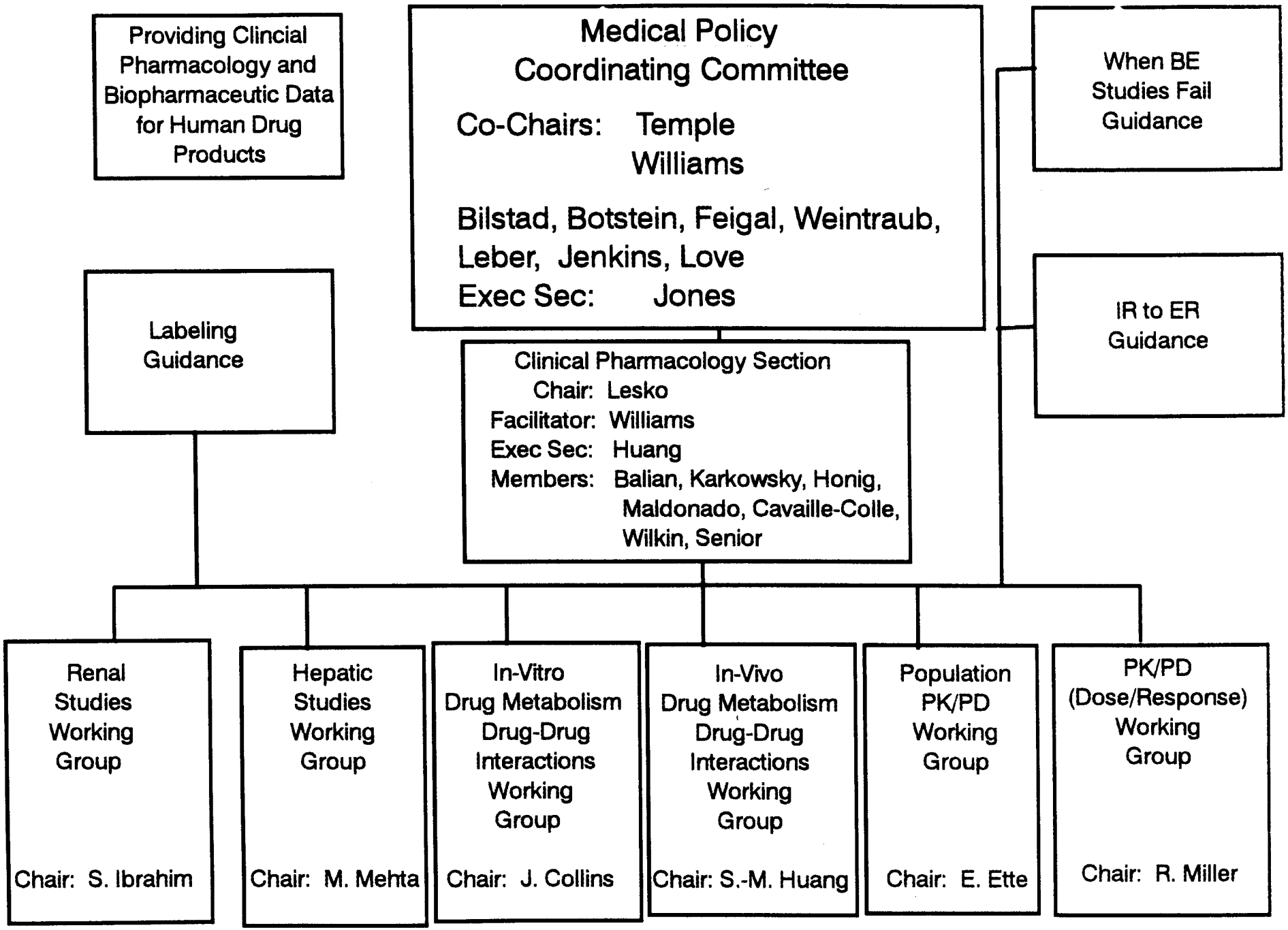

Chemistry Manufacturing Controls Coordinating Committee
Co-Chair : Eric Sheinin
Co-Chair: Doug Sporn
Chen, Cooney, Gibbs, Hoiberg, Holcombe, Patel
Rotating: Harrison, Leutzinger, Tolgyesi
Executive Secretary: Valerie Whipp
Team Leader Chemists
Chemistry Reviewers
Packaging
Chair: Schroeder
Vice Chair: Adams
Drug Master File
Chair: Shaw
Stability
Chair: Furnkranz
Vice Chair: Seevers
Biotechnology
Chair: Moore
Vice Chair: Wu
TECHNICAL COMMITTEES
Q1A/Q1C
Q5A-D
Analytical Methods
Chair: Ng
Vice Chair: Brown
Q2A/Q2B
Drug Substance
Chair; Srinivasachar
Vice Chair: Duffy
Q3A
Drug Product
Chair: D'Sa
Vice Chair: Gill
Q3B
Labeling and Nomenclature
Chair: Boring
Vice Chair: Grace
SUPAC-MR
Chair: Hossain
Vice Chair: Malinowski
SUPAC
SUPAC-TDS
Chair: Hussain
Complexing Agents and Liposomes
Co-Chair: Liu
Co-Chair: Koble
Ad Hoc
Residual Solvents (Q3C)
Chair: Gibbs
WORKING GROUPS
SUPAC- SS
Chair: Shah
SUPAC-IR
PAC - SAS
Chair: Cooney
Tests and Specifications (Q6A)
Chair: Sheinin
Botanicals/Quality
Chair: Chiu
Vice Chair: Chen
Gelatin Capsule
Chair: Malinowski
Vice Chair: Schmuff
Photostability (Q1B)
Chair: Layloff
Vice Chair: Wolters
Vice Chair: Sager
BSE
Chair: Chiu
= Committee
= Working Group
5-5-97

CMC CC


IND Reform
PRE-APPROVAL
POST-APPROVAL
Tests/Spec
Drug
Substance
Drug
Product
Q6A, Q6B
DMF
Drug
Substance
Q3A, Q3C
Drug
Product
Q3B, Q3C
Packaging
Sterilization Process
Validation (SPV)
Analytical Methods
Q2A, Q2B
BACPAC
IVD-IR
IVD-MR
IR - Update
MR
TDS
SS
Miscellaneous
PAC-PAC
PAC-SAS
AMPAC
Stability
Q1A, B, C


CDER Management
Medical Policy Coordinating Committee
Co-Chairs: Temple, Williams
Bilstad, Botstein, Feigal, Weintraub, Leber, Jenkins, Love
Exec Sec: Jones
OSHA Project Working Group
Chair: Weiss
Facilitator: Woodcock
Rheumatology Working Group
Chair: Johnson
Facilitator: Woodcock
Exec Sec: Cunningham
Medical Policy Drafting Subcommittee
Chair: Behrman
Facilitator: Temple
Exec Sec: Jones
Division Directors
Medical Reviewers
Dietary Supplements Working Group
Chair: Bowen
Facilitator: Bilstad
Exec Sec: Hedin
Women's Health Subcommittee
Chair: Behrman
Facilitator: Temple
Exec Sec: Cunningham
Information Technology Subcommittee
Chair: DeLap
Facilitator: Feigal
Pediatric Subcommittee
Chair: Roberts
Facilitator: Botstein
Exec Sec: Martin
Botanicals Subcommittee
Chair: Bilstad
Facilitator: Temple
Exec Sec: Hedin
CFC Working Group
Chair: Otuiana
Facilitator: Jenkins
Exec Sec: Pani
CMCCC
PTCC
Medical Errors Subcommittee
Chair: Weiss/Buehler
Facilitator: Leber
Exec Sec: Vacant
Research Synthesis Working Group
Chair: Anello
Facilitator: Temple
Thalidomide Working Group
Chair: Bimkrant
Facilitator: Feigal
Exec Sec: Delawter
ICH Efficacy Section
Topic Coordinator: Siegel
GRP
Chair: Woodcock
Facilitators: Carlston, Henderson
Track 2
Track 4
Track 3,5
Track 8
Track 11
Clinical Pharmacology Section
Chair: Lesko
Facilitator: Williams
Exec Sec: Huang

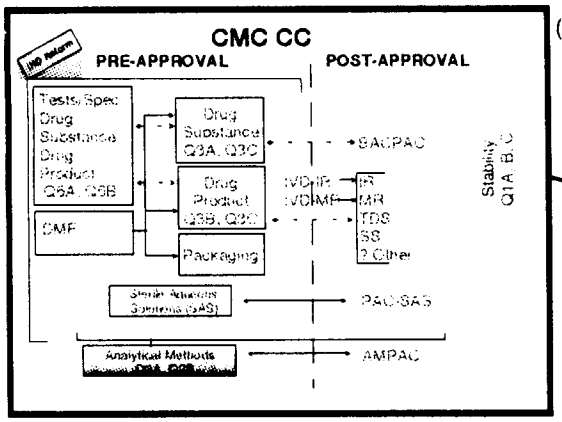
4-29-97


Providing Clincial Pharmacology and Biopharmaceutic Data for Human Drug Products
Medical Policy Coordinating Committee
Co-Chairs: Temple
Williams
Bilstad, Botstein, Feigal, Weintraub, Leber, Jenkins, Love
Exec Sec: Jones
When BE Studies Fail Guidance
IR to ER Guidance
Labeling Guidance
Clinical Pharmacology Section
Chair: Lesko
Facilitator: Williams
Exec Sec: Huang
Members: Balian, Karkowsky, Honig, Maldonado, Cavaille-Colle, Wilkin, Senior
Renal Studies Working Group
Chair: S. Ibrahim
Hepatic Studies Working Group
Chair: M. Mehta
In-Vitro Drug Metabolism Drug-Drug Interactions Working Group
Chair: J. Collins
In-Vivo Drug Metabolism Drug-Drug Interactions Working Group
Chair: S.-M. Huang
Population PK/PD Working Group
Chair: E. Ette
PK/PD (Dose/Response) Working Group
Chair: R. Miller

5/3/97

OPS GUIDANCE PROCESS

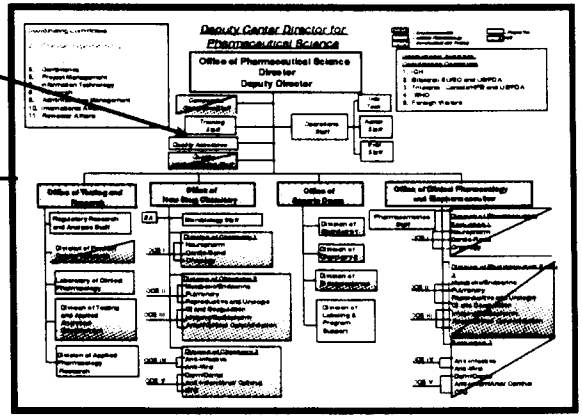
Guidances



(Clinical Pharmacology Section/MPCC)

(2 Years)

Training
Implementation
Management



(1 Year)

Updating

(1 Year)

Lessons Learned

(3 Years)

CDDI

PQRI

ATTERS TO BE CONSIDERED:

1. Approval of the minutes of the February 10, 1997, Board member meeting.
2. Thrift Savings Plan activity report by the Executive Director.
3. Briefings by National Finance Center and Board staff on:
   a. National Finance Center;
   b. Thrift Savings Plan system replacement effort;
   c. Thrift Savings Plan improvements;
   d. Capability maturity model;
   e. Software methodology;
   f. Project tracking and controls;
   g. Service Office enhancements;
   h. Local area network; and
   i. Thrift Savings Plan costs.

CONTACT PERSON FOR MORE INFORMATION: Tom Trabucco, Director, Office of External Affairs (202) 942–1640.

Dated: February 24, 1997.

Roger W. Mehle,

Executive Director, Federal Retirement Thrift Investment Board.

[FR Doc. 97–5013 Filed 2–25–97; 11:37 am]

BILLING CODE 6760–01–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 95P–0110]

The Food and Drug Administration's Development, Issuance, and Use of Guidance Documents

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is publishing a document entitled "Good Guidance Practices" (GGP's), which sets forth the agency's policies and procedures for the development, issuance, and use of guidance documents. Issues relating to FDA's development and issuance of guidance documents were raised in a citizen petition submitted by the Indiana Medical Devices Manufacturers Council, Inc. (IMDMC) (see Docket No. 95P–0110). In an effort to improve its guidance document procedures, FDA has adopted the GGP's described and included in this notice.

DATES: Although the agency already has begun to follow the procedures set forth in the GGP's, the GGP's will not be fully implemented until FDA's proposal to amend its regulations in part 10 (21 CFR part 10) to clarify that advisory opinions and guidelines do not bind the agency (57 FR 47314, October 15, 1992) is finalized and in effect.

FOR FURTHER INFORMATION CONTACT: Margaret M. Dotzel, Office of Policy (HF–22), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–3360.

SUPPLEMENTARY INFORMATION: The IMDMC petition requested that FDA control the initiation, development, and issuance of guidance documents by written procedures that assure the appropriate level of meaningful public participation. In response to the petition, FDA agreed to take steps to improve the agency's guidance document procedures. In the Federal Register of March 7, 1996 (61 FR 9181), FDA published a notice, which set forth its proposal on how best to improve its guidance document procedures and solicited comment on these and additional ideas for improvement (the March 7 Notice). On April 26, 1996, the agency held a public meeting to further discuss these issues (the April 26 public meeting). The comment period for the March 7 Notice closed on June 5, 1996. This notice: (1) Sets forth the agency's position on how it will proceed in the future with respect to guidance document development, issuance, and use; and (2) includes the agency's GGP's, which set forth the agency's policies and procedures for developing, issuing, and using guidance documents.

I. Definition of Guidance

In the March 7 Notice, FDA provided the following definition for guidance documents:

> [T]he term "guidance documents" means: (1) Documents prepared for FDA review staff and applicants/sponsors relating to the processing, content, and evaluation/approval of applications and relating to the design, production, manufacturing, and testing of regulated products; and (2) documents prepared for FDA personnel and/or the public that establish policies intended to achieve consistency in the agency's regulatory approach and establish inspection and enforcement procedures. Guidance documents do not include agency reports, general information provided to consumers, documents relating to solely internal FDA procedures, speeches, journal articles and editorials, media interviews, warning letters, or other communications or actions taken by individuals at FDA or directed to individual persons or firms.

A number of the comments submitted in response to the March 7 Notice suggested alternative definitions for "guidance document." One comment suggested that the term include all internal documents intended to direct activities of FDA staff. Another suggested that a guidance document be defined as any document or other communication that in effect announces a regulatory expectation to a broad audience. And yet another suggested that a guidance document be defined as any statement that may substantively impact a regulatory evaluation or determination.

Documents relating to internal procedures, warning letters, information directed at individuals or individual firms, and speeches, journal articles, editorials, media interviews, press materials, agency reports, and general information documents provided to consumers are not guidance documents. FDA disagrees with suggestions for a definition of guidance documents that would effectively broaden the scope of the term "guidance document" to include such documents. Definitions such as "any document that announces a regulatory expectation," "any statement that may substantively impact a regulatory evaluation or determination," or "any agency-issued writing that establishes methods of compliance" would include some or all of these excluded documents. A definition such as "all internal documents that direct activities of FDA staff" would include all documents relating to internal FDA procedures, even if they have no bearing on the regulated industry. Accordingly, FDA is rejecting these suggestions.

In the GGP document, attached to this notice, the agency is using the same basic definition as set forth in the March 7 Notice, with minor revisions to clarify what is and is not in the universe of guidance documents. It provides:

> The term "guidance documents" includes documents prepared for FDA staff, applicants/sponsors, and the public that (1) relate to the processing, content, and evaluation/approval of submissions; (2) relate to the design, production, manufacturing, and testing of regulated products; (3) describe the agency's policy and regulatory approach to an issue; or (4) establish inspection and enforcement policies and procedures. "Guidance documents" do not include documents relating to internal FDA procedures, agency reports, general information documents provided to consumers, speeches, journal articles and editorials, media interviews, press materials, warning letters, or other communications directed to individual persons or firms.

Despite the agency's reluctance to broaden the definition of guidance, the agency is sensitive to the concern expressed during the April 26 public meeting and in the comments that too narrow a definition might permit agency employees to use documents or communications such as speeches, editorials, or journal articles to announce regulatory expectations without following the GGP's discussed herein. Although FDA employees should be able to respond to questions about how an established policy applies

a specific situation or to questions out areas that lack established policy, the agency should not use these other means of communication to release guidance. The GGP's explicitly state that when the agency is first communicating new or different regulatory expectations not readily apparent from the applicable statute or regulations to a broad public audience, the GGP's and officially-designated guidance document procedures should be followed. As part of the agency's effort to monitor the use of guidance documents (see section III. of this document), the agency will spot check its staff to ensure that "unofficial" guidance documents or other means (such as speeches) are not being used to first transmit to a broad public audience new or different regulatory expectations that are not readily apparent from the applicable statute or regulations.

II. Nomenclature

In the March 7 Notice, FDA suggested that a standardized nomenclature for guidance might help the public better understand the nature and legal effect of guidance documents and might help to eliminate any confusion regarding which documents are guidance. Both the discussion at the April 26 public meeting and comments submitted to the docket indicated overwhelming support for a standardized nomenclature for guidance documents. Nevertheless, some comments cautioned the agency not to elevate form over substance. Moreover, there was no real consensus on what the standardized nomenclature should be.

