M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: **July 21, 1997**

FROM: **Rita Hassall**

TO: **Doug Sporn**

SUBJECT: **History of Narrow Therapeutic Index (NTI) Drug Designation**

You requested that I research our files for the background of the listing of "narrow therapeutic index" drugs. It is apparent that the list was considered a starting point in an effort to assess certain potential problem products about the time of the generic drug scandal. Also, it is clear from the information available that the initial listing was not based in 21 CFR 320.33 which defines "narrow therapeutic ratio" as one of several criteria to assess actual or potential bioequivalence problems. **It is also important to note that, according to a 1990 HHS press release, tests on 429 batches of 24 narrow therapeutic generic and brand name drugs showed virtually all met applicable standards of purity and quality. There was only one of the 24 products that showed a potential problem.**

HISTORY

In the late 1980's several problems were discovered in the generic review process and questionable data was found to have been submitted in some Abbreviated New Drug Applications (ANDA). For example, some data was found during an FDA inspection of one contract laboratory which did studies for both generic and innovator firms that showed evidence of "such practices as manipulation of control data, selective reporting of sample values, improper calculation of results, etc." Congressman Dingell asked for a plan from FDA to determine the validity of studies conducted in that laboratory. In addition, prior to and during the discovery of the generic drug problems, there were reports in the literature suggesting that generic substitution was not advised in all drug categories. Anti-convulsants, certain cardiovascular products, and theophylline were examples of products for which generic substitution was questioned. Those who expressed this opinion alleged the generic approval process was not adequate to fully assess potential differences in products which, because of the necessity of maintaining a narrow blood level range, might manifest as either clinical ineffectiveness or toxicity.

A November 13, 1989, memo from Dr. B. Burlington to Dr. Carl Peck and Mr. Dan Michels said the Commissioner had expressed concern that drugs with a "narrow therapeutic range" were not targeted in the list of top 30 drugs screened through the field sample acquisition and assay program (see below) developed to assess the extent of the generic drug scandal. After some additional explanation, Dr. Burlington said that Dr. Dighe had been asked to develop a list of multi-source drugs that would not receive bioequivalence waivers, for which there was information on the therapeutic range in the literature and for which that range was relatively narrow. The list was circulated to ODE and Division Directors (now ORM Divisions) for comment and concurrence. He added in the memo, "while we may update and refine this list, given the understanding that it is not considered definitive, it nonetheless seems like a reasonable starting place for this purpose."

A parallel Center evaluation was also undertaken about the same time to identify products that were considered likely to be hard to manufacture in a consistent fashion by a new company. I was unable to locate a complete list of such drugs. However, accompanying the categories of products which might be difficult to make, there were examples given which included some of the products listed as having a narrow therapeutic range.

The trade press reported on November 19, 1989, a nationwide testing program was begun for sampling and analysis of 24 identified narrow therapeutic index (NTI) products as a part of the agency's effort to assess and "clean up" problems in the generic industry. The focus on narrow therapeutic range drugs was due to concern that quality failure in this area might represent a public safety hazard.

In a November 30, 1989 memorandum thanking the Division Directors who had commented on the list, Dr. Burlington noted "we expect this to be adequate for the purpose for which it was intended," i.e., reevaluation of those products available from multiple sources with ANDA's that also had bioequivalence studies performed, where there is special reason to be concerned that deviation from the specifications for the generic product and potential change in bioavailability could cause problems clinically. A copy of the list as published at that time is attached to this memorandum along with a listing of a current version of the list appearing in an FDA publication.

Dr. Burlington's memo mentions that Drs. Park and Pradhan in the Division of Bioequivalence (DBE) had prepared a more comprehensive list of those products for which there is information available to indicate a probable narrow therapeutic range based on reports in the literature and on information in standard texts. Copies of that list are in the file and it is a much longer list than the one produced by Dr. Burlington. It also provides therapeutic plasma levels and toxic plasma levels for most of the products. **There is no indication that list was ever used for anything.**

A September 12, 1990 HHS press release noted that "based on tests of more than 400 drug samples, it has found that virtually all "narrow therapeutic range" generic and brand name drugs meet applicable standards of purity and quality". The specific samples were of 24 generic and brand name versions of drugs for which quality specifications are

generally considered to be critical. The samples were tested for potency and other USP and/or ANDA/NDA quality specifications, including (where appropriate) dissolution and content uniformity.

The only exceptions to meeting the required quality standards were five batches of aminophylline tablets from two manufacturers which were found to contain incorrect amounts of a necessary stabilizing ingredient. Samples of aminophylline from four other manufacturers were tested and found to be satisfactory. The deficiency identified did not pose a health hazard but the lots were recalled and the firms eliminated the problems that caused the five lots to fail.

The October 1, 1990 letter from J. Benson to the Commonwealth of Pennsylvania noted:

> FDA does not formally designate narrow therapeutic range drugs either in the publication "Approved Drug Products with Therapeutic Equivalence Evaluations" or elsewhere. FDA has developed working draft lists of drugs it believes may have narrow therapeutic range but we have no plans to develop a formal list. We have used these lists for various internal purposes such as for selecting products to include in our recently completed market product survey.

He added that because of FDA's strict bioequivalency standards, the agency believes that drugs do not fall into discreet groups that would allow one to consider narrow range drugs as being clearly different from other drugs from a substitution point of view.