Some comments suggested that the nomenclature be based on the intended use of the guidance, (e.g., compliance guidance versus 510(k) review guidance); others suggested that it be based on the intended user (e.g., guidance for industry versus guidance for reviewers). A number of comments suggested that FDA differentiate guidance documents on the basis of their type or function (e.g., educational, interpretive, and descriptive or premarket review, compliance/enforcement, and educational). Some comments even suggested that the distinction be drawn on the basis of what procedure is used to develop the guidance.

Specific suggestions included calling all guidance either "guidance documents" or "compliance policy guides" or calling all guidance either "guidelines" or "recommendations." A number of comments suggested using an umbrella term (such as guidance or guideline) together with additional identifying information, such as the Center producing the document, the intended users, and the industrial, regulatory, or professional activities to which the document applies.

After considering these comments and the universe of guidance documents, the agency has decided that all guidance documents should include the following: (1) The umbrella term "guidance;" (2) information that identifies the Center or Office producing the document; and (3) the regulatory activity to which the document applies and/or the intended users of the document. The agency anticipates that, in practice, the majority of guidance documents will be called "compliance guidance," "guidance for industry," or "guidance for FDA reviewers/staff." The agency believes that this approach incorporates a number of the suggestions made during the April 26 public meeting and in the comments and ensures that guidance document nomenclature is uniform and informative (i.e., by identifying the producing Center or Office and the regulatory activity to which and/or the persons to whom the document applies).

One comment suggested that, as an additional means of ensuring uniformity and clarity, FDA should use a consistent format with headed paper for all guidance documents. Given the diversity of guidance documents and the subjects that they address, the agency believes that it would be difficult to use a consistent format. The agency believes, however, that the benefit that might be achieved from a consistent format could be achieved, more easily, by using a standardized cover sheet for all guidance. Therefore, the GGP's include a standardized cover sheet that should be used as a model for all future guidance documents.

Existing Guidance. In response to the agency's request for comment on what to do with existing guidance documents if a standardized nomenclature is adopted, most comments suggested that FDA update the nomenclature as documents are revised. In the meantime, it was suggested that the agency create an interim method of cross-referencing the older documents with the new nomenclature. One comment suggested that the agency agree to undertake the review and revision of all existing guidance within some specified period of time. Specifically, the comment suggested a "managed review" approach pursuant to which the agency would set progressive goals, with a defined percentage of the documents to be reviewed for nomenclature changes within a specified period of time (e.g., 25 percent per year for 4 years).

FDA agrees with the majority of comments, which suggested that the best approach would be to update the nomenclature of existing guidance documents as they are revised. In the meantime, when the agency publishes its comprehensive list of guidance (see section V. of this document), it will list guidance documents under the issuing Center or Office and, where possible, will separate guidance documents by their intended users and/or the regulatory activities to which they apply.

The agency will not undertake a "managed review" of all existing guidance documents pursuant to which the agency would review a defined percentage of documents for nomenclature changes within a specified period of time. While the agency agrees that guidance documents should be reviewed and updated as appropriate, the agency does not agree that the expenditure of resources for what may be mere name changes is warranted, particularly when those resources could be applied more productively to the development of new guidance documents. Over the past year, the Centers and Offices have been taking stock of their guidance documents and have been identifying obsolete guidance documents as well as those needing updates or revisions. Moreover, as set forth in section IV. of this document, the agency is providing the public an opportunity to identify guidance documents that need to be reviewed/updated. Thus, the agency believes that it is taking steps to ensure that any necessary updates and revisions to guidance documents will be made.

III. Effect of Guidance Documents

The March 7 Notice described the legal effect of guidance documents. Specifically, it stated that a guidance document is not binding on the agency or the public; rather, it represents the agency's current thinking on a certain subject. Most of the participants at the April 26 public meeting and the comments to the March 7 Notice agreed that guidance documents should not be binding. There was significant support for including a statement of the nonbinding effect of guidance on each guidance document and for education (particularly of FDA employees) regarding the legal effect of guidance. A number of comments suggested that the agency monitor FDA employees to ensure that they are not applying guidance as binding.

Nonbinding effect of guidance. Although most comments agreed with the agency's position that guidance should not be binding on the public, a

umber did argue that FDA should be equired to follow its own guidance (i.e., should not be able to require more than is stated in guidance documents). One comment argued that FDA's position about the nonbinding nature of guidance is inconsistent with its own part 10 regulations.

The only binding requirements are those set forth in the statute and FDA's regulations. Under the Administrative Procedure Act (§ 10.40(d)), in order to bind the public, FDA must (with limited exceptions) follow the notice and comment rulemaking process. Moreover, the principle that guidance documents are binding on FDA is inconsistent with *Community Nutrition Institute* v. *Young*, 818 F.2d 943 (D.C. Cir. 1987), which calls into question FDA's procedures for issuing advisory opinions and guidelines that purport to bind the agency and thereby constrain the agency's discretion. In fact, consistent with the D.C. Circuit's decision in *CNI*, FDA proposed to revise its part 10 regulations to clarify that advisory opinions and guidelines do not bind the agency (57 FR 47314). The agency expects to publish that final rule shortly.[1] The GGP's will not be fully mplemented until that final rule is in effect.

Although guidance documents cannot legally bind FDA or the public, the agency recognizes the value of guidance documents in providing consistency and predictability. A company wants assurance that if it chooses to follow a guidance document, FDA generally will find it to be in compliance with the statute and regulations. Moreover, FDA issues guidance to its staff so that they will apply the statute and regulations in a consistent manner. With these principles in mind, FDA's decisionmakers will take steps to ensure that their staff do not deviate from guidance documents without appropriate justification and without first obtaining concurrence from a supervisor. This practice will provide assurance to companies that choose to follow a guidance, yet will not legally bind the agency or its decisionmakers to a guidance document.

The statement of nonbinding effect. In the March 7, 1996 Federal Register Notice, FDA proposed to include language such as the following in each guidance document:

Although this guidance document does not create or confer any rights for or on any person and does not operate to bind FDA or the public it does represent the agency's current thinking on * * *.

A number of comments suggested changes to the proposed statement. Some of the recommended changes reflect the comments' position that guidance is binding. Others apparently seek to clarify that approaches other than those set forth in the guidance are permitted if the applicable statutory or regulatory requirements are met. Finally, a number of the comments opined that the statement alone would not ensure the public a real opportunity to rely on alternate methods to comply with the statute and regulations.

As set forth above, FDA disagrees with the concept that guidance documents are binding. In response to the comments regarding flexibility in complying the statute and regulations, FDA is changing the statement to read:

This guidance document represents the agency's current thinking on * * *. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

In addition, as part of GGP's, the agency is providing an opportunity for discussion regarding alternate methods of complying with the applicable statute and regulations.

Absence of Mandatory Language. Because guidance documents are not binding, the GGP's provide that mandatory words such as "shall," "must," "require" and "requirement" should not be used unless they are being used to describe or discuss a statutory or regulatory requirement. The GGP's further provide that, prior to issuance, all new guidance documents should be reviewed to ensure that mandatory language has not been used.

Education. In the March 7 Notice, FDA recognized the importance of educating both agency employees and the public regarding the nonbinding nature of guidance. Comments to the March 7 Notice agreed that education is an important step in assuring that guidance is not applied as a binding requirement. The comments suggested that FDA's GGP's include a section that describes the legal effect of guidance.

As part of its GGP's, FDA will provide all current and new FDA employees involved in the development, issuance, or application of guidance documents a copy of the GGP's, which include a section that describes the legal effect of guidance. FDA will direct these employees to review the GGP's and will provide additional training that describes, in more detail, how to develop and use guidance documents.

For purposes of educating the public, the comments suggested education through mailings and public service announcements in trade journals and newsletters. FDA agrees that it is important to take advantage of opportunities to educate the public about the legal effect of guidance. The GGP's and the statement of the nonbinding effect of guidance that will be included in all future guidance documents and on the list of guidance documents (see section V. of this document) should help to educate the public about the legal effect of guidance. In addition, as part of the GGP's, FDA is encouraging its employees to state and explain the effect of guidance when speaking in public about guidance documents. The agency believes that public education efforts will be most effective if targeted to specific discussions of guidance documents.

Monitoring. A number of the participants at the April 26 public meeting and a number of the comments to the March 7 Notice suggested that FDA monitor and evaluate the agency's performance in not applying guidance as binding. The agency agrees that it is important to monitor the agency's use of guidance. Therefore, as a part of GGP's, the Centers and Offices will monitor the development and issuance of guidance documents to ensure that GGP's are being followed. In addition, they will spot-check the use of guidance documents to ensure that they are not being applied as binding requirements and the use of documents and communications that are not defined as guidance, such as warning letters and speeches, to ensure that they are not being used to initially express new regulatory expectations to a broad public audience.

Three years after the GGP's have been implemented, the agency will convene a working group to review whether they have improved the agency's development and use of guidance documents. The working group will determine whether the GGP's are ensuring: (1) Appropriate public participation in the development of guidance, (2) that guidance documents are readily available to the public, and (3) that guidance documents are not being applied as binding requirements. The working group will review the results of the Center and Office monitoring efforts as well as the number and results of appeals relating to guidance documents.

IV. Development/Public Input

In the March 7 Notice, FDA committed to implementing an agency-wide practice of soliciting or accepting

[1] One comment asked FDA to retain § 10.45(d) (21 CFR 10.45(d)) and establish that the agency regards guidance documents as final agency action. FDA believes that this issue is more appropriately addressed in the final rule pertaining to the revisions to the part 10 regulations.

blic input in connection with the velopment of guidance documents. FDA sought comment on a proposed three-tiered system, which encompassed a different approach to public comment for each of the three tiers. For the proposed Tier 1 documents, FDA would notify the public of its intent to issue a guidance and solicit comment before issuing that guidance. In addition, where appropriate (e.g., when complex scientific issues are raised), FDA might also hold a public meeting or workshop to discuss the guidance or could involve advisory committees in the development process. For the proposed Tier 2 documents, FDA would notify the public after it issues the guidance and solicit comment at that time. For the proposed Tier 3 documents, FDA would regularly notify the public of new guidance that recently has been issued and would not specifically solicit comment, but would accept comment.

FDA suggested that whether a guidance would be in Tier 1, 2, or 3 would depend on a number of factors. For example, Tier 1 guidance might be guidance that represents a significant change, is novel or controversial, or raises complex issues about which FDA would like to have significant public input; Tier 2 guidance might be guidance that merely states FDA's current practices or does not represent a significant or controversial change; Tier 3 guidance might be guidance directed largely to FDA's own staff and that has a limited effect on the public.

In the March 7 Notice, the agency opined that an approach such as the three-tiered one would allow it to make public input genuinely meaningful. The agency did not (and does not) want to make a commitment to extensive public participation in the development of large numbers of guidance documents and then find itself unable to issue needed guidance promptly.

Most of the speakers at the April 26 public meeting and many of the comments to the March 7 Notice did not support the agency's proposed three-tiered approach. The major criticisms were that it is too complicated, would not provide sufficient public participation, and would not sufficiently focus on public participation before a decision to issue guidance is made and before a proposed guidance is drafted. Some comments suggested changes to the tiers; others suggested completely different approaches.

Specific Criticism of the Proposed Three-Tiered Approach. A number of the comments on the March 7 Notice opined that FDA's proposed three-tiered approach would be too complex. Many thought that the proposed approach would make the classification itself a separate burden on the agency. Moreover, some thought that the agency's determination of "significance" would be problematic. For example, what might appear insignificant to the agency could be significant to the public.

Many of the comments stated that the three-tiered approach would not provide adequate public participation—particularly with respect to Tier 3. In addition, a number of comments criticized FDA's approach for focusing too much on revision of guidance that has already been drafted. These comments noted the importance of allowing participation at the earliest stages of the development process.

One comment opined that because guidance documents are used to explain interpretations of existing requirements, there is no need for an opportunity to comment. Rather, users should be encouraged to provide informal feedback at any time. If all of the public's comments are negative, FDA should consider rewriting the guidance.

Finally, one comment noted that FDA should not use the term "tier" because it will lead to confusion with the current "tier" system for device section 510(k) submissions.

Suggested Alternatives to the Three-Tiered Approach. Many of the comments agreed with a tiered approach, but suggested different ways of deciding which documents fall into each tier. A number suggested distinguishing between "educational documents," "interpretive documents," and "descriptive documents." Some suggested distinguishing between "significant public interest documents," "general public interest documents," and "FDA interest only documents." Others suggested looking at whether the documents: (1) Represent a significant change in policy, a complex issue, or are new and have wide applicability; (2) involve no significant or controversial changes; or (3) affect only FDA staff and have no effect on the public. A number of comments thought it important for FDA to look at the impact the guidance document has on the industry.

A comparable number of comments disagreed with a tiered approach. For example, one comment suggested that any agency statement having the potential for compliance or enforcement consequences must be subject to notice and comment rulemaking. Product specific guidance (e.g., bioequivalence protocols or biopharmaceutical guidance) alone could be excepted, provided the guidance is binding on FDA and industry unless a clearly demonstrated public health safety issue arises.

Some comments suggested that all guidance be available for comment before issuance through publication in the Federal Register (although an abbreviated procedure could be employed). Under this approach, a reasonable amount of time, at least 60 days, would be allowed for submission of comments.

One comment suggested that advanced public comment always be required except when it would not be in the public interest to wait for advanced public comment. The latter guidance documents would undergo comment after issuance.

Several comments recommended that the agency try processes other than soliciting comment from the public after a guidance document has been drafted. For example, some suggested that the agency employ a negotiated guidance development process, patterned after negotiated rulemaking. Another comment recommended creation of an internal task force to evaluate the agency's management procedures for ensuring consistency in the application of statutes and regulations, identifying interpretations of how to apply the statutes and regulations, and determining when the interpretations should be formed into guidance documents. Another recommended creation of a joint agency-industry committee to coordinate the development, promulgation, issuance, and overall management of guidance documents.

At least one comment suggested that FDA experiment with different models to determine how best to solicit public input in the long run.

In response to the agency's request for comment on how to treat the comments that are submitted for guidance documents, some suggested that all comments be available for public review; others said that it is inappropriate for the general public to have access to comments by named individuals regarding certain issues. Several comments indicated that comments need not be in the public docket. Rather, it would be sufficient to have them sent to the Center or Office issuing the guidance. Most of the comments agreed that it was important that the agency commit that all comments received will be considered, and not just filed.

FDA's Approach. FDA disagrees with many of the suggested alternatives because they fail to recognize that the agency does not have unlimited resources to dedicate to the development of guidance documents.

As set forth in the March 7 Notice, if FDA commits to a development process that is akin to rulemaking, it will not be able to issue many guidance documents. Moreover, what guidance documents could be issued, could not be issued promptly.

FDA disagrees with other suggested alternatives because they appear to be even more complex than FDA's proposed three-tiered approach. For example, under one approach FDA would have to determine whether a document is "educational," "interpretive," or "descriptive" before deciding what type of public participation should go into the development process. There is overlap between these different types of guidance documents and would likely be disagreement over the appropriate categorization of a guidance document. Under another suggested approach, FDA would have to look at whether a guidance is of "significant public interest," "general public interest," or "FDA only interest." The latter would require very subjective determinations. Moreover, it is doubtful that many guidance documents would fall outside of the category of "significant public interest."

Nevertheless, FDA agrees with some of the criticisms to its proposed three-tiered approach and believes that many of the comments were constructive. As set forth below, FDA is revising its proposed approach to public input to: (1) Simplify it; (2) increase public participation; and (3) ensure that public participation will be at the earliest stages of the process. Moreover, FDA will not use the term "tier" in differentiating the degree of public participation.

As part of its GGP's, FDA will adopt a two-level approach. Level 1 documents generally will include guidances directed primarily to applicants/sponsors or other members of the regulated industry that set forth first interpretations of statutory or regulatory requirements, changes in interpretation or policy that are of more than a minor nature, unusually complex scientific issues, and highly controversial issues. Level 2 guidance documents will include all other guidances.

For Level 1 guidance, the agency will solicit public input prior to implementation, unless: (1) There are public health reasons for immediate implementation; (2) there is a new statutory requirement, executive order, or court order that requires immediate implementation and guidance is needed to help effect such implementation; or (3) the guidance is presenting a less burdensome policy that is consistent with the public health. In the latter situations, the agency will solicit public input upon issuance/implementation. When the agency determines that even greater public participation is warranted, for example when there are highly controversial or unusually complex new scientific issues, the agency may hold a public workshop to discuss a draft guidance document. In these situations, the agency may also present a draft of the guidance document to an advisory panel.

In an effort to help ensure that public participation will occur at the earliest stages of the guidance development process, the agency is implementing policies pursuant to which the public will have an opportunity to suggest areas for guidance development or revision and to suggest drafts of guidance documents for adoption by the agency. (See "Proposing New Guidance," below.) Through these processes, the agency often will solicit input prior to its decision to issue a guidance and/or prior to the development of a draft.

In addition, FDA may solicit or accept early input on the need for new or revised guidance or assistance on the development of particular guidance documents from individual nongovernmental groups such as consumer groups, trade associations, patient groups, and public interest groups. The agency may participate in meetings with these various parties to obtain each party's views on priorities for developing guidance documents. The agency may also hold meetings and workshops to obtain input from each interested party on the development or revision of guidance documents in a particular FDA subject area.

Comments submitted for Level 1 documents will be submitted to the public docket and will be available to the public for review. The agency will review all comments, but in issuing a final guidance, need not specifically address every comment. The agency will make changes to a guidance document in response to comments as appropriate.

For Level 2 guidance, the agency will provide an opportunity for public comment upon issuance. Unless otherwise indicated, the guidance will be implemented upon issuance. The agency will make changes to Level 2 guidance if comments indicate that such changes are appropriate. Comments submitted for Level 2 guidance documents will be sent directly to the issuing Center or Office. Each guidance will identify the Center or Office to which such comments should be sent. The Center or Office will review all comments and will make changes to the guidance in response to such comments, as appropriate.

For all guidance documents—Levels 1 and 2—comments will be accepted at any time. Guidance will be revised in response to comments, as appropriate. These comments will be submitted to the issuing Center or Office identified in the guidance document.

Public Notification of Proposed/New Guidance Documents. In the March 7 Notice, the agency solicited comment regarding what approach would best ensure that the public is kept apprised of new guidance document developments. Comments responding to the question regarding how best to notify the public and solicit input on proposed or new guidance suggested a variety of vehicles including the Federal Register, the world wide web (WWW), the trade press, trade associations/organizations, public workshops, and grassroots meetings.

In an effort to ensure that notice is provided both electronically and by hard copy, the agency will be providing notice both in the Federal Register and on the FDA WWW home page. FDA has established a home page on the WWW at "http://www.fda.gov". Each of the Centers and the Office of Regulatory Affairs also have established home pages, which are linked to the FDA home page. These Center and Office home pages can be accessed directly or by going through the FDA home page. Guidance document notices and/or drafts will be posted on the FDA home page or will be accessible from there.

The availability of all new guidance documents, both Levels 1 and 2, will be posted on the appropriate FDA WWW home page as each guidance is issued. Notices of availability of Level 1 guidance documents will appear in the Federal Register when each new guidance is issued. If several new Level 1 guidance documents are being issued at the same time, a single Federal Register notice may be issued for all of those new documents. The agency will issue Federal Register notices of all new Level 2 guidance documents on a quarterly basis.

Proposing New Guidance. A number of comments on the March 7 Notice suggested that it is more important for the agency to ensure adequate public participation in the process that leads to the development of a guidance document than in the process following the agency's development of a draft guidance. These comments urged the agency to provide a mechanism for the public to recommend subjects for new guidance or drafts of proposed new

iidance documents. One comment iggested utilizing a "Guidance Proposal Policy" pursuant to which FDA employees or the public would propose topics for guidance and the proposals would be reviewed and approved/not approved by FDA management. Another comment suggested that a central location, such as a guidance document calendar, be designated for industry to propose new guidance development and to learn of new development activities. One comment suggested that the Centers and Offices solicit comments about the need for guidance through a Federal Register notice. Finally, one suggested that possible topics for development of guidance be published in the agency's annual regulatory agenda.

The agency agrees that it is important to provide for the public's involvement in the process that leads to the development of a draft guidance document. As part of its GGP's, therefore, the agency is instituting procedures for involving the public in decisions to develop or revise guidance documents and prioritize the development and revision of guidance documents. The agency will accomplish this in two ways. First, as a part of its GGP's, the agency will, on a semiannual basis, publish (in the Federal Register and on the FDA WWW home page), possible topics for guidance document development during the next year. At that time, FDA will solicit input from the public regarding these and additional ideas for new guidance documents or guidance document revisions or priorities. The purpose of publishing this "guidance document agenda" is to encourage the public to participate in the process that leads to the development of guidance documents. The agency will not be bound by the list of possible topics—i.e., it will not be required to issue every guidance document on the list and it will not be precluded from issuing guidance documents that are not included on the list.

The second way that the agency will involve the public in decisions to develop, revise, or prioritize guidance documents will be to include, as part of its GGP's, a "Guidance Proposal Policy." The "Guidance Proposal Policy" will provide the public an opportunity to propose topics for new or revised guidance or to propose draft guidance documents. The guidance proposal policy not only provides the public a meaningful opportunity to participate in the prioritization and development of guidance documents, it also allows the agency to take advantage of outside expertise and resources.

Review and Revision of Guidance Documents. A number of comments to the March 7 Notice suggested that the agency establish periodic review of guidance documents at predetermined intervals and create mechanisms for the public and agency personnel to suggest earlier review. Several comments suggested that a policy should be adopted whereby if a guidance document cannot be reviewed and revised within a reasonable time (e.g., 3 years), it should be deemed obsolete. At least one comment objected to the sunset concept.

FDA agrees that it would be valuable to periodically review and, where appropriate, revise all guidance documents. As a practical matter, guidance documents are regularly used by FDA and thereby undergo an informal review process. The agency's current workload will not permit it to commit to formal strict review/revision deadlines without diverting resources from other tasks. The agency does not think it is in the public's best interest for guidance documents that have not been reviewed or revised within some certain period of time to be deemed obsolete. The result would be to eliminate many current, valuable guidance documents. The agency believes that the guidance proposal policy will help to keep the agency apprised of potentially outdated guidance documents. Thus, as part of its GGP's, the agency is recommending review of existing guidance regularly and when appropriate (e.g., when there are significant changes in the statute or regulations), but it is not adopting a policy whereby certain guidance documents automatically are deemed obsolete with the mere passage of time.

Other Quality Control Measures. A number of the comments suggested additional quality control measures to help improve the quality of guidance. For example, one suggested that the agency adopt a uniform sign-off policy whereby each guidance document has concurrence at least at the level of an Office director. Others suggested that FDA employ other standard elements such as clearly marking superseded and superseding documents, identifying the underlying statutory and regulatory requirements, including a glossary of terminology, cross-referencing other relevant agency publications, and incorporating the following information: Relevant dates (issuance, effective, implementation, review, withdrawal, expiration), status (under development, draft, final), tier, revision history, superseded/superseding documents, available appeals mechanisms, draft number, and a summary/description of the document.

FDA agrees that many of the above standard elements would help to ensure uniformity throughout the agency and to make the documents more useful to the public. The agency thinks that it is important to include the issuance date of a guidance, its status (e.g., draft), and, where applicable, the date of the document's last revisions. When a guidance document supersedes another document, it also is important to identify the document that the new guidance is superseding. In addition, superseded documents that remain available for historical purposes should be stamped or otherwise identified as superseded.

Finally, as part of GGP's, the agency is implementing a uniform sign-off policy that directs that, at a minimum, all Level 1 guidance documents receive the sign-off of an Office Director and Level 2 guidance receive the sign-off of a Division Director. The Office of the Chief Counsel (OCC) will review and sign off on Level 1 guidance documents that set forth new legal interpretations and any other guidance documents that the Office Directors (or other issuing officials) determine should have (OCC) review. The Office of Policy (OP) will review and sign off on Level 1 guidance documents that constitute significant changes in agency policy and any other guidance documents that the Office Directors (or other issuing officials) determine should have OP review.

V. Dissemination/Availability to Public

In the March 7 Notice, FDA solicited comment on how best to provide the public access to guidance documents. FDA's Centers and Offices currently use a variety of mechanisms to make guidance documents available to the public. Nevertheless, many of the comments stated that there is room for improvement in FDA's current access programs.

Guidance Document Lists. In the March 7 Notice, the agency expressed its intent to ensure that all current guidance documents are included on a list and that the public is aware that the list exists. FDA solicited comment on how best to make the list available—electronically, on the established FAX information systems, or in the Federal Register.

Most comments were in favor of one centralized system (with the individual Centers and Offices keeping copies as well); most agreed that the centralized system must include one electronic method and one hard copy method; some urged use of the Federal Register

because it is available electronically and / hard copy.

As part of its GGP's, FDA will make a comprehensive list of all guidance documents available on the FDA WWW home page and in the Federal Register. The WWW list will be updated continuously. The Federal Register list will be published annually and updated quarterly. The quarterly update will list all new guidance documents issued during that quarter and all guidance documents that have been withdrawn during that quarter. The list will include the name of each guidance document, the guidance's issuance/revision dates, and information on how to obtain copies of all of the guidance documents included on the list. The list will be organized by Center and Office and should group guidance documents by their intended users or the regulatory activities to which they apply.

Guidance Documents. In the March 7 Notice, the agency sought comment on the agency's current systems for providing access to the actual guidance documents. Specifically, the agency asked whether the current systems provide adequate access, whether it would be feasible to rely principally on the FAX systems and electronic methods—such as the WWW—or whether hard copies are necessary.

Comments submitted to the docket suggested that improvements could be made to FDA's current access systems. For example, some comments suggested that there were difficulties in using the FAX-ON-DEMAND systems. Others complained that the current systems were not kept up to date.

The Centers and Offices each will retain responsibility for maintaining a comprehensive, current set of their guidance documents and making those guidance documents available to the public. All guidance documents made available by the Centers and Offices should be included on the comprehensive list. To the extent feasible, guidance documents will be made available electronically (e.g., on the WWW). The Centers and Offices will make all guidance documents available in hard copy upon request.

VI. Appeals

In the March 7 Notice, FDA emphasized the importance of an effective appeals mechanism to ensure that there will be full and fair reconsideration and review of how guidance documents are being applied. The agency expressed its belief that an effective appeals process would protect against guidance documents being applied as binding requirements.

Comments submitted to the docket and presentations at the April 26 public meeting indicated that the issue of appeals may not be an appropriate way to address this issue. According to these comments, if the agency involves the public in the development of guidance and takes steps to ensure that its employees do not apply guidance as binding requirements, there would be fewer appeals relating to guidance documents. Nevertheless, a number of comments stated that the public is not sufficiently aware of the agency's current appeals processes and/or that the agency's current appeals processes are not adequate.

The agency agrees that improving the development and use of guidance documents should limit the need for appeals. Nevertheless, the agency believes that an effective appeals mechanism is needed for those times when someone believes the GGP's may not have been followed or the GGP's fail to achieve their purpose. The agency has appeals mechanisms in place. However, there is a lack of knowledge regarding their existence and a lack of clarity about how they work—both of which likely contribute to the criticism that they are inadequate. Accordingly, the agency is including, in its GGP's, a section that describes the appeals mechanisms relating to guidance.

As a general matter, a person with a dispute involving a guidance document can appeal a decision by going up the Center and Office chains of command, which are described in the GGP's. The Office of the Chief Mediator and Ombudsman (the Ombudsman) may be asked to become involved if the matter is not resolved by going up the chain of command, little progress is being made going up the chain of command, or a person does not know where to begin an appeal. The GGP's provide information regarding the Office of the Ombudsman and provide Center- and Office-specific information regarding telephone and/or mail contacts for questions on appeals.

The text of the GGP's document is set forth below.

Dated: February 18, 1997.

William B. Schultz,

Deputy Commissioner for Policy.

Good Guidance Practices

I. Purpose

This "Good Guidance Practices" (GGP's) document sets forth FDA's general policies and procedures for developing, issuing, and using guidance documents. The purpose of this document is to help ensure that agency guidance documents are developed with adequate public participation, that guidance documents are readily available to the public, and that guidance documents are not applied as binding requirements. The agency wants to ensure uniformity in the development, issuance, and use of guidance documents.[1]

II. Definition

The purposes of guidance documents are to: (1) Provide assistance to the regulated industry by clarifying requirements that have been imposed by Congress or issued in regulations by FDA and by explaining how industry may comply with those statutory and regulatory requirements and (2) provide specific review and enforcement approaches to help ensure that FDA's employees implement the agency's mandate in an effective, fair, and consistent manner. Certain guidance documents provide information about what the agency considers to be the important characteristics of preclinical and clinical test procedures, manufacturing practices, and scientific protocols. Others explain FDA's views on how one may comply with the relevant statutes and regulations and how one may avoid enforcement actions.

The term "guidance documents" includes documents prepared for FDA staff, applicants/sponsors, and the public that: (1) Relate to the processing, content, and evaluation/approval of submissions; (2) relate to the design, production, manufacturing, and testing of regulated products; (3) describe the agency's policy and regulatory approach to an issue; or (4) establish inspection and enforcement policies and procedures. "Guidance documents" do not include documents relating to internal FDA procedures, agency reports, general information documents provided to consumers, speeches, journal articles and editorials, media interviews, press materials, warning letters, or other communications directed to individual persons or firms.

III. Legal Effect of Guidance Documents

Guidance documents do not themselves establish legally enforceable rights or responsibilities and are not legally binding on the public or the agency. Rather, they explain how the agency believes the statutes and regulations apply to certain regulated activities. However, because a guidance document represents the agency's current thinking on the subject addressed in the document, FDA's decisionmakers will take steps to ensure that their staff do not deviate from the guidance document without appropriate justification and appropriate supervisory concurrence.

Alternative methods that comply with the relevant statute or regulations are acceptable. If a regulated company or person wishes or chooses to use an approach other than that set forth in a guidance document, FDA will, upon request, discuss with that company or person alternative methods of complying with the applicable statutes and regulations.

[1] This document represents the agency's current practices for developing, issuing, and using guidance documents. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. Individual FDA Centers or Offices may have additional/more detailed procedures to implement the general principles set forth herein.

FDA encourages industry to discuss ...rnative approaches with the agency ...re implementing them to avoid ...necessary or wasteful expenditures of resources.

IV. Application of GGP'S

FDA staff involved in the development, issuance, and application of guidance documents are expected to adhere to these GGP's. Documents and other means of communication excluded from the definition of guidance should not be used to initially communicate new or different regulatory expectations not readily apparent from the applicable statute or regulations to a broad public audience. Whenever such regulatory expectations are first communicated to a broad public audience, these GGP's should be followed. This does not limit the agency's ability to respond to questions as to how an established policy applies to a specific situation or to questions about areas that may lack established policy. However, such questions may signal the need to develop guidance in that area.

V. Procedures for Developing Guidance Documents

FDA has adopted a two-level approach to the development of guidance documents. The procedures for developing a guidance document will depend on whether that guidance document is a "Level 1" guidance or a "Level 2" guidance. Level 1 guidance ...cuments generally include guidances ...ected primarily to applicants/sponsors or ...ner members of the regulated industry that set forth first interpretations of statutory or regulatory requirements, changes in interpretation or policy that are of more than a minor nature, unusually complex scientific issues, or highly controversial issues. Level 2 guidance documents include all other guidance documents.

Development of Level 1 Guidance Documents. For Level 1 guidance documents, the agency will solicit public input prior to implementation, unless: (1) There are public health reasons for immediate implementation; (2) there is a new statutory requirement, executive order, or court order that requires immediate implementation and guidance is needed to help effect such implementation; or (3) the guidance is presenting a less burdensome policy that is consistent with public health. In the latter situations, the agency will solicit public input upon issuance/implementation.

For Level 1 guidance, the agency will, at a minimum, solicit public input by (1) issuing a notice of availability of a draft of the guidance in the Federal Register and indicating its availability on the appropriate FDA world wide web (WWW) home page[2], and (2) posting the draft on the appropriate FDA WWW home page or making the draft otherwise available. The notice of availability will provide information regarding how to obtain a copy of the draft guidance; hard copies of the draft will be available upon request. The agency may use one Federal Register notice of availability to solicit public input on several different draft guidance documents. For Level 1 guidance documents, the agency also may hold a public workshop to discuss a draft and/or present a draft to an advisory panel when, for example, there are highly controversial or unusually complex new scientific issues.

Because the agency recognizes that it is important to solicit input prior to its decision to issue a guidance and also, perhaps, during the development of a draft of a Level 1 guidance, the agency is implementing various practices to obtain input at the earliest stages of Level 1 guidance document development. For example, these GGP's provide that the public will have an opportunity to comment on and suggest areas for guidance development or revision and to submit draft guidances for possible adoption by the agency. (See the "Guidance Document Agenda" and "Guidance Proposal Policy" set forth below.)

In addition, FDA may solicit or accept early input on the need for new or revised guidance or assistance in the development of particular guidance documents from individual nongovernmental groups such as consumer groups, trade associations, patient groups, and public interest groups. The agency may participate in meetings with these various parties to obtain each party's views on priorities for developing guidance documents. The agency may also hold meetings and workshops to obtain input from each interested party on the development or revision of guidance documents in a particular FDA subject area.

Comments submitted on draft Level 1 guidance documents will be submitted to the docket identified in the Federal Register notice and on the appropriate FDA WWW home page. All comments will be available to the public for review. The agency will review all comments, but in issuing the guidance, need not specifically address every comment. The agency will make changes to the guidance document in response to comments, as appropriate.

Development of Level 2 Guidance Documents. For Level 2 guidance, the agency will provide an opportunity for public comment upon issuance. Unless otherwise indicated, the guidance will be implemented upon issuance.[3] The availability of new Level 2 guidance documents should be posted on the appropriate FDA WWW home page as each guidance is issued. Each quarter, the agency will publish a list in the Federal Register of all new Level 2 guidance documents.

Comments submitted for Level 2 guidance documents will be sent directly to the issuing Center or Office. Each guidance will identify the Center or Office to which such comments should be sent. The Center or Office will review all comments. The agency will make changes to the guidance in response to comments, as appropriate.

Comments on Guidance Documents In Use. For all guidance documents—Levels 1 and 2—comments will be accepted at any time. Comments on the guidance documents in use should be submitted to the issuing Center or Office identified in the guidance. Guidance will be revised in response to such comments, as appropriate.