It is clear from this file that the list put forth at that time was not based in 21 CFR 320.33 which lists criteria and evidence to assess actual or potential bioequivalence problems. The regulation says the FDA will consider the "the following factors, when supported by well-documented evidence, to identify specific pharmaceutical equivalents and pharmaceutical alternatives that are not or may not be bioequivalent drug products." One of the factors listed is if there is evidence that the drug product exhibits a narrow therapeutic RATIO. There are others factors which might be considered listed in the cited regulation, also.

The first list appeared in an HHS press release in 1990 as a listing of the products examined. The second list is the list of Narrow Therapeutic Range Drugs that is contained in the SUPAC-IR document dated November, 1995. I was unable to determine why the original list was modified.

Aminophylline Tablets	Aminophylline Tablets, ER Tablets
Carbamazepine Tablets	Carbamazepine Tablets, Oral Suspension
Clindamycin Capsules	Clindamycin Hydrochloride Capsules
Clonidine Tablets	Clonidine Hydrochloride Tablets
	Clonidine Transdermal Patches
Diphylline Tablets	Dyphylline Tablets
Disopyramide Capsules	Disopyramide Phosphate Capsules, ER Capsules
Ethinyl estradiol Tablets	Ethinyl Estradiol/Progestin Oral Contraceptive Tablets
Guanethidine Tablets	Guanethidine Sulfate Tablets
Isoetharine Inhaler	Isoetharine Mesylate Inhalation Aerosol
Isoproterenol Inhaler	
	Isoproterenol Sulfate Tablets
Lithium Carbonate Capsules; Tablets	Lithium Carbonate Capsules, Tablets, ER Tablets
Metaproterenol Tablets	Metaproterenol Sulfate Tablets
Minoxidil Tablets	Minoxidil Tablets
Oxtriphylline Tablets	Oxtriphylline Tablets, DR Tablets, ER Tablets
Phenytoin Capsules and Tablets	Phenytoin, Sodium Capsules (Prompt or Extended), Oral Suspension
Prazosin Capsules	Prazosin Hydrochloride Capsules
Primidone Tablets	Primidone Tablets, Oral Suspension
Procainamide HCL Capsules Tablets	Procainamide Hydrochloride, Capsules, Tablets, ER Tablets
Quinidine Gluconate Tablets	Quinidine Gluconate Tablets, ER Tablets
Quinidine Sulfate Capsules; Tablets	Quinidine Sulfate Capsules, Tablets, ER Tablets
Theophylline Capsules and Tablets	Theophylline Capsules, ER Capsules, Tablets, ER Tablets
Valproic Acid Capsules	Valproic Acid Capsules
Valproate Sodium Syrup	Valproic Acid Syrup
	Divalproex, Sodium DR Capsules, DR Tablets
Warfarin Sodium Tablets	Warfarin, Sodium Tablets

April 16, 1997

National Association of Boards of Pharmacy
Attention: Mr. Carmen A. Catizone
Executive Director/Secretary
700 Busse Highway
Park Ridge, IL 60068

Dear Mr. Catizone:

I am responding to your letter of March 18, 1997, to Mr. Douglas Sporn, Director, Office of Generic Drugs (OGD), that inquires about the position of the Food and Drug Administration (FDA) on narrow therapeutic index (NTI) drugs, and their substitutability. As you are aware, in the process of evaluating applications for generic drugs, the FDA makes recommendations via a document entitled *Approved Drug Products with Therapeutic Equivalence Ratings* (the *Orange Book*) that approved multiple source drug products, including NTI drugs, are therapeutically equivalent. This term indicates that they can be substituted with the full expectation by the patient and physician that they will have the same clinical effect and safety profile as the innovator drug.

Before I respond to your four specific questions, I would like to briefly describe some important historical events and decisions that pertain to these questions and the FDA's current position. In a 1979 Federal Register notice, the Agency proposed the development of the *Orange Book* and definition of the criteria to be used by FDA in evaluating therapeutic equivalence. The *Orange Book* and the therapeutic equivalence criteria were finalized in 1980. Since then this publication has proven to be a constructive and important resource for all parties involved in the health-care delivery system, including, for example, manufacturers, physicians, pharmacists, hospitals, and federal and state agencies.

In 1986, FDA conducted a three-day public hearing to provide a forum to discuss the Agency's method of determining bioequivalence of generic drugs for immediate release, solid oral dosage forms. In addition to its use for generic products, the FDA method of determining bioequivalence is also used by innovator firms when their drug products are reformulated or certain other manufacturing changes are made. The goal of the workshop was to elicit data on claimed problems with the method of determination of bioequivalence. There were fifty speakers and over 800 participants. The meeting was chaired by former Commissioner Frank Young, M.D. In addition, three outside eminent scientists participated as expert consultants. The agenda of the hearing consisted of five topics that were broken down into sub-topics. One of the topics, the "Design of Bioequivalence Studies" included a sub-topic relevant to the issues you have raised: "Should FDA Develop Individual Criteria for Each Drug or Class of Drugs?"

Commissioner Young, subsequently, appointed a Task Force to analyze the issues raised at the hearing and make recommendations for actions the Agency should take concerning its

bioequivalence program. Among the task force conclusions was: "FDA is prepared to use a more stringent criterion if differences of this size [e.g., the 90% confidence interval for the ratio of the test product mean AUC to that of the innovator must lie entirely within the interval (0.80-1.20) (now 0.80 to 1.25 on log transformed data)] are shown to be clinically significant." No clinical data has been submitted to the Agency in the ten plus years since the hearing that would warrant the Agency narrowing the present confidence interval of 0.80 to 1.25 on any drug or class of drugs. If a tighter statistical interval was used for NTI drugs, it is even possible that if an innovator firm reformulated its product, the product might not be bioequivalent to itself.

Subsequent to the hearing, two relevant studies were conducted on a drug thought to have a narrow therapeutic index, carbamazepine. These were done at the University of Tennessee and at Wake Forest University. Neither study could demonstrate problems with bioequivalence between innovator and generic products nor a difference in the efficacy or safety profiles.

Using the FDA bioequivalence criteria, the first 224 post-1962 drugs approved over the two year period after the Waxman Hatch amendments were passed, including some NTI drugs, had an observed mean bioavailability difference between the generic and innovator products of only 3.5%.

The above background is necessary to fully understand my responses to your four questions as follows:

1. **Is there an official FDA or government agency category of narrow therapeutic index drugs?**

   Currently, the NTI designation is not a formal designation by the FDA. A list of so called narrow therapeutic index drugs was prepared by the Center for Drug Evaluation and Research in order to assist the FDA District Offices in their testing program that came about because of problems with the generic industry in the late 1980's. This working list of drugs is also currently being used as one of the factors to determine if an *in vivo* study or other data are needed to determine the impact of **post-approval** changes in the manufacture of a drug product. The list is in the "Scale-Up and Post-Approval Changes for Intermediate Release Products" (SUPAC-IR) guidance document and is used in conjunction with other factors such as drug permeability and solubility to assess the impact of changes made after approval.

   In 1990, the Acting Commissioner of the Food and Drug Administration, in a letter to the Pennsylvania Department of Health said that the FDA does not formally designate narrow therapeutic index drugs either in the publication "Approved Drug Products with Therapeutic Equivalence Evaluations" or elsewhere.

2. **Do you plan to develop a formal list of "NTI" drugs?**

   Narrow therapeutic **INDEX** is a term of art which has come into current use, including use by the agency. The term, more correctly, is narrow therapeutic ratio. Narrow therapeutic

ratio is defined in the regulations at 21 CFR 320.33(c). This subsection deals with criteria and evidence to assess actual or potential bioequivalence problems. This ratio, as defined in the regulation, is one of a number of factors to be considered is assessing these actual or potential problems. No listing of drugs is included in this regulation. At some point in the future, appropriate guidance could be developed based on this criterion to provide guidance to assess bioequivalence, potentially including a listing of drug products.

According to 21 CFR 320.33(c), narrow therapeutic ratio is defined as follows:

a. There is less than a 2-fold difference in median lethal dose (LD50) and median effective dose (ED50) values, or
b. There is less than a 2-fold difference in the minimum toxic concentrations and minimum effective concentrations in the blood, and
c. Safe and effective use of the drug products require careful titration and patient monitoring.

3. Is there a direct relationship between narrow therapeutic index and substitutability?

FDA recognizes the scientific concept that drugs differ in their therapeutic range. However, because of FDA's strict bioequivalence criteria, we believe that drugs do not fall into discrete groups that would allow one to consider NTI drugs as being clearly different from other drugs for purposes of therapeutic substitution. No data has been submitted to FDA to cause any revision in the bioequivalence criteria for these products. Therefore, there has been no scientific or regulatory purpose at this time for the agency to create and implement a mechanism to designate some products as being narrow therapeutic index products, or to define any other specific group of products. The FDA is now considering a different approach to documenting bioequivalence. This approach is termed 'individual bioequivalence.'

This approach allows the possibility of scaling the bioequivalence 'goalposts' (e.g., the boundary of 80 - 125%) based on variability of the reference listed (innovator) drug. One possible aspect of the approach may be that for certain drug products, which might be termed narrow therapeutic index or ratio drugs, the goalposts would always be scaled to the variability of the reference listed drug. This might have the effect of widening or narrowing the goalposts, depending on the performance of the reference listed drug. Examination of the new approach is based on improvements in our scientific understanding of how to document bioequivalence. It is not based on any information to suggest that any drugs in the marketplace, either innovator or generic, narrow therapeutic range or not, are not performing as they should and as designated in the *Orange Book*.

4. Are there any "A" rated drugs in the publication "Approved Drug Products with Therapeutic Equivalence Evaluations" that have a narrow therapeutic index?

Yes, there are a number of "A" rated drugs products in the Orange Book that could be considered "NTI" drugs, e.g., carbamazepine and theophylline.

FDA is aware of the NTI initiatives that are occurring at the state level. These include, but are not limited to, the proposed legislation you mentioned, the lobbying of state Boards of Pharmacy, the establishment of an organization to oppose NTI substitution, and the proposals by the state Drug Utilization Review Committee(s) to require tighter confidence intervals than the present 80 - 125 and different study designs. To date, we have not seen data to support such proposed changes. FDA is also aware that the practice of pharmacy and medicine is regulated at the state level and not by the Federal Government. However, we feel that any change or desire to change FDA's bioequivalence standards should be based upon appropriate data.

Finally, FDA's position on drug substitution is summarized in the preface and introduction to the Orange Book. The evaluations on therapeutic equivalence are "prepared to serve as public information and advice to state health agencies, prescribers and pharmacists to promote public education in the areas of drug product selection and to foster containment of health costs." Also, "it does not mandate the drug products which may be purchased, prescribed, dispensed, or substituted for one another nor, does it conversely, mandate the products that should be avoided." If one therapeutically equivalent drug is substituted for another, the physician, pharmacist, and patient have FDA's assurance that the physician should see the same clinical results and safety profile. Any differences that could exist should be no greater than one would expect if one lot of the innovator's product was substituted for another.