Sign-off Policy. All drafts of Level 1 guidance documents that are being made available for public comment will receive the sign-off of at least an Office Director in a Center or the Office of Regulatory Affairs equivalent. All final versions of Level 1 guidance documents will receive the sign-off of at least an Office Director in a Center or the Office of Regulatory Affairs equivalent. The Office of the Chief Counsel (OCC) will review and sign off on Level 1 guidance documents that set forth new legal interpretations and any other guidance documents that the Office Directors (or other issuing officials) determine should have OCC review. The Office of Policy (OP) will review and sign off on Level 1 guidance documents that constitute significant changes in agency policy and any other guidance documents that the Office Directors (or other issuing officials) determine should have OP review. All Level 2 guidance documents will receive the sign-off of an official at the Division Director level or higher. The agency employees with sign-off authority should ensure that these GGP's have been followed whenever a guidance document is issued. If GGP's were not followed, the person with sign-off authority should withdraw the guidance document and reissue it in accordance with GGP's.

Guidance Document Agenda. On a semiannual basis, the agency will publish in the Federal Register and on the FDA WWW home page possible topics for guidance document development or revision during the next year. At that time, the agency will specifically solicit input from the public regarding these and additional ideas for new guidance documents or guidance document revisions or priorities. The agency is not bound by the list of possible topics—i.e., it is not required to issue every guidance document on the list and it is not precluded from issuing guidance documents that are not included on the list.

"Guidance Proposal Policy." If a member of the public wishes to propose one or more topics for new guidance or guidance revisions or to propose one or more draft guidance documents for adoption by FDA, that person should submit the proposal to the Centers or Offices with responsibility for overseeing the regulatory activity to which the guidance document would apply. The submission should include a statement regarding why new or revised guidance is necessary.

If the Center or Office agrees that the proposed topic should be covered by a guidance document, it will develop a guidance document in accordance with these GGP's. If the Office or Center agrees that a guidance document should be updated/revised, it will develop a revision in accordance with these GGP's. If the submitter

[2] FDA has established a home page on the WWW "http://www.fda.gov". Each of the Centers and ...e Office of Regulatory Affairs also have ...stablished home pages, which are linked to the FDA home page. These Center- or Office-specific home pages can be accessed directly or through the FDA home page. Guidance document notices and/or drafts will be posted on the FDA home page or will be accessible from there.

[3] The agency may, at the discretion of the issuing Office, solicit comment before implementing a Level 2 guidance document.

has proposed a draft of the guidance ment that the agency agrees can form the for a guidance document, the agency follow the GGP's for issuing and implementing a guidance document based on that proposed draft.

Review and Revision of Guidance Documents. The agency intends to review existing guidance documents on a regular basis. As part of the "Guidance Proposal Policy," members of the public may request review or revision of a particular guidance document on the basis that it is no longer current. Such requests should be accompanied by an explanation of why the guidance is out of date and how it should be revised. The agency will review such requests to determine if the guidance document at issue needs to be updated/revised. The Agency will, when appropriate, update or revise that guidance document in accordance with these GGP's. In addition, when significant changes are made to the statute or regulations, the agency will, on its own initiative, review and, as appropriate, revise guidance documents relating to that changed statute or regulation.

VI. Standard Elements

Nomenclature. All guidance documents will include: (1) The umbrella term "guidance," (2) information that identifies the Center or Office producing the document, and (3) the regulatory activity to which and/or the persons to whom the document plies. In practice, the majority of guidance ments issued in the future will be called pliance guidance," "guidance for industry," or "guidance for FDA reviewers/staff."

Statement of Nonbinding Effect. All guidance documents will include language such as the following:

This guidance document represents the agency's current thinking on * * *. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

Absence of Mandatory Language. Because guidance documents are not binding, mandatory words such as "shall," "must," "require" and "requirement" are inappropriate unless they are being used to describe or discuss a statutory or regulatory requirement. Before a new guidance is issued, it should be reviewed to ensure that mandatory language has not been used.

Other Standard Elements. Each guidance document will include the dates of issuance and latest revision. Documents that are being made available for comment should include a "draft" notation. When a guidance supersedes another guidance document, the new guidance document will identify the document that it is superseding. Superseded documents that remain available for historical purposes should be stamped or erwise identified as superseded. All dance documents should include a cover eet that is modeled after the samples attached to this document.

The agency will update existing guidance documents (to include these standard elements) as they are revised.

VII. FDA Implementation of GGP's

Education. All current and new FDA employees involved in the development, issuance, or application of guidance documents will be provided a copy of and directed to review the agency's GGP's. The Centers and Offices will conduct additional training of employees involved in the development and use of guidance documents that will describe in more detail how to develop and use guidance documents under these GGP's. This training will emphasize the principles set forth in section III., above, regarding the legal effect of guidance documents.

The agency also will educate the public about the legal effect of guidance. These GGP's and the statement of the nonbinding effect of guidance that will be included in every future guidance document and on the comprehensive list of guidance documents (discussed in section VIII. below) should help to educate the public about the legal effect of guidance. FDA staff should take the opportunity to state and explain the legal effect of guidance when speaking to the public about guidance documents.

Monitoring. FDA will monitor agency employees' use of guidance documents. As part of this process, the Centers and Offices will monitor the development and issuance of guidance documents to ensure that these GGP's are being followed. In addition, they will spot-check the use of guidance documents to ensure that they are not being applied as binding requirements. Finally, the Centers and Offices will spot-check the use of documents and communications that are not defined as guidance, such as warning letters and speeches, to ensure that these documents are not being used to initially express a new regulatory expectation to a broad public audience.

Three years after these GGP's have been implemented, the agency will convene a working group to review whether these GGP's have been successful in achieving the agency's goal in issuing them. The working group will determine whether the GGP's are ensuring: (1) Appropriate public participation in the development of guidance, (2) that guidance documents are readily available to the public, and (3) that guidance documents are not being applied as binding requirements. The working group will review the results of the Center and Office monitoring efforts as well as the number and results of appeals relating to the development and/or use of guidance documents.

VIII. Dissemination/Availability to Public

Lists of Guidance Documents. A comprehensive list of all current guidance documents will be maintained on the FDA WWW home page. New guidance documents should be added to the list within 30 days of issuance. The agency will publish the comprehensive list in the Federal Register annually. Each quarter, the agency will publish a Federal Register notice that lists all guidance documents that were issued during that quarter and all guidance documents that have been withdrawn.

The guidance document lists will include the name of each guidance document, the document's issuance/revision dates, and information on how to obtain copies of the document. The lists will be organized by Center and Office and should group guidance documents by their intended users and/or the regulatory activities to which they apply. The list also will include (properly identified) draft documents being made available for public comment.

Guidance Documents. The Centers and Offices each will retain responsibility for maintaining a comprehensive set of their guidance documents and making those guidance documents available to the public. All guidance documents made available by a Center or Office should be included on the comprehensive list. To the extent feasible, guidance documents will be made available electronically (e.g., on the WWW). The Centers and Offices will make all guidance documents available in hard copy, upon request.

IX. Appeals

These GGP's should improve the agency's development and use of guidance documents. Nevertheless, an effective appeals mechanism is needed for those times when the GGP's may not have been followed or the GGP's fail to achieve their purpose. FDA intends to provide an opportunity for appeal to a person who believes that GGP's were not followed in issuing a particular guidance document or who believes that a guidance document has been treated as a binding requirement.

As a general matter, a person with a dispute involving a guidance document should begin with the supervisor of the person issuing or applying the guidance document. If the issue cannot be resolved at that level, the matter should be brought to the next level. This process would continue on up the chain of command.[4] If a matter is unresolved at the level of the Center Director, or if little progress is being made going through the chain of command, the Office of the Chief Mediator and Ombudsman (the Ombudsman) may be asked to become involved.[5] The Office of the Ombudsman can be reached at 301–827–3390.

The chains of command for such appeals generally are as follows:

Center for Drug Evaluation and Research (CDER)

-Reviewer/Project Manager
-Branch Chief/Team Leader/Supervisory Project Manager
-Division Director
-Office Director

[4] This general agency-wide process for appealing decisions is described in FDA's regulations (21 CFR 10.75).

[5] The Ombudsman reports directly to and acts on behalf of the FDA Commissioner in investigating and resolving issues and problems that affect products under FDA's jurisdiction. The office was created to investigate industry complaints about FDA's regulatory processes, identify deficiencies in those processes, respond to problems affecting a product under FDA's jurisdiction, and ensure that FDA policy is fairly and evenly applied throughout the agency. The Ombudsman also mediates disputes or issues between FDA and the regulated industry that have not been resolved through other means.

-Deputy Center Director
-Center Director

In addition, CDER has its own Ombudsman in the Office of the Center Director (301–594–5443) to help assist with appeals and dispute resolution. Additional information about this office can be found on the CDER home page at "http://www.fda.gov/cder".

Center for Biologics Evaluation and Research (CBER)

-Reviewer/Consumer Safety Officer
-Branch Chief/Laboratory Chief
-Division Director
-Office Director
-Associate Director
-Deputy Center Director
-Center Director

In addition, CBER has its own Ombudsman in the Office of the Center Director (301–827–0379) who handles appeals and dispute resolution.

Center for Veterinary Medicine (CVM)

-Reviewer
-Division Director
-Office Director
-Deputy Center Director
-Center Director

In addition, CVM has procedures in place to handle appeals of written decisions on issues involving science or policy. These procedures, which may apply to certain guidance document appeals, are outlined in a staff manual guide (#1240.3130). For additional assistance regarding the appeals process in CVM, persons can contact the Associate Director for Policy at 301–827–0139.

Center for Devices and Radiological Health (CDRH)

-Reviewer/Consumer Safety Officer
-Branch Chief/Team Leader
-Division Director
-Office Director
-Deputy Center Director
-Center Director

Questions related to the CDRH appeals process may be answered by the Division of Small Manufacturer's Assistance at 800–638–2041 or 301–443–6597. Questions may also be faxed to 301–443–8818.

Center for Food Safety and Applied Nutrition (CFSAN)

-Reviewer/Consumer Safety Officer
-Division Director
-Office Director
-Deputy Center Director
-Center Director

In CFSAN, the Industry Activities staff at 202–205–5251 is the contact point for appeals and will direct inquiries relating to appeals of guidance documents to the appropriate CFSAN office.

Office of Regulatory Affairs (ORA)

-Field Investigator/Field Inspector
-Supervisor/Team Leader
-Branch Chief
-District Director
-Regional Director

The Regional Directors report to the Associate Commissioner for Regulatory Affairs.

In addition, FDA's District Offices and resident posts nationwide have a variety of small business representatives, public affairs specialists, and others who can respond to questions from outside the agency regarding appeals. A listing of FDA's offices is found in the blue pages of local telephone directories and on FDA's home page at "http://www.fda.gov". Questions related to an appeal of guidance documents in ORA may be answered by the Division of Compliance Policy, which can be reached at 301–827–0420.

If it is unclear which Center or Office produced a guidance document or a person does not know where to begin an appeal, the Office of the Ombudsman handles jurisdictional questions and is available to refer those outside the agency to the appropriate place.

In summary, appeals regarding guidance documents can be made either by going up the chain of command, using specific Center or Office procedures, or going directly to the Office of the Ombudsman.

BILLING CODE 4160–01–F

MEMORANDUM

TO: Members, Advisory Committee for Pharmaceutical Science

FROM: Ajaz S. Hussain, Ph.D.
Chair, The Biopharmaceutic Classification System (BCS) Working Group

Date: 12 November 1997

RE: The Biopharmaceutics Classification System Guidance: Current thinking and issues for considerations

Dear ACPS Members,

At the 10 December 1997 ACPS meeting the BCS Working Group is planning to provide you with our recommendations for the proposed guidance document on the BCS. This will be the fourth presentation of BCS concepts to the ACPS, third presentation by the current working group.

Since the May 7, 1997, ACPS meeting, we have further evaluated the BCS class boundaries and experimental methods for classification according to solubility and intestinal permeability of drugs and dissolution of immediate release solid oral dosage forms. Our analysis was presented at the following meetings/workshops to obtain input from the scientific community:

The Biopharmaceutics Classification System: How useful is it in assessing and maintaining quality of oral dosage forms? At the Fourth International Conference on Drug Absorption, Edinburgh, Scotland, 15-17 June 1997.

The Biopharmaceutic Classification System: Current thinking. At the workshop entitled "Strategies for Oral Drug Delivery," September 29 - October 3, 1997, Baltimore, MD.

The following three poster presentations at the American Association of Pharmaceutical Scientists Annual Meeting, November 2-5, 1997, Boston;

1) Evaluation of the Proposed Biopharmaceutic Classification System's Class Boundaries: A Survey of Recent Neuropharmacology Drugs.
2) The Effect of In Vivo Dissolution and Gastric Emptying Rate on the Peak Concentration of Drugs with Different Gastrointestinal Permeabilities.
3) Influence of Gastric Emptying Variation on Plasma Peak Concentration Variation for a High Solubility and High Permeability Drug.

On 18 October 1997 we held an Expert Panel meeting at the FDA to discuss the BCS. Membership of this panel consisted of the following individuals:

Professor Gordon L. Amidon (University of Michigan)
Professor Leslie Z. Benet (University of California, San Francisco)
Professor Ronald T. Borchardt (University of Kansas)
Dr. Henning H. W. F. Blume (Zentrallaboratorium Deutscher Apotheker)
Professor Win L. Chiou (University of Illinois)
Dr. Elizabeth A. Lane (Generic Industry Representative)
Professor Hans Lennernas (University of Uppsala)
Dr. Ian J. McGilvery (Health Canada, Therapeutic Products Directorate)
Dr. Norman Pound (Health Canada, Therapeutic Products Directorate)
Dr. Arnold Repta (PhRMA Industry Representative)
Dr. Steve C. Sutton (AAPS, Oral Absorption Focus Group, Representative)
Professor Thomas N. Tozer (University of California, San Francisco)

Issues discussed at this meeting were:

1. What data or evidence should be determined for the classification of a drug as either high or low permeability?
    a. How rigorous should the permeability class boundary be? [Should the lower bound of a 95% Confidence Interval for the estimated extent of absorption be ≥ 90%?]
    b. How should this data be obtained?
    c. What assumptions do we need to make?
2. Is the "high solubility" class boundary too rigorous in requiring the largest dose strength to be soluble in ≤ 250ml over the pH range of 1 - 8?
    a. Should we define an "intermediate solubility" class (for example, high solubility in pH 3-8)?
3. To be classified as "rapidly dissolving" is it sufficient for a product to meet the 85% in 15 minutes specification in acid (0.1 N HCl) media?
    a. Should a product also meet the "rapid dissolution" specification in a media of higher pH (for example, pH 4.5)?
4. What other considerations are necessary when applying the BCS for regulatory decisions?
    a. Narrow Therapeutic Index drugs?
    b. Dose proportionality study information?
    c. Any other considerations?
5. When in drug development, can BCS be first applied?
    a. Biowaiver for changes in clinical trial formulation?
    b. Biowaiver for approving generic drug products?

Professors Benet and Tozer were unable to attend this meeting. The working group is planning to meet with these experts in the next few weeks. A summary of these

meetings will be presented to you on 10 December 1997.

The attached document is a summary of our "current thinking" on the issue of the use of dissolution test for assessing bioequivalence for some immediate release solid oral dosage forms. We are currently engaged in both lab based research and literature review of permeability methods and will plan to present our analysis on 10 December.

Sincerely,

/s/

Ajaz Hussain, Ph.D.

Attachment

APPEARS THIS WAY ON ORIGINAL

BIOEQUIVALENCE ASSESSMENT FOR IMMEDIATE RELEASE SOLID ORAL DOSAGE FORMS USING *IN VITRO* DISSOLUTION TESTS?

Current Thinking of the BCS Working Group

I. Background Information

A. Bioequivalence

Two formulations of the same drug substance whose rate and extent of drug absorption differ by -20%/+25% or less are generally considered bioequivalent. The standard Bioequivalence study is conducted in a crossover fashion in a small number of volunteers, usually with 18 to 24 healthy normal adults. Single doses of the test and reference drug products are administered and blood or plasma levels of the drug are measured over time. The peak drug concentration in the blood or plasm (C_{max}) and the Areas Under the Curve (AUC) are examined by statistical procedures to verify that the -20%/+25% criteria are satisfied for these pharmacokinetic measures.

Bioequivalence may sometimes be demonstrated using an *in vitro* bioequivalence standard, especially when such an *in vitro* test has been correlated with human *in vivo* bioavailability data. In other situations, bioequivalence may sometimes be demonstrated through comparative clinical trials or pharmacodynamic studies (Approved Drug Products with Therapeutic Equivalence Evaluations, US DHHS, PHS, FDA, CDER, 1996).

B. When are *In vivo* Bioequivalence Tests Conducted?

Bioequivalence tests are conducted by the sponsors of New Drug Applications during pre- and post approval phases of their applications. In the preapproval phase bioequivalence tests are used to compare the so called "clinical trial formulation" with the "to-be-marketed" formulation, if the two formulations differ in their composition or other aspects such as manufacturing processes. Certain post approval changes in formulation may require bioequivalence tests.

Under the Drug Price Competition and Patent Term Restoration Act of 1984, manufactures seeking approval to market a generic drug must demonstrate bioequivalence to the innovator drug product. Certain post approval changes in the generic formulation may necessitate re-demonstration of

bioequivalence.

C. When are *In vivo* Bioequivalence Test Not Required?

The Title 21 of the Code of Federal Regulations describes situations when *in vivo* bioequivalence tests may not be necessary. Excerpts concerning oral dosage forms form this Title are presented below.