We suggest that you consider providing this information to the members of your association.

Thank you for requesting the FDA position on this very important topic.

Sincerely yours

/s "RLW"/

Roger L. Williams, M.D.
Deputy Center Director for
Pharmaceutical Science
Center for Drug Evaluation and
Research

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

October 1, 1990

N. Mark Richards, M.D.
Commonwealth of Pennsylvania
Department of Health
P.O. Box 90
Harrisburg, Pennsylvania 17108

Dear Dr. Richards:

I apologize for the delay in responding to your letter of July 25 in which you asked if the Food and Drug Administration (FDA) identifies some drugs designated "A" in the "Approved Drug Products" publication as having a narrow therapeutic range.

FDA does not formally designate narrow therapeutic range drugs either in the publication "Approved Drug Products with Therapeutic Equivalence Evaluations" or elsewhere. FDA has developed working draft lists of drugs it believes may have a narrow therapeutic range but we have no plans to develop a formal list. We have used these lists for various internal purposes such as for selecting products to include in our recently completed market product survey. In this survey, we considered a number of the "A" rated drugs and reconfirmed that these drugs could be substituted for their "A" rated generic counterpart.

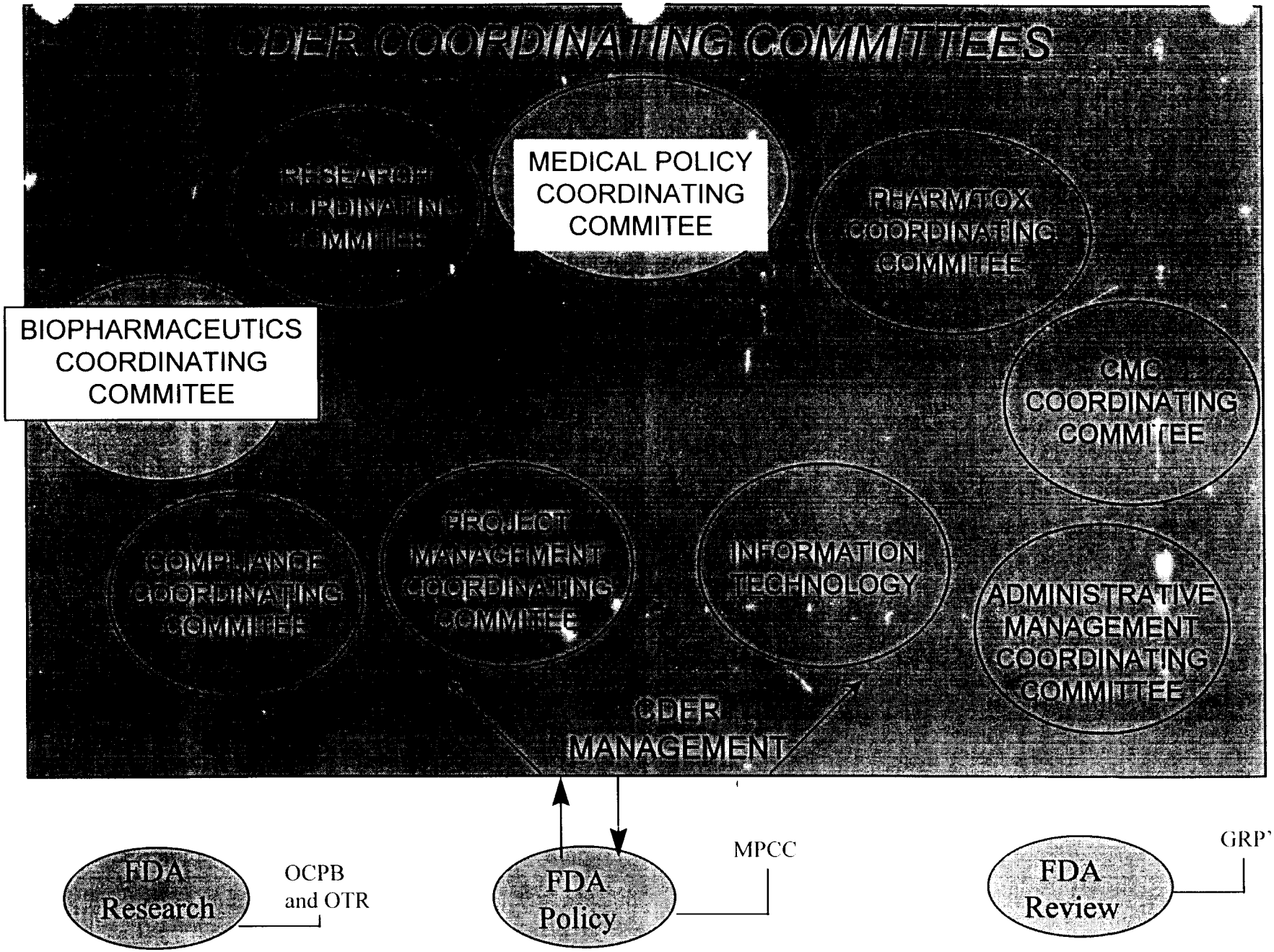
We recognize the scientific concept that drugs differ quite markedly in their therapeutic range. However, because of FDA's strict bioequivalency standards, we believe that drugs do not fall into discreet groups that would allow one to consider "narrow range drugs" as being clearly different from other drugs, from a substitution point of view. Therefore, there has been no regulatory purpose for the agency to create and implement a mechanism to designate some products as being of narrow therapeutic range.

If I can be of further assistance, please contact me.

Sincerely yours,

/S/

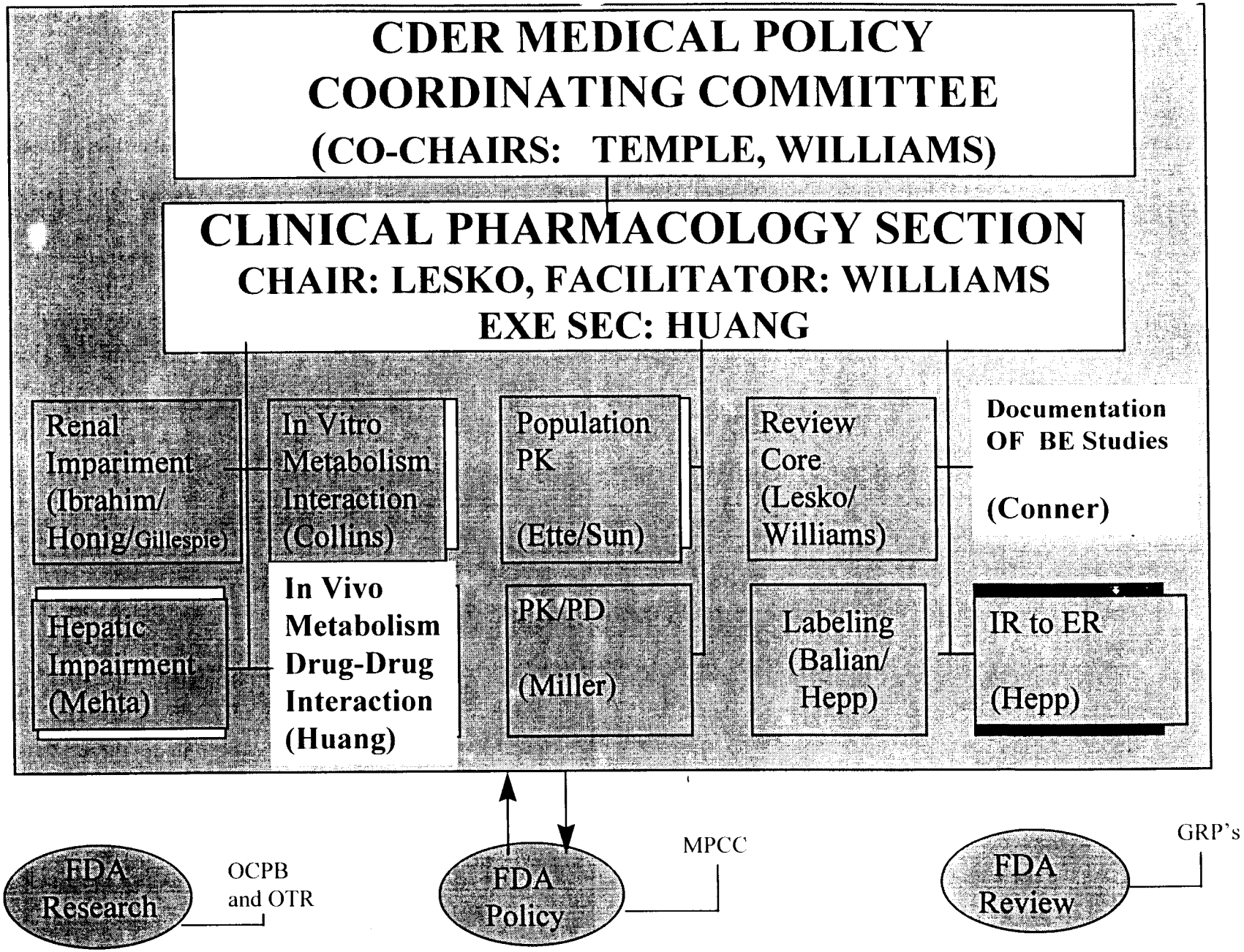
James S. Benson
Acting Commissioner
of Food and Drugs



FDA Research — OCPB and OTR

FDA Policy — MPCC

FDA Review — GRP's



11/17/97

Background Information for the Drug-Drug Interaction Guidance Discussion (December 12, 1997)

1. Presentations/Summary at the PhRMA Metabolism Workshop (9/22-23/97)

    1-a. S.-M. Huang, "Metabolism-Based Drug-Drug Interactions: Regulatory Perspectives"

    1-b. K. Thummel, "Interpretation of In Vitro Drug-Drug Interaction Data: Factors Determining Clinical Relevance"

    1-c. Summary of the Breakout Session Discussion

2. Background document on Drug-Drug Interaction Studies

1997 Drug Metabolism Fall Workshop
(PhRMA/FDA Educational Workshop Series Part I)

METABOLISM-BASED DRUG-DRUG INTERACTIONS: REGULATORY PERSPECTIVES

Shiew-Mei Huang, Ph.D.