21 CFR 320.22 Criteria for waiver of evidence of *in vivo* bioavailability or bioequivalence.

> 21 CFR 320.22 (b) 3, i, ii, iii. Waivers of *in vivo* bioavailability and bioequivalence studies are allowed for oral solution dosage forms such as elixirs and syrups as along as it can be justified that excipients used in the formulation do not affect bioavailability.
>
> 21 CFR 320.22 (c) allow use of dissolution tests for bioequivalence demonstration for conventional solid oral dosage forms generally referred to as "immediate release dosage forms" for drug products determined to be effective for at least one indication in a Drug Efficacy Study Implementation (DESI) notice. The criteria and evidence needed to assess actual or potential bioequivalence problems (21 CFR 320.54) were developed in 1977. These criteria were used to determine whether a DESI effective drug could demonstrate bioequivalence through *in vitro* or *in vivo/in vitro* methodology (Note: these criteria have been retained in the current CFR as 21 CFR 320.33). The list of DESI effective drug products that required an *in vivo* study to demonstrate bioequivalence were previously included in 21 CFR 320.22. With the publication of the Orange Book in 1979 those DESI effective drug products that were not on the "bio- problem" list were coded "AA."
>
> 21 CFR 320.22 (d) Dissolution *in vitro* data may be used in lieu of *in vivo* data for immediate release products of drugs that are proportionally similar in their active and inactive ingredients, or meet established specifications of an *in vitro* test correlated with *in vivo* data, or, other situations such as reformulated products that differ only in color, flavor, or preservative that could not affect the bioavailability.

The guidance document entitled "Immediate Release Solid Oral Dosage Forms; Scale-Up and Post Approval Changes: Chemistry, Manufacturing, and Controls; *In vitro* Dissolution Testing; *In vivo* Bioequivalence

Documentation" (SUPAC-IR; Federal Register 60: 61638, November 30, 1995) provides additional clarification and recommendations for post approval changes that do not require *in vivo* bioequivalence. This is further discussed in the next section.

D. SUPAC-IR Guidance Recommendations on Bioequivalence Tests Based on the Biopharmaceutic Drug Classification System

This guidance classified various post approval changes into three levels based on their potential to alter product quality and performance. Changes unlikely to have any detectable impact of product quality and performance were defined as Level 1 Change. These changes do not require additional *in vitro* or *in vivo* tests to demonstrate bioequivalence.

Level 2 post approval changes are identified as changes that could have a significant impact on product quality and performance. The test recommendations are based on three drug factors: therapeutic index/range, solubility in physiologic pH range, and intestinal permeability. Changes beyond Level 1 for narrow therapeutic index drugs are considered as Level 3 changes. The solubility and permeability characteristics of the drug were based on the Biopharmaceutic Drug Classification System (Amidon et al., Pharm. Res. 12: 413-420, 1995). The classification system serves as a tool to enhance confidence in dissolution tests.

A drug is considered "Highly Soluble" when the largest dose strength is soluble in $\leq$ 250 ml of water over a pH range of 1- 8. To be considered as "Highly Permeable," extent of absorption of a drug need to be greater than 90% and the drug must be stable in the gastrointestinal tract. A drug may be classified in one of the following four classes: 1) High Solubility - High Permeability, 2) High Solubility-Low Permeability, 3) Low Solubility-High Permeability.

1. Class I: Highly Soluble - Highly Permeable Drugs

   Class I definition is intended to identify drugs that are rapidly and completely absorbed when administered as a solution or in a rapidly dissolving dosage form. The dissolution rate of these drugs is intrinsically rapid, especially when formulations are designed to disintegrate rapidly exposing these drugs to the gastric fluid. The rate of absorption from such products may primarily vary with the gastric emptying and absorption is essentially complete by definition. Low

absolute bioavailability, if observed, is generally due to first-pass metabolism. Products (pre-change and post Level 2 changes) of wide therapeutic index drugs that conform to the following dissolution specification do not require additional testing: the dissolution *in vitro* of 85% of the dose in 15 minutes in the USP apparatus I (basket) or II (paddle) containing 900 ml of 0.1 N HCl at 37 °C, under moderate rate of agitation (such as 100 rpm for basket and 50 rpm for paddle apparatus). Those products that do not meet the Case A dissolution specification must demonstrate similar dissolution profiles (Case B dissolution specification) by the criteria referred to as the "f2" metric in the SUPAC-IR. Bioequivalence demonstration, *in vivo*, may be necessary if products fail to meet Case B dissolution specification.

2. Class II: High Solubility - Low Permeability Drugs

The rate and the extent of absorption of rapidly dissolving High Solubility - Low Permeability class of drugs may primarily vary with the gastric emptying, intestinal transit, and/or intestinal permeability. The permeability and extent of absorption of this class of drugs are low due to several factors such as; polar nature of the drug and possibly site specific absorption. Slow dissolution can potentially further reduce the extent of absorption, which is less likely to occur for Highly Permeable drugs. Therefore, the dissolution test recommendations are more rigorous in requiring multi-point profile comparison (Case B dissolution tests).

3. Class III: Low Solubility - High Permeability Drugs

Class II drugs either are poorly soluble irrespective of the media pH, or having low solubility in a certain pH range. Therefore dissolution rate evaluations under different dissolution media pH conditions (Case C dissolution tests) are recommended. Sometimes a surfactant may be needed in the dissolution media to emulate the influence of physiologic surfactants on dissolution *in vivo*. The multi-point profile comparison approach is recommended to ensure similar rates of dissolutions over time and pH. Failure to demonstrate similar profiles may necessitate bioequivalence demonstration *in vivo*, unless scientific justification is provided about why observed differences are not due to the proposed change and could not have significant impact beyond what is normally seen for batches prepared without the change.

4. Class IV: Low Solubility - Low Permeability Drugs

   For this class of drugs Level 2 changes are treated as Level 3 changes that require *in vivo* bioequivalence demonstration.

In vivo bioequivalence study is generally recommended for Level 3 changes. The bioequivalence study may be waived if a suitable *in vitro - in vivo* correlation has been developed and verified.

E. Summary

The current regulations and guidance documents on bioequivalence evaluation recognize dissolution differences (*in vivo*) as the primary reason for observed differences in bioavailabilites of two immediate release products containing the same drug. These regulations also recognize the potential for excipients or "inactive ingredients" to alter bioavailability, and mechanisms have been developed to safeguard against such impact. For example, the Agency periodically publishes (for internal use only) a list entitled "Inactive Ingredient Guide" that lists excipients in approved products along with the dosage forms, amount used or % range, and other information. The SUPAC-IR change Levels also recognize the potential impact of excipients. Any qualitative change in excipient is categorized as Level 3 change.

The concept of a classification system for identifying "bio-problem" drugs was first developed in 1977 (21 CFR 320.54, now in 21 CFR 320.33). This was used to decide whether a DESI effective drug could show bioequivalence through *in vitro* or *in vivo/in vitro* methodology. This could provide a historical database to evaluate successes or failures of dissolution tests for assuring bioequivalence.

The Biopharmaceutic Classification System serves as a tool for identifying when *in vitro - in vivo* correlations are expected or not expected. The mechanistic approach proposed by the BCS allows for setting meaningful dissolution specifications that enhance confidence in these tests, even without an *in vitro - in vivo* correlation. Extension of this approach to the preapproval phase of drug development is warranted. Waiving bioequivalence requirements for some immediate release products that dissolve rapidly to let gastrointestinal physiology dictate both the rate and extent of drug absorption may be a possible. This hypothesis is the subject of the following investigation.

II. INTRODUCTION

Dissolution *in vivo*, transit through the gastrointestinal tract, and intestinal permeability are three important factors that govern both the rate and extent of absorption of a drug that is stable in the gastrointestinal tract. In comparison to other parts of the gastrointestinal tract, the small intestine is a major site of absorption into the intestinal tissue because of its large surface area, its high rate of blood flow, and its possibly higher intrinsic membrane permeability.

Gastric emptying is a complex time-dependent process with significant inter- and intra-subject variability. In the fasted state, gastric emptying rate varies with motility Phase 1, 2 and 3, administered volume, and other factors. For drugs administered as a solution or as rapidly dissolving solid dosage forms, gastric emptying has a significant effect on the rate of absorption, becoming rate limiting if intra-gastric dissolution is rapid enough to allow most of the drug to be in solution prior to entering the small intestine. Under these conditions, dosage forms which dissolve rapidly in stomach may behave as solutions and minimal differences can be observed between solution and solid oral dosage forms. In contrast, when dissolution is slow in relation to gastric emptying and/or intestinal permeability, rate of dissolution can profoundly affect absorption. In this situation, significant differences in absorption can be observed between solution and solid oral dosage forms, where the latter have varying differences in dissolution rate.

Dissolution tests *in vitro* are used for batch-to-batch quality control and, when correlated to *in vivo* bioavailability data, may be used to demonstrate bioequivalence. Successful *in vitro/in vivo* correlations have been demonstrated for a small number of immediate release dosage forms and for a number of extended dosage forms. *In vitro/in vivo* correlations are only expected when dissolution in the gastrointestinal tract limits absorption and *in vitro* dissolution test conditions reflect the *in vivo* dissolution process. Even under conditions where gastric emptying and/or permeability are rate-limiting, *in vitro* dissolution may be related to *in vivo* bioavailability data by developing specifications that will identify when absorption is likely to be dissolution or permeability limited. For dosage forms that dissolve rapidly in the stomach, an *in vitro/in vivo* correlation may not be possible because physiologic as opposed to dosage factors are controlling the rate and extent of absorption. Thus, the CFR requirement that *in vitro* dissolution tests may be relied upon to document bioequivalence only when they have been correlated with and are predictive of human *in vivo* bioavailability data are applicable here in the sense that drug products that dissolve with sufficient rapidity may be presumed to be optimally available, as are solutions, even though this optimal availability precludes the development of an *in vitro/in vivo* correlation.

Rapidly dissolving solid oral dosage forms of highly soluble and highly permeable drugs may be considered to pose minimum bioequivalence problems when no inactive ingredients are present that may significantly affect drug absorption. Products meeting these criteria may be considered as candidates for which bioequivalence demonstration could be based solely on *in vitro* dissolution tests. The following discussion examines this hypothesis.

The analysis is designed to addresses the following questions:

1) When, in the current drug development process, are the dissolution test specifications established?

2) Are dissolution tests reliable for identifying rapidly dissolving products?

3) If dissolution tests are reliable indicators of rapid dissolution *in vivo*, what additional considerations would be necessary to ensure current standards of bioequivalence?

III. DISSOLUTION TEST SPECIFICATIONS: CURRENT APPROACH

Dissolution specifications for a new drug product are generally based on the cumulative history with respect to stability and bioavailability/bioequivalence of various batches prepared during the Phase I - III of the drug development process. Generally, "interim specifications" are established early in drug development that may be adjusted to reflect actual performance of the batches tested in clinic. The choice of the initial dissolution test apparatus, media, etc., appear to be based on past history/experience of the sponsor. For soluble drugs that are stable in acid, first choice for dissolution tests appears to be; medium - 0.1 N HCl, volume - 900 ml, apparatus USP 2 (paddle) or USP 1 (basket) at 50 and 100 rpm, respectively. The specification may vary both in time and % released. For soluble drugs, 70 -80% release in 30 minutes appears to be a generally preferred specification. It is not uncommon for sponsors to submit dissolution data obtained under a variety of different test conditions (for example, different pH media). Developing dissolution specification for poorly soluble drugs are generally more difficult and requires additional considerations such as choice of a surfactant and its concentration in the media.

Pharmacokinetic studies that provide opportunities for *in vitro - in vivo* comparison include: 1) absolute bioavailability, 2) relative bioavailability studies (test formulation vs. a solution or other reference formulations such as a suspension), 3) bioequivalence studies, and 4) "mapping" studies specifically designed to evaluate dissolution

specifications. Mapping studies are bioavailability/bioequivalence studies with three products that differ in their *in vitro* dissolution characteristics. Unfortunately these studies are rare. Other pharmacokinetic studies such as dose-escalation, dose-proportionality, food-drug interaction and drug-drug interactions may also provide some opportunity for *in vitro-in vivo* comparison.

Final dissolution specifications are evaluated and approved by the FDA reviewers. Their decision are based on *in vitro-in vivo* comparisons, stability data, and physiologic relevance of media composition and other test conditions. In majority of cases a one-point specification is adopted. On rare occasions two-point specifications may be defined. The established dissolution specifications then serve as a lot-lot quality assurance tool.

After several years of commercial application the USP may adopt a innovator's dissolution specifications when it develops drug monographs. The generic manufactures have to provide both *in vitro* and *in vivo* data to demonstrate bioequivalence (to the innovator product) in order to obtain approval to market their products.

Application of BCS for waiver of preapproval (NDA) bioequivalence studies will reduce, to some extent, the opportunity of *in vitro - in vivo* comparisons that is the basis by which we currently develop dissolution specification. This is not considered to be a serious problem since there are many instances when no changes are made to the clinical trial formulation, and, therefore, no bioequivalence studies are submitted.

IV. ARE DISSOLUTION TESTS RELIABLE FOR IDENTIFYING RAPIDLY DISSOLVING PRODUCTS?

The BCS application during the preapproval phase requires a priori identification of dissolution tests and specification that are predictive of rapid dissolution *in vivo*. As discussed above rapid dissolution *in vivo* allows a solid dosage form to provide a drug concentration in plasma vs. time profile similar to that of a simple oral solution. This also necessitates use of dissolution as part of the classification system, in addition to solubility and permeability. The classification system as first proposed by Amidon et al., in 1995 (Pharm. Res. 12: 413, 1995) and applied in SUPAC-IR, was referred to as the Biopharmaceutics Drug Classification System (BDCS). This was appropriate for the post-approval phase. Since the current thinking of the working group is to use product dissolution as part of the classification system, in addition to drug's solubility and permeability, and the concept is referred to as BCS in this document. The SUPAC-IR Case A dissolution was selected for evaluation as the rapid/slow dissolution boundary.

A. Dissolution Tests: Historical Perspective

Over the last two decades dissolution tests have become an important tool for product development and lot - lot quality assurance. Significant progress has been made by the pharmaceutical community, especially the USP, in standardizing the equipment and methodology which has improved reproducibility of these tests.

The following observations are made upon literature review of dissolution studies:

1. The USP 1 (basket) and the USP 2 (paddle) apparatus are the most commonly used apparatuses. Typical test conditions:

   Stirring rate settings often used are 100 rpm and 50 rpm for apparatus 1 and 2, respectively.

   Dissolution media volume of 1000 - 500 ml are generally used, more often 900 ml of media is used.

   Composition of media may vary. Water, 0.1 N HCl, USP's Simulated Gastric fluid (without enzymes), USP's Simulated Gastric fluid (without enzymes) are most commonly used. For poorly soluble drugs surfactants such as sodium lauryl sulfate are generally used.

   For products (such as hard gelatin capsules) that tend to float "sinkers" may be necessary to minimize variability.

2. USP dissolution specifications are generally one-point specifications, for example Not Less Than 80% drug released in 30 minutes. For a small number of products a two-point specification is required, for example Digoxin: Q not > 60% in 30 min; not < 85% in 60 minutes. The specified % drug released and the time (15 - 180 minutes) for this release to occur vary widely.

4. The USP's dissolution test methods and specifications serve as quality standard for products marketed in this country. The USP's experience with the dissolution tests may be summarized by the following text quoted from its introductory chapter (page lvi):

"Whenever a medically significant difference in bioavailability has been found among supposedly identical articles, a dissolution test has discriminated among these articles. Because the USP sets forth attributes of an acceptable article , such a discriminating test is satisfactory because dissolution standard can exclude definitively any unacceptable article. Therefore, no compendial requirements for *in vivo* tests of bioavailability have been necessary for the public standard. The practical problem has been the obverse. Dissolution tests are so discriminating for formulation factors, factors that may only sometimes affect bioavailability of immediate-release products, that it is not uncommon for a clinically acceptable article to perform poorly in a typical dissolution test."

"Medically significant cases of bioinequivalence rest mainly on four causal factors: particle size of an active ingredient; magnesium stearate in excess as a lubricant-glidant; coatings, especially shellac; and inadequate disintegrant. Each of these factors is reactive to dissolution testing. There is no known medically significant bioinequivalence problems with articles where 75% of an article is dissolved in water or acid at 37°C in 45 minutes in the official basket or paddle apparatus operated at the usual speed, that is, USP First Case. A majority of monographs have such requirements. USP First Case performance is recognized as a reliable formulation objective in the United States and bears attention worldwide for product development where *in vivo* bioavailability testing is not readily available."

The accumulated knowledge and experience with dissolution tests clearly steer us to examine the question - When are *in vivo* bioequivalence tests not necessary? The USP's experience and literature data does suggest that dissolution tests are sensitive tools for discriminating between products. However, there are a number of instances where these tests appear to fail in assuring bioequivalence.

B. Failure of Dissolution Tests to Assure Bioequivalence

Several reported cases were identified where dissolution tests failed to distinguish between "bioinequivalent" products. These cases may be categorized as: 1) inappropriate test specification, and 2) inappropriate test conditions. Selected cases are presented here to illustrate the key issues with respect to reliability of dissolution tests.

1. Inappropriate Test Specifications?

In this category dissolution tests were able to discriminate between two bioinquivalent products but due to improper specification the two products were judged to be equivalent. These cases suggest that one-point dissolution specification at time 30 minutes or longer are not sufficient to discriminate between some bioinequivalent products and emphasize the need for early sampling.

Case 1: Propantheline bromide tablets (a DESI "AA" drug) on the market were approved based on a dissolution test. The USP dissolution specifications are Not Less Than 75% of the labeled amount is dissolved in 45 minutes, in 500 ml of pH 4.5 buffer using USP 2 apparatus at 50 rpm . Recently the "AA" classification was revoked (changed to "BP" or bio-problem) based on bioequivalence data that demonstrated that one generic product on the market, which met the USP dissolution specification, was not bioequivalent to the innovator product. Figure 1 and 2 (next page) provide an *in vitro - in vivo* comparison for these products (data on file in OGD/CDER/FDA, 9331B.694).

Figure 1 illustrates the significant difference in Cmax between the two products. The 90% CI for Cmax ranged from about 105.3 - 164.2, while 90% CI for AUC (0 to infinity) was 94.6 - 123.6 and for AUC (0-last quantifiable point) 89.1 -130. The current USP specification of 75% in 45 minutes (Figure 2) failed to discriminate between the two products. An early time specification such as Case A dissolution

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Figure 1. PROPANTHELINE BROMIDE BIOEQUIVALENCE DATA (EARLY TIME POINTS ONLY)

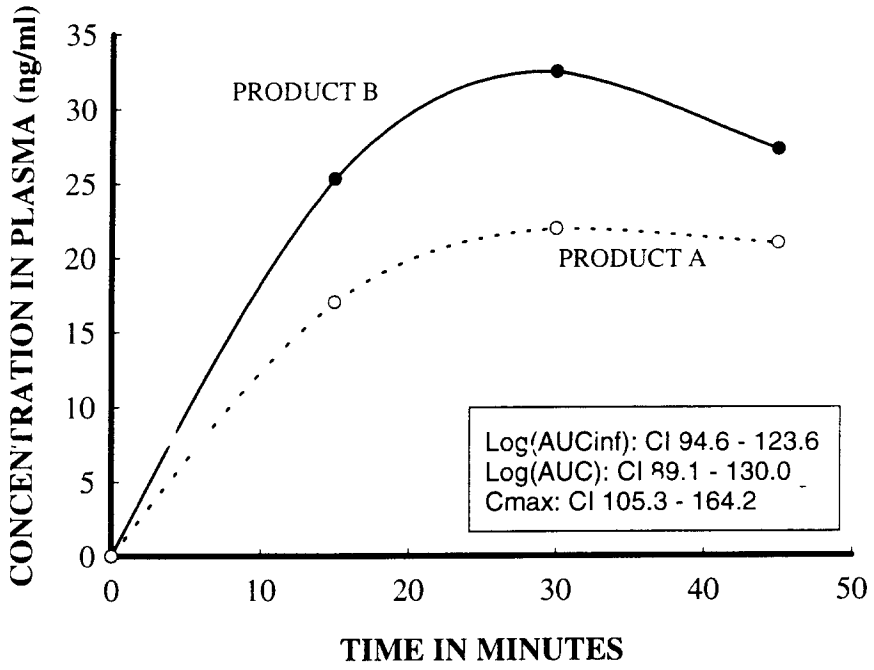
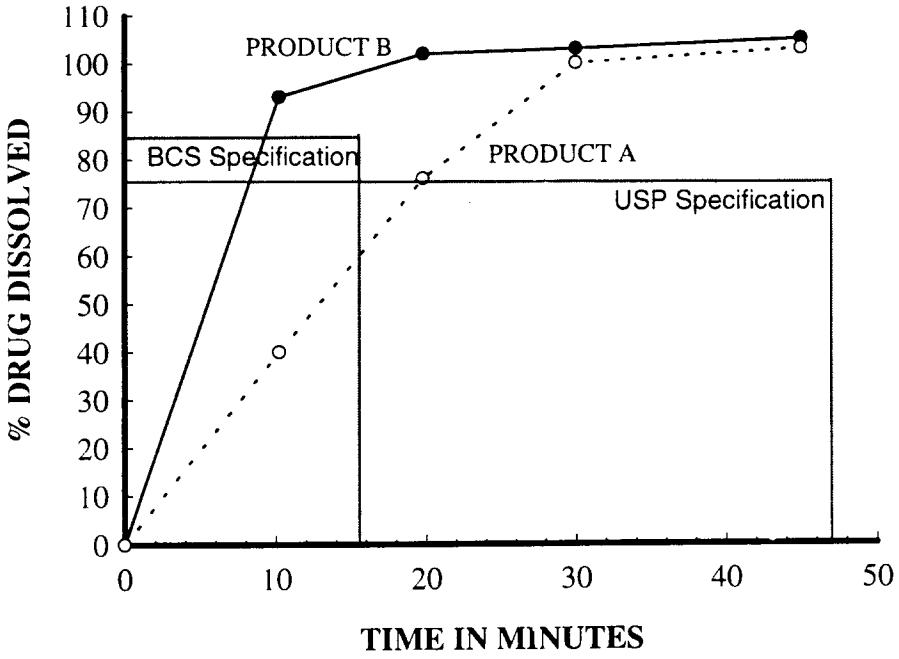


Figure 2. PROPANTHELINE BROMIDE DISSOLUTION IN VITRO



would be more appropriate.

Case 2. Tolmetin Sodium Capsules (V. P. Shah and L. J. Lesko. Drug. Info. J. 29: 885-891, 1995). Dissolution profiles of a test product, which failed to meet the current bioequivalence criteria, and the reference formulations were different at 10 minutes (69% vs. 88%) but nearly identical at 30 minutes (93% vs. 98%). The USP specification is NLT 85% in 30 min., in 900 ml of pH 4.5 phosphate buffer at 50 rpm using USP paddle method. Dissolution data (% dissolved in 10, 20, 30 minutes) and the 90% confidence interval for two studies is summarized in Table 1 below.

	10 min	20 min	30 min	In Vivo CI
Study 1 Test	69	90	93	Cmax: 78-99
Study 1 Ref.	88	96	98	AUC: 94-107
Study 2 Test	66	95	99	Cmax: 84-104
Study 2 Ref.	88	97	98	AUC: 91-101

The test product, in both studies, appears to have lower bioavailability than reference. Study 1 failed to demonstrate bioequivalence, while study 2 (with similar dissolution as study 1 products) conforms to the bioequivalence criteria. This example also suggests that early sampling times better reflect *in vivo* difference between products.

2. Inappropriate Test Conditions?

Dissolution data in a single pH media may not necessary reflect *in vivo* dissolution processes for those drugs that exhibiting sharp decline in solubility/dissolution with increasing pH. *In vitro - in vivo* relationship in such cases may take the form of: 1) two products with similar dissolution *in vitro* exhibiting different *in vivo* pharmacokinetic profiles, or 2) under more extreme situation an inverse relationship may be observed, i.e., product with rapid *in vitro* dissolution may have lower rate of absorption (dissolution "flip-flop"). One case is described below to illustrate this scenario.

This case was brought to the working groups attention by the review staff in the Office of Clinical Pharmacology and Biopharmaceutics (V.

Tammara, R. Harris, and M. Hossain: OCPBReview 25 September 1995). A new drug indicated for amyotropic lateral sclerosis was reformulated during the clinical trials and once again after the clinical trials were completed (to-be-marketed product) and bioequivalence tests were performed (clinical product A vs. clinical product B; clinical product B vs. to-be-marketed product C). Dissolution specification for these products were set at; not less than 80% released in 30 minutes in 0.1 N HCl using USP apparatus 2 at 50 rpm

Product A was prepared by a wet-granulation process and contained small particles of the drug (diameter D50% - 80 microns, D90%- 138 microns). This product disintegrated in about 10-12 minutes and dissolved about 68% in 15 minutes and 99% in 30 minutes.

Product B was prepared by direct compression and contained large particles of the drug (diameter D50%-290 microns, D90%-700 microns). This product disintegrated in about 1 minute and dissolved about 85% in 15 minutes and 95% in 30 minutes.

Bioequivalence study results, 90% confidence interval using A as reference, for AUC were 90 - 101% and for Cmax 62 - 85%. The Cmax values for product B, which *in vitro* dissolved 85% in 15 minutes, were about 30 % lower that for product A.

A closer examination of dissolution data suggests that product A dissolved slowly initially, in comparison to B, due to slow disintegration. However, after 15 minutes the dissolution rate of A is more rapid and at 30 minutes A released more drug than B. It appears in this situation slow disintegration (A) over shadowed slow dissolution as a result of large particle size (B).

Under *in vivo* situation A appears to dissolve more rapidly, why? The drug is highly soluble in 0.1 N HCl but exhibits low solubility (and dissolution) in water or simulated intestinal fluid. Dissolution (and disintegration) in simulated intestinal fluid was very slow and incomplete (only about 45% dissolved in 60 minutes). It is postulated that *in vivo* dissolution occurs part in gastric fluid and part in intestinal fluid, larger drug particles in product B are likely to dissolve at a slow rate compared to smaller particles of product A. Product A, due to

its slow disintegration may be retained in the stomach longer and may dissolve more in gastric fluid, thus resulting in higher drug concentration being presented to the small intestine.

Product C (to-be-marketed) was prepared by direct compression and contained small (similar to A) particles of the drug (diameter D50%-78 microns, D90%- 154 microns). This product dissolved about 77% in 15 minutes and 88% in 30 minutes (disintegration time not reported).

Bioequivalence study results, 90% confidence interval using B as reference, for AUC were 102 - 116% and for Cmax 106 - 144%. The products were judged not bioequivalent with respect to Cmax. The higher Cmax of product C with lower particle size than product B with larger particle size suggests *in vivo* pH conditions are higher (compared to *in vitro*) and smaller particle size products dissolves faster.

Definitive conclusions could not be drawn with this case study. The sponsor also provided a three way crossover study (intravenous, tablet B, tablet B) in which bioequivalence, with respect to Cmax, for product B could not be established with itself. However, this study point to fact that drugs exhibiting very different solubility/dissolution behavior in gastric and intestinal fluids are likely to have highly variable absorption. Large particle size (along with wide distribution of sizes) adds to this variability.

The last case suggests dissolution test, *in vitro*, in one pH media, such as 0.1 N HCl, may not reflect *in vivo* dissolution processes for drugs that exhibit widely different solubility/dissolution in gastric and intestinal fluids.

C. Rapid dissolution *in vitro* is a good indicator of rapid dissolution *in vivo* for Highly Soluble drugs

Analysis of literature, in-house (NDA and ANDA) data and simulation studies strongly suggests that Case A dissolution specification is a good indicator of rapid dissolution *in vivo* for Highly Soluble drugs (that exhibit similar dissolution in both gastric and intestinal fluids). In other words, rapidly dissolving (*in vitro*) solid oral dosage forms of highly soluble drugs are likely to produce drug concentration time profiles in plasma similar to that of an

simple aqueous oral solution.

Some examples of supporting data are presented below:

1. Immediate release tablets of metoprolol tartrate (100 mg)

   Metoprolol tartrate has been extensively studied with respect to BCS and SUPAC-IR issues. It has been classified as an highly soluble and highly permeable drug. The USP dissolution specification are 75% in 30 minutes (USP 1, 100 rpm, 900 ml 0.1 N HCl). A composite of NDA, ANDA, and FDA-UMAB research data is shown in Figures 3 and 4 on the next page.

   Dissolution profiles in Figure 3 are for the innovator (inverted triangles), generic (closed circles) and the research product designed to fail the current dissolution specification. In Figure 4, AUC and Cmax ratios for the Test (solution, generic or experimental products)/Reference (innovator) are plotted as function of Test/Reference ratio of % drug released at 10 minutes *in vitro* (solution = 100%). Note that the data included in this plot are derived from several different bioequivalence trials. These studies are linked by normalizing the values of the various test products to that of the reference product used in each study (different batch/lot).

   Figure 4 demonstrates that dissolution differences *in vitro* are more pronounced which is not reflected in the rate (Cmax) and extent of absorption (AUC). This suggests that dissolution *in vivo* is not rate-limiting and that variability in the rate and extent of absorption are mainly due to gastrointestinal and other physiologic variability. *In vivo* comparison of the rate and the extent of absorption, to establish bioequivalence, for such products may not be necessary.

   All tablet products conform to the current bioequivalence requirements (90% CI for AUC and Cmax ratios within 80 - 125%) and the rate and extent of absorption of metoprolol from a solution was similar to that of the reference product. This suggests that the proposed BCS rapid dissolution specification of 85% in 15 minutes may be conservative.

   Further analysis of this case was carried out using computer simulations to investigate the impact of gastric emptying time and time of 85% dissolution on the Cmax ratio using an oral solution as the reference.

Figure 3: METOPROLOL 100 mg CONVENTIONAL TABLET DISSOLUTION DATA FROM ANDA/FDA-UMAB RESEARCH

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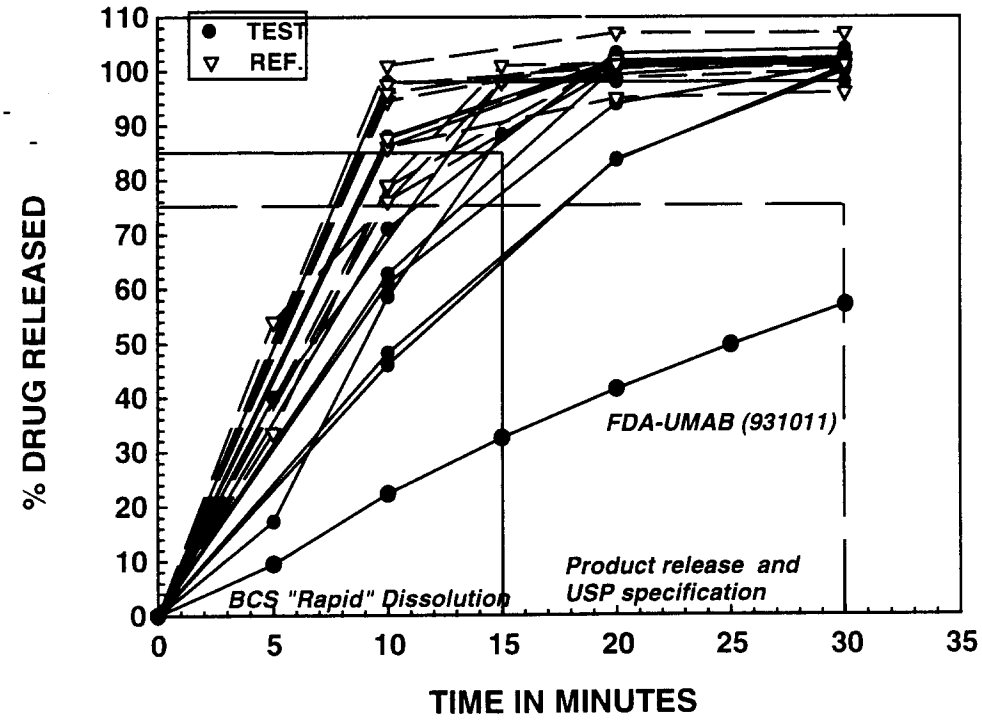

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Figure 4: IN VITRO DISSOLUTION AND BIOEQUIVALENCE RELATIONSHIP METOPROLOL 100 mg CONVENTIONAL TABLET