Special Assistant to the Director

Office of Clinical Pharmacology and Biopharmaceutics

OPS, CDER, FDA

<301-594-5671, fax 301-594-2503, email: huangs@cder.fda.gov>

CDER MEDICAL POLICY COORDINATING COMMITTEE

CO-CHAIRS: TEMPLE, WILLIAMS

CLINICAL PHARMACOLOGY SECTION

CHAIR: LESKO

IN VIVO DRUG METABOLISM/ DRUG INTERACTION WORKING GROUP

CHAIR: HUANG

MEMBERS: AJAYI, BALIAN, BARNETTE, BAWEJA, COLLINS, HONIG, RAHMAN

(MARROUM, MACHADO, HIGGINS, SCHUIRMANN, HEPP, YUAN AL-HABET, VENITZ, HAUCK, WATKINS, BRANCH, LU)

CFR ON DRUG-DRUG INTERACTION

21CFR 210.57 Labeling

(d) Contraindications:...Use of drug in patients.....because of concomitant therapy,...have a substantial risk of being harmed by it...

(f) Precautions:(4)(i) Drug Interaction .....practical guidance for the physicians on preventing clinically significant drug/drug ..interactions.

Specific drugs or classes of drugs... may interact in vivo shall be identified, and the mechanism(s) of the interaction shall be described

IN VIVO DRUG-DRUG INTERACTION (D-DI) STUDIES IN HUMANS

CDER NDA Survey

#Oral NME's	**14**
#NME's /c D-DI	**13 (93%)**
Median (Range)	**6 (2-16)**
(# Studies/NME /c D-DI)	

<This survey was based on Clinical Pharmacology and Biopharmaceutics Briefings, 9/96-5/97; Total NDA reviewed: 35; total drug-drug interaction studies reviewed: 87>

CLINICALLY SIGNIFICANT DRUG-DRUG INTERACTION

- What Do We Want to Know?
- What Assumptions Are We Willing to Make?
- How Sure Do We Want to Be?

<L. Sheiner>

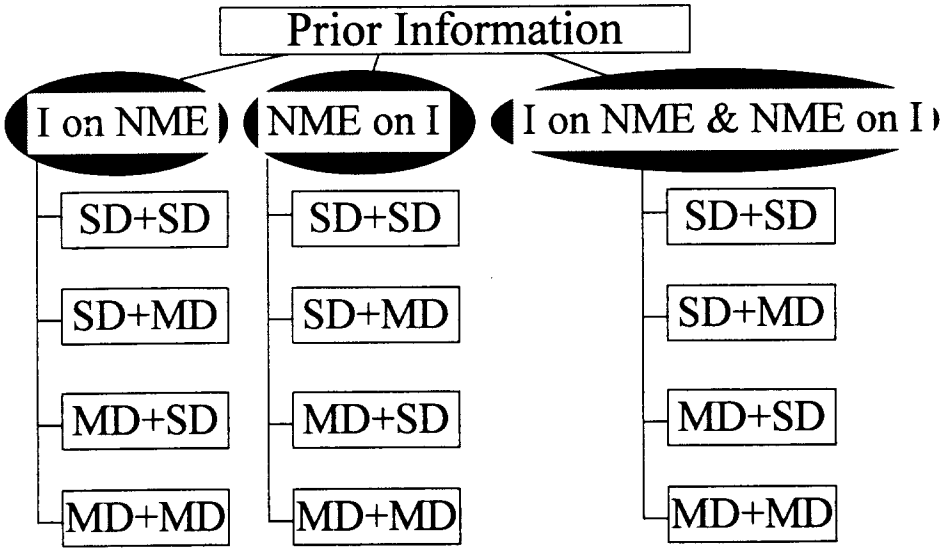
ISSUES IN *IN VIVO* DRUG - DRUG INTERACTION

- **In Vitro - In Vivo Relationship:**
  When In Vivo Studies Are Not Necessary
- **Study Design/Data Analysis:**
  Specific Studies and Population Studies
- **Labeling:**
  What In Vitro and In Vivo Data Can Be Used for Labeling

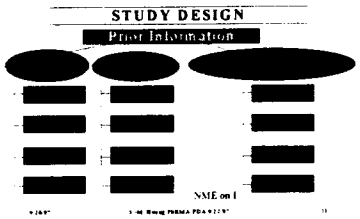
STUDY DESIGN

- **Subject** - Normal vs. Patients
- **Dose** - Single vs. Multiple
- **Inhibitor/Inducer Drugs**
  - Which one
  - Dose; Dosing Regimen
  - Extrapolation to others
- **Design** - Timing of Dosing
  - Crossover vs. Parallel
  - Open vs. DB
  - Number of Subjects

STUDY DESIGN



I: Interactant; NME:New Molecular Entity; SD: Single Dose; MD: Multiple Dose



FACTORS TO CONSIDER:

- Mechanism of Interaction
- Pharmacokinetics/Pharmacodynamics
- Recommended Dosing Regimen
  = Optimal Dosing Regimen ?

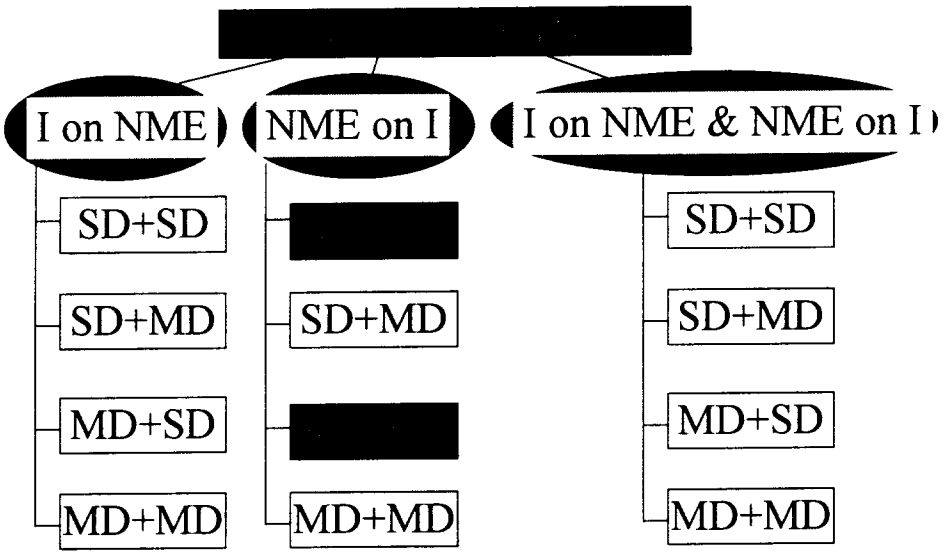
STUDY DESIGN ISSUES:
Single vs. Multiple Dose