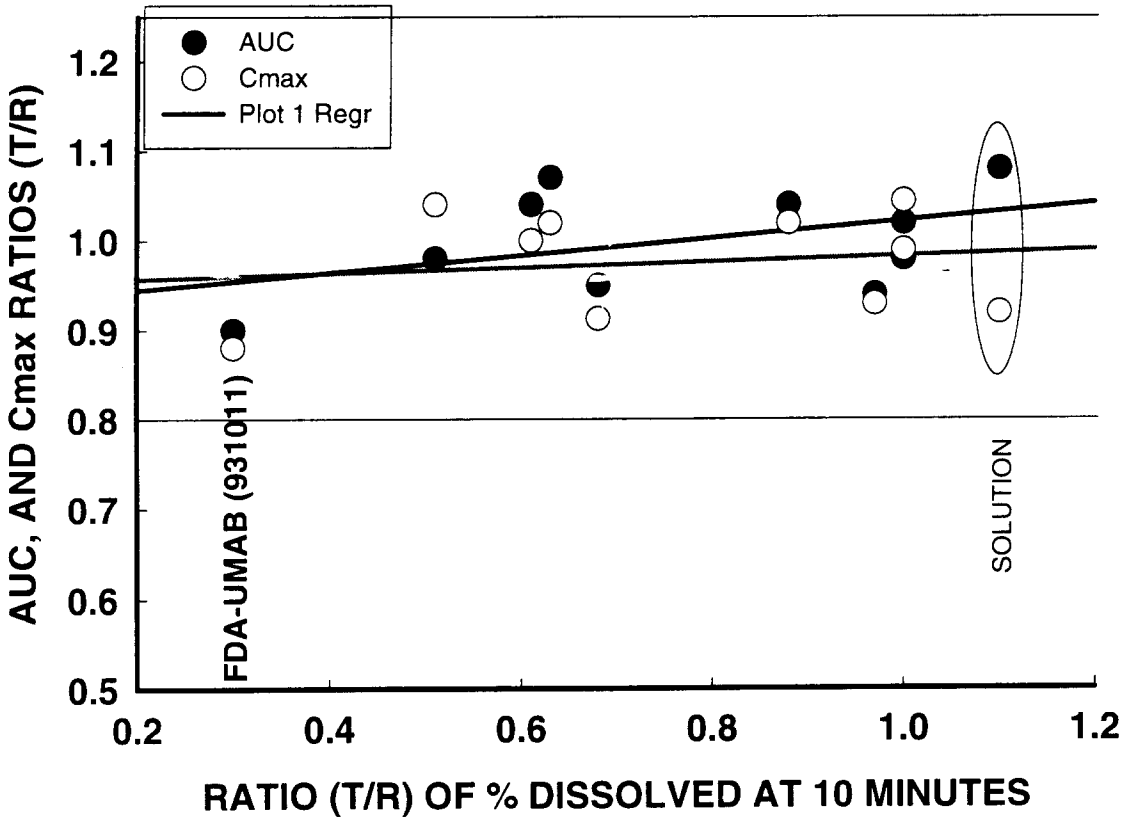

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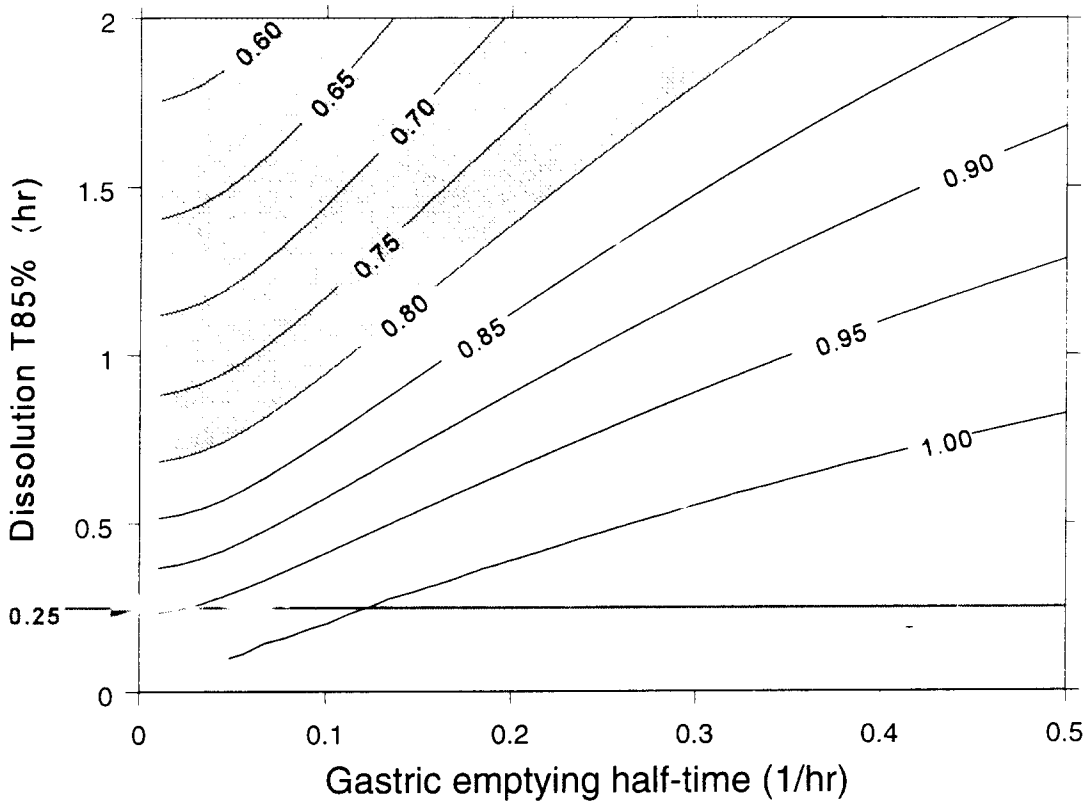
Figure 5.



Simulation were based on computer models constructed from physiological parameters (gastric emptying rates and intestinal transit times) and pharmacokinetic parameters of metoprolol. The results are summarized as an couture plot in Figure 5. Figure 5 shows that the Cmax ratio (Tablet/Solution) of about 1.0 is observed when 85% drug dissolves (*in vivo*) in 0.25 hours (15 minutes) and gastric emptying time is greater than 0.1 hours (6 minutes). For a typical gastric emptying time of 15 minutes the Cmax ratio continues to be above 0.8 even if time to dissolve 85% increases to 1.6 hours.

It is generally assumed that failed bioequivalence studies may not be reported to the Agency. Availability of an experimental formulation deliberately designed to fail current dissolution specification, solution data, and supportive computer simulation study provide sufficient evidence to conclude that metoprolol tartrate tablets that meet the established or proposed dissolution specifications are bioequivalent.

2. Data supporting generalization of the metoprolol conclusion to other highly soluble drugs.

The metoprolol data set is only one example and in the course of this investigation several such examples were identified. In the following table lists additional examples of highly soluble drugs for which relative bioavailability (simple solution vs. tablet) data were available.

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As can be seen from the table below, in 5 submissions 0.1 N HCl was the dissolution media. The only capsule product in the data set used 0.01N HCl as the dissolution media to avoid "gelation" at 0.1N HCl. In one submissions a pH 4.5 media was used to avoid HPLC "peak-splitting."

Dissolution	Relative Bioavailability AUC, Cmax, Tmax Ratios
85% in 30 min (USP 2, 50 rpm, 900 ml, 0.1 N HCl)	1.0, 1.0,1.0
80% in 15 min (USP 2, 500 ml, 0.1 N HCl)	0.93, 0.94, 2.1
85% in 15 min (USP 1, 50 rpm, 500 ml pH 4.5 buffer)	0.85, 0.88,1.0
80% in 30 min (USP 2, 50 rpm, 900 ml, water)	1.0, 1.0, 1.0
80% in 30 min (Capsule) (USP2, 50 rpm, 900 ml, 0.01 N HCl)	0.89, 1.1, 1.0
80% in 30 min (USP 2, 50 rpm, 0.1 N HCl)	1.0, 0.9, 1.6
80% in 15 min (USP 2, 50 rpm, 900 ml, 0.1 N HCl)	0.95, 0.9, 1.0
80% in 20 min (USP 2, 50 rpm, 900 ml, water)	0.82, 0.86, 0.5

When water was used, data was provided to demonstrate similar dissolution in 0.1 N HCl.

The AUC and Cmax ratios (solid/solution) were in 0.82 to 1.1 range suggesting very similar plasma profiles between solid and solution. Differences in Tmax ratios were noted (0.5 to 2.1). The higher ratio of 2.1 did not suggest (in this case) a delay in absorption (Tmax for solution about 0.5 hr and for solid about 1 hr).

Of these eight drug applications, one bioequivalence failure was reported. This was with respect to Cmax failing to meet the upper bound of the 90% CI when comparing multiple units of small strength product with a single unit of the highest strength in a multiple dose study in patients. The test was repeated, now a single dose fasted study,

and bioequivalence was demonstrated for the two treatments. High variability in clearance generally results in higher variability in Cmax during multiple dose administration, especially in patients (variability in volume of distribution). In this submission a total of 11 bioequivalence studies were carried out. All 10 single dose fasting studies demonstrated bioequivalence between rapidly dissolving formulations of this drug. Use of BCS would have eliminated all of these studies.

V. WHAT ADDITIONAL CONSIDERATIONS WOULD BE NECESSARY TO ENSURE CURRENT STANDARDS OF BIOEQUIVALENCE?

Our analysis suggests that for Rapidly Dissolving products of Highly Soluble drugs bioequivalence could be demonstrated based on *in vitro* dissolution profile comparison (in reflecting gastric and intestinal pH). For this class of drugs dissolution tests are generally sensitive to changes in pharmaceutic variables that influence drug dissolution, for example: particle size, crystal habits, formulation/processing variables, and excipient affect on dissolution (mg-stearate, surfactant, drug/excipient ratios, etc.). Although historical data seems to suggest that rapid dissolution specification is an reliable indicator of *in vivo* performance, there continues to be lingering doubt that the current dissolution apparatuses, media volume (500 - 900 ml), rates of stirring (hydrodynamics) may not always reflect *in vivo* processes. Concerns have often been raised in the working group, and elsewhere. that dissolution tests do not provide information on the potential *in vivo* effect of excipients. The working group current thinking is that this approach should be limited to: 1) Highly Permeable, and 2) wide therapeutic index drugs.

High permeability classification assures bioequivalence with respect to extent of absorption between rapidly dissolving products. These drugs are generally considered to be less sensitive to excipients effects on gastrointestinal motility and the current dissolution test methods (especially media volume of 900 ml) may be more appropriate for highly permeable drugs (rapid absorption will maintain "sink" conditions *in vivo* and hence impact dissolution).

With respect to the potential for excipients to alter metabolism, the working group is conducting extensive evaluation of available in house data. Relative bioavailability studies (solution vs. Tablets), bioequivalence studies (differing excipients) for highly metabolized drugs is the focus of our ongoing investigation. The preliminary assesment is that excipients used in conventional tablets/capsule formulations do not impact metabolism. In addition, disintegration, distribution, and dilution effects reduce the likelihood of excipient interactions, if any. Since rapid gastric dissolution

may allow the gastric emptying process to be "rate-limiting," the rate of drug input is not likely to influence metabolism during first-pass Evaluation of NDA data for drugs that are were highly metabolized (some with active metabolites) seems to support this statement. Our analysis seems to suggest that excipients in conventional solid oral products are likely to be inert compared to oral liquid products such as syrups and elixirs. Several examples are availbale which indicate bioequivalence between table and simple solution but not with syrups/elixirs.

Figure 6 and 7 illustrate the type of data being collected by the working group. Figure 6 is a plot of inactive ingredients in bioequivalent verapamil tablets. Figure 7 is a plot of AUC and Cmax ratios for propranolol tablets as a function of *in vitro* dissolution ratios. Three oral liquid (relatively simple solution and two pediatric syrup formulations)are also included.

In summary, the following BCS hypothesis appears to be valid for rapidly dissolving, highly soluble drugs: *two drug products, containing the same drug, will have the same rate and extent of absorption if they produce the same concentration time profile at the intestinal membrane surface (Amidon et. al., 1995).*

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Figure 6: INACTIVE INGREDIENTS IN 5 VERAPAMIL "AB" RATED TABLETS

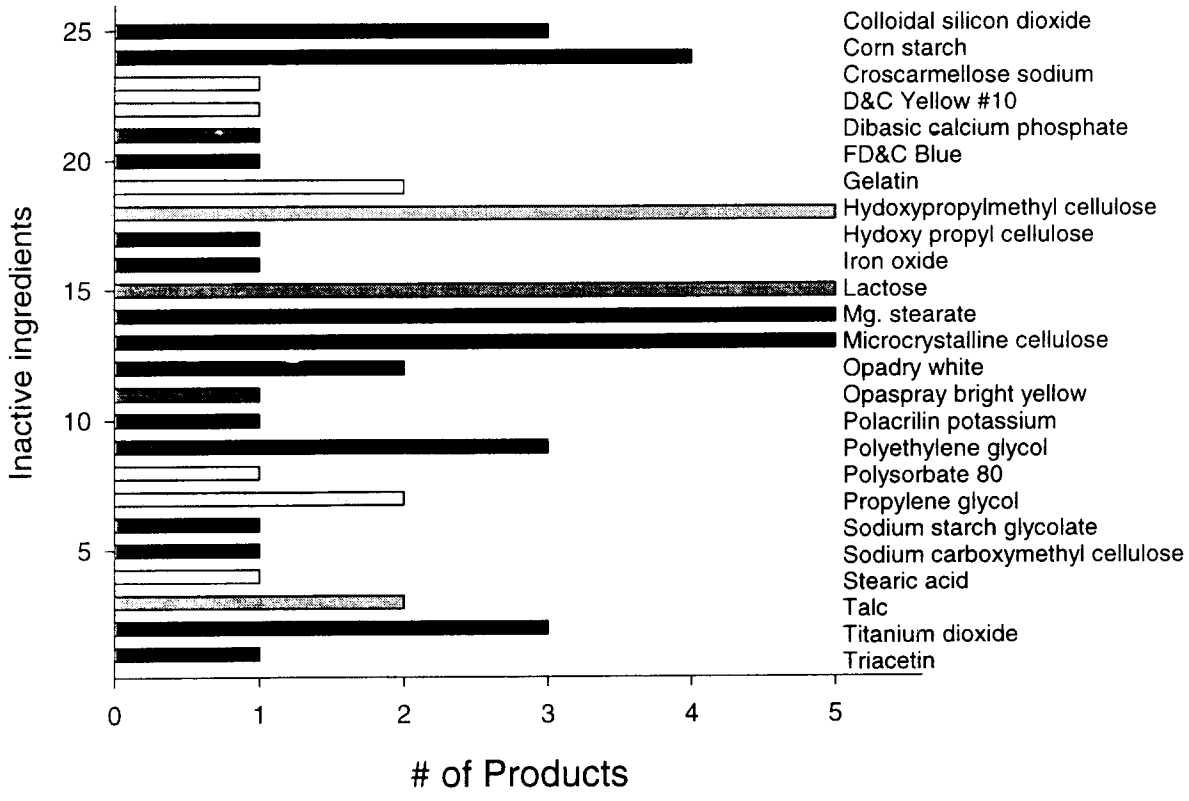
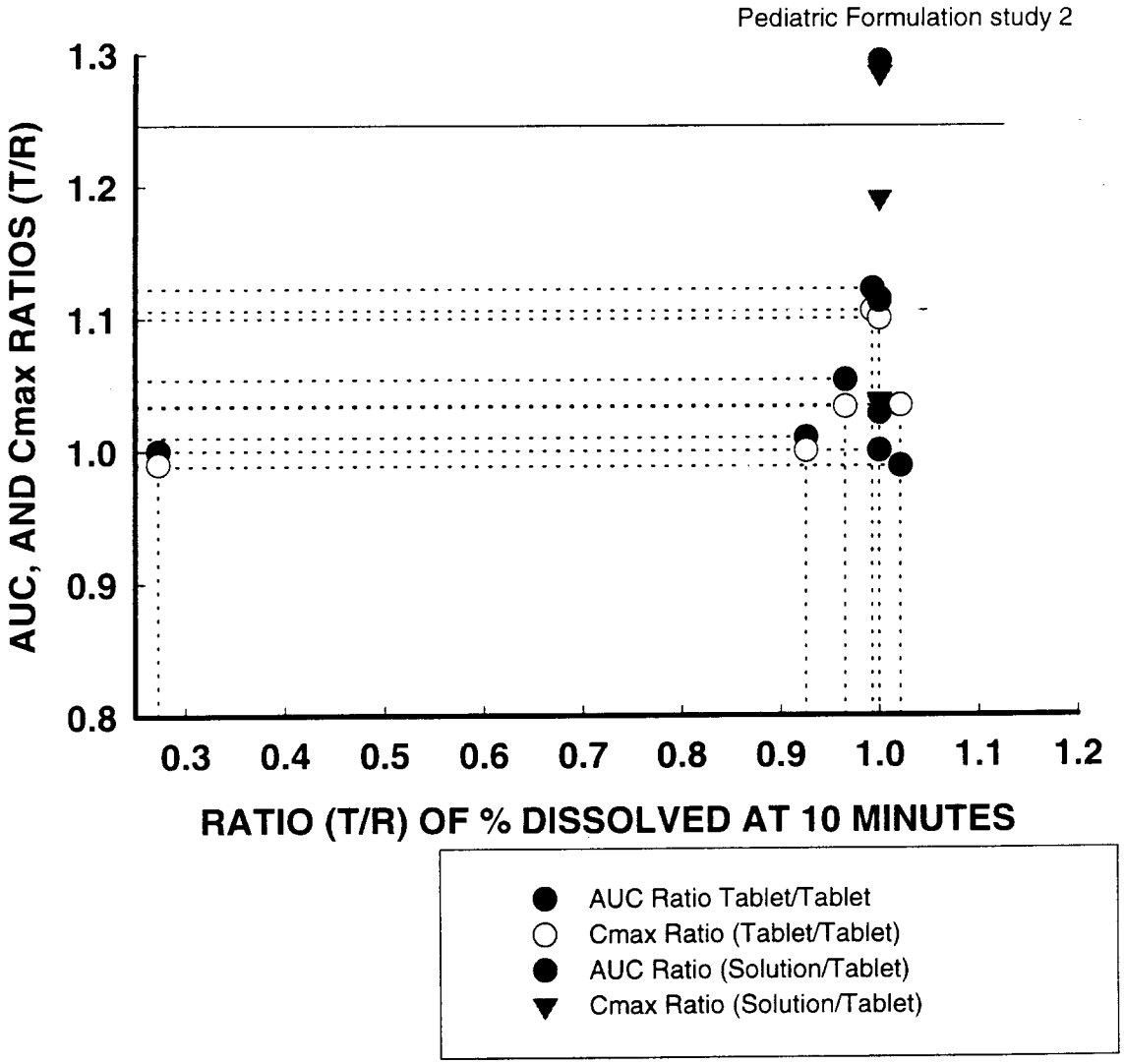


Figure 7: IN VITRO DISSOLUTION AND BIOEQUIVALENCE RELATIONSHIP PROPRANOLOL 80 mg CONVENTIONAL TABLET



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AAPS/ FDA Workshop Report

Bioequivalence of Topical Dermatological Dosage Forms - Methods of Evaluation of Bioequivalence

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The three-day AAPS/FDA workshop on "Bioequivalence of Topical Dermatological Dosage Forms - Methods for Evaluating Bioequivalence," held on September 4-6, 1996 in Bethesda MD was attended by 260 scientists from industry, academia and regulatory authorities. The goals and objectives of the workshop were to:

1. Discuss scientific issues and approaches for bioequivalence (BE) evaluation of topical drug products;

2. Explore principles of dermatopharmacokinetics (DPK) in BE evaluation;

3. Discuss DPK and statistical evaluation for BE of dermatological products; and

4. Review other methodologies applicable to BE demonstrations for topical drug products.

Introduction:

With the exception of topical corticosteroids, the only means an US generic company has to demonstrate bioequivalence of a topical dermatological product to an innovator's product is through comparative clinical trials with a bioequivalence endpoint. An innovator company wishing to replace an already approved post-1962 topical dermatological product with a new formulation exhibiting appreciable compositional changes is also faced with the need to demonstrate bioequivalence using clinical studies, again with the exception of topical corticosteroids. In the specific instance of topical corticosteroids, the demonstrations of BE of two physically alike (e.g., cream versus cream) formulations may now be done using a vasoconstriction protocol, as outlined in FDA Guidance *(Topical Dermatologic Corticosteroids: In Vivo Bioequivalence, June 2, 1995)*, irrespective of whether the product is for an Abbreviated New Drug Application or for updating an existing New

Drug Application.