Case 1: Sertraline(S) on Imipramine(I) and Sertraline on Desipramine(D)

Day	1 - - - - 8 - - - -15 - - - -21 22 23 - - - - 28
GP1	D.....D.....D.....
(N=6)	.....S.....S S S S S S S S S S S S S S
GP2	I.....I.....I.....
(N=6)	.....S.....S S S S S S S S S S S S S S

12 healthy, male subjects randomized to gps 1 and 2
S: 150 mg; I or D: 50 mg
<Kurtz DL et al., Clin Pharmacol Ther 62 (2): 145-56, August, 1997>

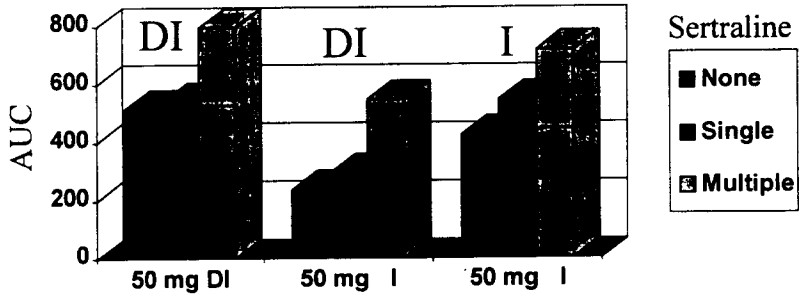
STUDY DESIGN



I: Interactant; NME:New Molecular Entity; SD: Single Dose; MD: Multiple Dose -

STUDY DESIGN ISSUES:
Single vs. Multiple Dose

Case 1: Sertraline(S) on Imipramine(I) and Sertraline on Desipramine(DI)



Since similar results for t1/2 (except I), Cmax, AUC, and Cl/F were obtained; only AUC data are shown; data taken from the following paper:
<Kurtz DL et al., Clin Pharmacol Ther 62 (2): 145-56, August, 1997>

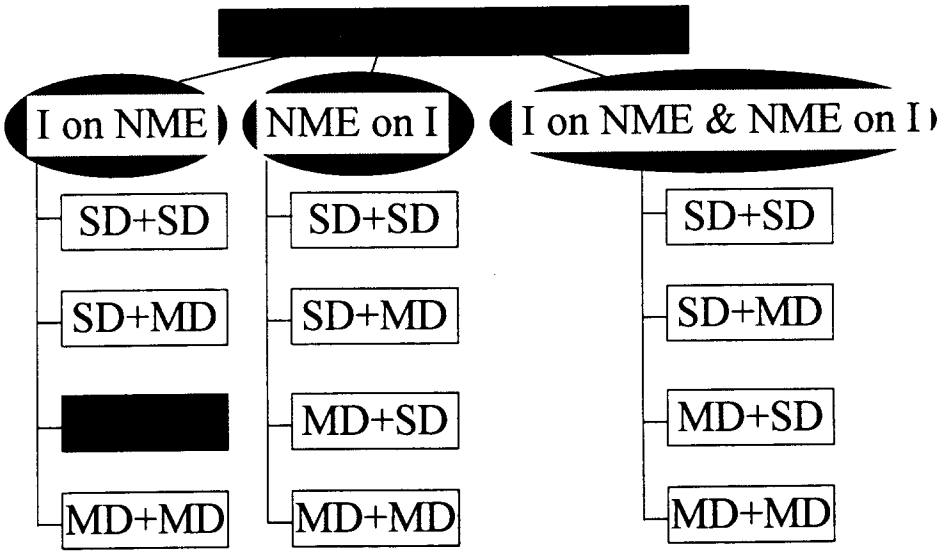
INDUCER/INHIBITOR CURRENT STATUS

- **I on NME**
  - **Cimetidine (6)**
- **NME on I**
  - **Digoxin (8)**
  - **Warfarin (7)**
  - **Oral contraceptives, Nifedipine (4)**
  - **Theophylline,, Terfenadine, Atenolol (3)**

< This survey was based on clinical Pharmacology and Biopharmaceutics Briefings, 9/96-5/97; Total NDA reviewed: 35; total drug-drug interaction studies reviewed: 87 >