Clinical efficacy trials aimed at showing the bioequivalence of topical dermatological products are relatively insensitive, time-consuming, and costly. To gain adequate statistical power required to make a clear BE determination, they may require as many as 300 patients. A problem in the topical dermatological area is that no recognized surrogate measures are currently available that might be used in replace of clinical efficacy studies. For drugs where effect is related to concentration in the systemic circulation, the concentrations of a drug and/or active metabolite in blood and/or urine have been viewed as surrogate measures of clinical safety and efficacy For many years, FDA has thus relied on blood and/or urine concentration time curves as a measure ot BE. A key assumption in this approach is that concentrations of a drug in blood are also in equilibrium with concentrations in the target organ/tissue. This workshop explored the possibility that a dermatopharmacokinetic characterization might provide an alternative approach to clinical trials for the determination of BE of topical dermatological products, analogously to the use of concentration-time curves for systemically administered drugs. If accepted, this approach might allow dermatopharmacokinetic studies to replace comparative clinical trials as a means of documenting bioequivalence of selected topical drug products.

The DPK approach includes any measure of drug concentration in the skin, whether directly or indirectly related to the drug's therapeutic action, which can be determined continuously or at least intermittently for a period of time. This may include measurement of either drug concentrations in stratum corneum (SC) over time and/or drug concentrations in serial biopsy samples. To be a useful DPK measure, the time-integrated DPK response must reflect both local safety and efficacy of the topical drug product. One assumption in the DPK approach is that excipients are pharmacologically inactive. In some instances, however, an excipient may exert a direct or an indirect effect, by enhancing or inhibiting drug penetration into the skin. Such effect should be accounted for by DPK methodology through implementation of proper experimental controls (i.e., placebo formulations).

DPK methods should be validated and verifiable. Validation should include all aspects of sampling, e.g., SC stripping and measurement of drug concentration in the SC, or any other analysis. At every critical step in the method development, accuracy, precision, sensitivity, specificity, and other standard aspects of validating an assay methodology should be established. Beyond these obvious checks and balances, all measurements must stand up to rigorous scientific scrutiny.

Before a DPK method is adopted as a basis for BE, it must be shown that differences in DPK capture or reflect significant clinical important differences in formulations. Delivery of a drug into the stratum corneum may not be the only factor in therapeutic efficacy. Other formulation factors may contribute to a topical product's therapeutic efficacy. Therefore, a multi-tiered approach to BE assessment may be a prudent strategy. For instance, one might determine that DPK, e.g., SC concentration-time profiles, are the same in the test and reference product which have qualitatively same composition (Q1), similar physicochemical properties such as pH, viscosity, consistency, residues upon drying, and comparable in vitro release rates.

The most promising DPK method involves assessment of drug concentrations in SC through skin stripping (SS). The SC is the rate limiting barrier for most topically applied drug products. The SC also lies in a direct path to the viable tissues of the skin where many diseases of the skin manifest themselves, making either the SC and/or the viable tissues below the site where most drugs must be delivered. Therefore, the concentration of a topically applied drug in the SC for therapeutic efficacy may theoretically be expected to be related to its concentrations in viable tissues such as the epidermis and dermis. Because dermatological products deliver the drug locally and close to the intended site of action in the skin, DPK measurement may provide a means of assessing BE of two dermatological drug products. Two formulations that produce comparable SC drug concentration-time curves may be bioequivalent just as two oral formulations are judged bioequivalent if they produce comparable plasma concentration-time curves. The successful application of DPK thus rests on the assumption that SC concentration-time curves are directly related to concentration-time curves of the active drug substance in the epidermis and dermis.

The results of preliminary investigations indicate that SS allows assessments of both drug uptake into and clearance from the SC. Assessments based on common pharmacokinetic metrics, such as area under the curve (AUC), maximum concentration (Cmax), and time to maximum concentration (Tmax) in SC, have been demonstrated. It should be pointed out that although the DPK metrics are similar to th[illegible] obtained from plasma based traditional BE studies, (AUC, Cmax, Tmax), the interpretation of DPK is different. SC parameters reflect the driving concentrations that deliver the drug to the epidermis or dermis (site of action). Although these results are useful, actual methodological details for a DPK study involving SS would necessarily be product specific. Because the formulation is removed prior to determining a drug's concentration from the SC, the Cmax obtained by this procedure is not functionally equivalent to Cmax of a drug following oral administration. Subjects employed in a DPK study would ordinarily be individuals exhibiting normal skin, similar to the use of normal healthy subjects in BE determination of oral drug products. Employing patients with diseased skin may introduce additional variability in drug penetration into SC, although it might suggest a subject by formulation interaction. Neither in vitro diffusion cell studies with human skin sections nor in vivo work performed on animals would be acceptable as the sole criteria for BE assessment of topical products. Both cadaver skin and animal skin are known to differ significantly in their physiological properties from normal human skin, and thus both are inappropriate for BE assessment. For this reason, DPK measurements obtained by harvesting SC from cadaver, animal, or ex-vivo human skin (the latter by surgical harvesting) will deviate in important ways from those obtained from live human skin. An important asset of the stripping DPK procedure is that the test and reference formulations can usually be applied to a given subject at the same time, allowing each subject to become his or her own control. Adequate sampling from a sufficient number of stripping sites would be required to characterize drug uptake into and clearance from the SC. Based on preliminary investigations, all the conditions important in the application of the DPK approach in assessing BE seemed manageable.

Specific Considerations/Concerns with the Skin Stripping Method:

Skin is known to be a highly variable organ in its chemical and physical properties. It exhibits

appreciable site-specific inter-intra subject permeability differences in its barrier function properties. Therefore, considerable thought and attention must be given to validation of the SS method and experimental design when conducting a BE study based on measurements of drug concentration in SC. These considerations are discussed in the following paragraphs.

Skin stripping is a technique sensitive operation. Each technician's ability to remove, reproducibly and carefully, the SC should be demonstrated. Appropriate tape or tape discs used for the purpose of SS should be demonstrated to have uniform adhesive properties and to have reproducible properties relative to SC removal. Validated in this regard can be achieved in terms of reproducible amount of skin (weights) or protein contents recovered from test sites. Within subject variability in SS recoveries may be minimized during the experiment through randomization of the product applications to specific sites.

A pilot study should be performed to optimize the sampling scheme for each investigation using a reference product. In the experimental design, both test and reference formulations should be applied simultaneously to each subject at separate, randomized sites for each paired treatment duration. As the next best alternative, crossover comparisons could be made at the selected times for sampling within a fixed study group. Two to five mg of a formulation should be applied to each square centimeter of designated area. As currently practiced and as envisioned for the future, sites on the volar surface of both forearms should be designated for the applications. Care should be taken to avoid positions too close to the wrists or the elbows due to differences in vasculature along the forearm.

Both drug uptake into and elimination from SC should be measured. The elimination phase is characterized after removing all residual formulation from the skin site by swab or other treatment and after taking one or two SS collections to further assure that no formulation (drug) residue remains on the surface. The swabbing of the treated skin site or other removal procedure(s) requires validation, since swabbing with solvents may affect the percutaneous penetration of the drug. A minimum of three time points for drug uptake and three to four time points for drug elimination from SC should be charted in terms of concentration for each phase.

Other experimental concerns with the procedure that needs to be addressed in the course of developing and implementing a DPK stripping study include the method of preparation of the skin site (e.g., a volar forearm) prior to applying any formulation. If the formulations are applied too close to one another, cross contamination between neighboring sites of application may occur and may affect the results. Preliminary work shows that a template or equivalent device should be used to block out each application area and assure consistent removal of stratum corneum from the exact treatment area. Dose consistency in terms of the amount applied per each designated area (square cm) should also be validated. To assure usefulness of the SS methodology, a dose proportionality study should be considered to assure that linearity exists between the amount of drug applied to the SC and the amount of drug collected via SS. Early studies suggest that dose proportionality is linear for standard concentrations of selected topical drugs.

Validating the surrogacy of DPK might be achieved either by developing suitable correlations with pharmacodynamic measurements. Existing data with corticosteroids suggest a relationship between the pharmacodynamic vasoconstrictor response and amounts of these drugs recovered through stripping. In vitro antiviral and antifungal bioactivity has also been shown to correlate with skin stripping data. Based on these preliminary findings, the DPK approach seems to offer a valid means by which to determine the BE of topical dermatological products. Although a need exists to unequivocally establish the linkage between clinical efficacy and the DPK measurements, correlations to establish this linkage will be difficult, if not impossible, because of the variability in clinical response to topical products. The simplicity of the DPK experimental design and procedure needs to be balanced against the need to avoid biases in the comparison of the test and reference formulations. Properly deployed, the stripping method promises to be less expensive than clinical studies, yet definitive and conclusive.

Protocol Outline for A Skin Stripping BE Study:

The following outlines an example of procedural steps involved in the SS methodology. In general, two studies (1) pilot study and (2) pivotal BE study should be carried out. The pilot study should be used to validate the methodology and to optimize the sampling scheme. The BE study should be used to demonstrate the BE between the test and reference products.

- Apply the test and/or reference drug products concurrently at multiple sites.
- After an appropriate interval, remove the excess drug (one site) by wiping three times lightly with a tissue or cotton swab. Appropriate time duration should be determined in the pilot study. For example, it can be 0.25, 0.50, 1.0, 3.0 hours.
- Apply the adhesive tape (e.g., Transpore tape from 3M Company, St. Paul, Minnesota or D-Squame tape from Cuderm Corporation, Dallas, Texas) with uniform pressure, remove and discard the first stripping, as this represents unabsorbed drug on the skin surface.

  Repeat the procedure if one tape strip is not sufficient to remove all excess/unabsorbed drug from the skin surface.
- Apply (at the same site), remove and collect nine successive tape strips (from the same site).

  Use more than nine skin strippings, if necessary to collect majority of the drug in SC.
- Repeat the procedure of removing excess drug and SS for each site at other designated time points.
- Extract the drug from combined nine SS (2-10 in this example) and determine the concentration using an appropriate validated analytical method.
- Express the results as amount of drug per square cm area of the adhesive tape (e.g., ng/sq cm)
- The above procedure will provide information about the drug uptake in SC.
- To determine a drug elimination phase from SC, apply the drug product (test and/or reference) concurrently at multiple sites (e.g., four sites), allow sufficient exposure period until it reaches apparent steady-state level (in this example, it is three hours); remove excess drug from the skin surface as described above, including the first SS. After predetermined time intervals, collect skin samples using nine (in this example) successive tape strips, and analyze them for drug content. The intervals in this case can be 1, 3, 5 and 21 hours after drug removal.

Other Techniques for Sampling Skin:

Other methods to determine the drug concentration profile in the local tissues of the skin following its topical application include surface biopsy, surface scraping, sebum collection, sampling of hair and/or nail, collecting fluid from suction blisters, or excising the epidermal roofs of such blisters, shave biopsy, and punch biopsy. Assessing the concentration of systemic deposition of drug substances in hair shafts and/or nail clippings might have its purpose in forensic medicine, but appears to have little utility in comparative drug delivery investigations. Of the other techniques, carefully sectioned horizontal punch biopsies have provided useful information concerning the gradients of drugs which are established across the skin's various strata. Work has also been performed in terms of charting drug delivery using suction blisters. However, because of scarring, pain and other drawbacks, neither of these techniques appears to offer the same possibilities as SS. Like SS, biopsies and the other mentioned procedures also have to be carefully validated for the specific application.

Additional Promising Approaches to Determining BE:

Certain other procedures may prove useful for specific drugs. For example, pharmacodynamic approaches have already proved used to document BE of selected topical corticosteroid drug products. This approach is based on the well-known skin blanching effects of corticosteroids. Another pharmacodynamic endpoint that may prove useful is the increase in TEWL and desquamation rate of the SC following the application of retinoic acid. Preliminary data demonstrate TEWL and SC desquamation increase in proportion to a topical retinoic acid dose. This happens over the course of several days, and the phenomenon is readily followed with respect to time.

Another tool which may prove useful is in vitro permeation assessment. Available evidence suggests that rate of permeation of drugs from their formulations and the temporal profiles of such permeation may be similar as long as the formulations themselves are the same. Where differences in clinical endpoints have been shown to exist, permeation rates have been shown to vary in kind. These findings, however, should be regarded now as investigational in nature. The methodology takes considerable skill and experience to work. All comparisons must be performed with skin membranes cut from the same section of unblemished excised skin. The skin sections must also be checked for leaks prior to applying the formulations. Applications of formulations to excised skin should approximate clinical application in the in vivo setting. Considerable work also shows that while in vitro permeation technique is not now suitable for BE assessment of two products, it might be useful for drug developmental purposes.

Confocal laser scanning microscopy appears to have future promise for DPK assessments. This tool allows an investigator to focus a beam to a given depth within a tissue and to take a reading of the concentration of an agent at the level of focus. Since the individual measurement is near instantaneous, a concentration profile can be generated following topical application of a drug product. To date the work done have been based on sectioned buccal mucosa and on fluorescence markers, but the method may possibly be extended to cornified epithelia and UV-absorbers in time. Elimination of interference in UV-absorption by endogenous substances may be difficult.

Another promising technique currently under investigation is microdialysis. In this methodology, a drug or other agent applied to the skin is detected and its concentration measured via an invasive probe placed at the dermis level. Because only trace amounts of compounds are collected, a high degree of analytical sensitivity is required. Exact positioning of the probe is difficult to accomplish, and reading from one placement to the next must therefore be taken at different depths. Nevertheless, since such probes can be left in place for multiple days, the possibility exists that a single probe can be used to study the delivery of drug from the test and reference formulations by applying these sequentially. Much work is needed on this method to establish its value in documenting BE.

SUPAC-SS:

The FDA guidance for "Nonsterile Semisolid Dosage Forms, Scale-Up and Post Approval Changes: Chemistry, Manufacturing and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation" (SUPAC-SS) is intended to lower the regulatory burden while assuring the safety and effectiveness of these products under certain post-approval changes. It defines three levels of changes, (1,2,3), tests and filing documentation associated with each level of change. Level 1 changes are those that are unlikely to have any detectable impact on formulation quality and performance; level 2 changes are those that could have a significant impact on formulation quality and performance; and level 3 changes are those that are likely to have a significant impact on formulation quality and performance. The SUPAC-SS guidance allows certain changes in the category of components and composition, manufacturing site, manufacturing process and equipment and scale of manufacturing. Changes in approved formulations graded as level 1 will require reporting in the annual report only. The manufacturer will have to show that in vitro release rates of pre-change and post-change formulations are the same for changes designated as level 2 changes. For changes designated as level 3 change in component and composition, bioequivalence between the pre-change formulation and the post-change formulation or between the post-change test and reference product has to be demonstrated. If the product is a corticosteroid, vasoconstriction comparability is all that needs to be established. In a recently held workshop on September 8-10, 1997 on *Assessment of value and application of in vitro testing of topical dermatological drug products*, it was concluded that in vitro release test is an appropriate tool to assess product sameness under SUPAC related changes for semi-solid dosage forms.

Conclusions

Skin stripping is a specific dermatopharmacokinetic method that assesses drug concentration in stratum corneum as a function of time. The method involves application of test and reference product to multiple sites on the forearm with each site yielding a single drug concentration. Both drug uptake and elimination phases of dermatopharmacokinetic (DPK) profile should be evaluated to determine traditional metrics, i.e., AUC, Cmax, and Tmax.

Two general views were expressed at the Workshop on the potential universality of skin stripping technique across different therapeutic classes. Some expressed the opinion that because only SC concentrations are assessed, then only diseases in which the SC is the site of action are amenable, i.e.,

antifungal class of topical dermatological drugs. Others noted that regardless of how far through the skin layers, stratum corneum - epidermis - dermis, the drug needs to penetrate, it needs to pass through the SC first before reaching deeper skin layers. Because the SC is the rate limiting barrier for drug penetration into the skin, concentration in the SC may provide meaningful information for comparative evaluation of topical dosage forms.

With proper validation, DPK is expected to be a viable method for BE evaluation of topical dermatological drug products. In addition to DPK data for BE, qualitatively same formulation of test and reference product, an in vitro drug release rate data, and, in certain instances, a comparative pharmacodynamic evaluation may be helpful in establishing the BE of the test to the reference product. A combination of these techniques may provide sufficient information for use of DPK in BE assessment in lieu of clinical trials. This will allow industry to pursue the development of safe and effective generic topical products in a scientifically and regulatorily sound manner.

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