S.-M. Huang, PhMRA/FDA 9/22/97 13

STUDY DESIGN

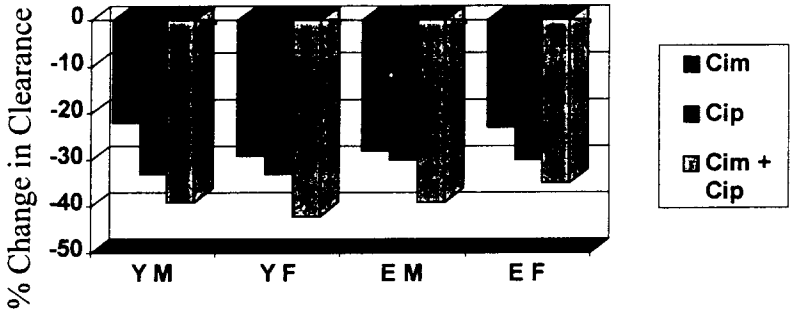


I: Interactant; NME:New Molecular Entity; SD: Single Dose; MD: Multiple Dose

S.-M. Huang PhRMA/FDA 9/22/97 14

STUDY DESIGN ISSUES:
Dose; Dosing Regimen

Case 2: Cimetidine (Cim) and Ciprofloxacin (Cip) on Theophylline (T) Metabolism



Data taken from the following paper:
<Loi C-M et al., J Pharmacol Exp Ther 280:627-637, 1997>
Cim: 400 mg bid; Cip: 500 mg bid, 5 days

STUDY DESIGN ISSUES:
Crossover: Number of Subjects

Case 3: Erythromycin and Terfenadine
Ketoconazole and Terfenadine

Day	1 - - - - - - 7 - - - - - - 14
Study 1 (N=9)	TTTTTTTTTTTTTT .....EEEEEEE
Study 2 (N=6)	TTTTTTTTTTTTTT .....KKKKKKK

Healthy, male and female subjects (4M, 5F for GP 1; 4M, 2F)
T: 60 mg bid; E: 500 mg tid; K: 200 mg bid
<Honig P. et al, JAMA 269:1513-1518, 1993 & Clin Pharmacol Ther 52:231-8, 1992>>

STUDY DESIGN

Prior Information

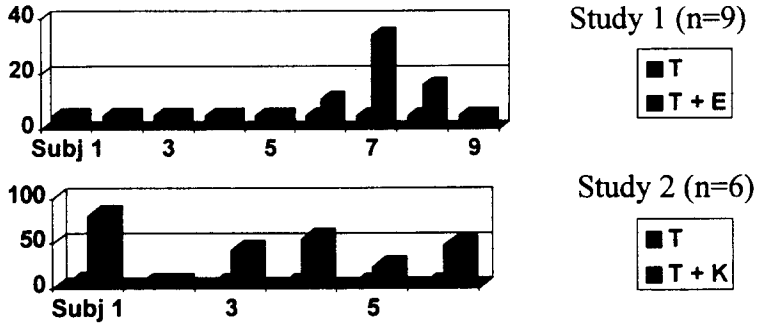
I on NME	NME on I	I on NME & NME on I
SD+SD	SD+SD	SD+SD
SD+MD	SD+MD	SD+MD
MD+SD	MD+SD	MD+SD
[redacted]	MD+MD	MD+MD

I: Interactant; NME:New Molecular Entity; SD: Single Dose; MD: Multiple Dose

STUDY DESIGN ISSUES:
Crossover: Number of Subjects

Case 3: Erythromycin and Terfenadine
Ketoconazole and Terfenadine

Terfenadine "Cmax" (ng/ml)



<Terfenadine Cmax Data (QL: 5 ng/ml) obtained from the following articles:
Honig P. et al, JAMA 269:1513-1518, 1993 & Clin Pharmacol Ther 52:231-8, 1992>

DATA ANALYSIS

Current Status:

1. Point Estimate
2. Null Hypothesis of No Interaction (P values)
3. Mean, SD, & Range
4. ANOVA; Mean & 90% Confidence Interval (CI)
5. Clinical Relevance
6. Supplemental PD Measurement

Case 4: Drug A

- Cimetidine on Drug A
  - AUC ratio 0.92 (0.89-0.96), p=0.002
  - Cmax ratio 1.07 (1.00-1.15), p=0.091
- Drug A on Warfarin (S-data listed)
  - AUC ratio 1.01 (0.94-1.09), p=0.781
  - Cmax ratio 1.11 (1.00-1.22), p=0.109

Case 4: Drug A

- Cimetidine on Drug A
  - AUC ratio 0.92 (0.89-0.96), p=0.002
  - Cmax ratio 1.07 (1.00-1.15), p=0.091
- Drug A on Warfarin (S-data listed)
  - AUC ratio 1.01 (0.94-1.09), p=0.781
  - Cmax ratio 1.11 (1.00-1.22), p=0.109

"Clinical interaction studies with cimetidine and warfarin indicated that the co-administration of A...with these drugs does not result in clinically significant drug interactions

Case 5: Indinavir

CRIXIVAN 800 mg Q8H (mean+SD)

- **Indinavir ↗↗ Rifabutin AUC (204+142%)**
  - Dose reduction of rifabutin to half the standard
- **Ketoconazole ↗↗ Indinavir AUC (68+48%)**
  - Dose reduction of Indinavir to 600 mg Q8H
- **Indinavir ↗ Zidovudine AUC (36%)**
  - No Dosage Adjustment Required
- **Indinavir ↗ Stauvudine AUC (25+26%)**
  - No Dosage Adjustment Required

<1997 PDR>

LABELING OPTIONS

Goal Post (GP)*: Clinical Relevance: Mean & ?

CI + Range; if CI within GP

>>> Can Claim "No Interaction"

CI + Range; if both mean & CI outside GP

>>> Claim "Interaction"

>>>Dosage Recommendation

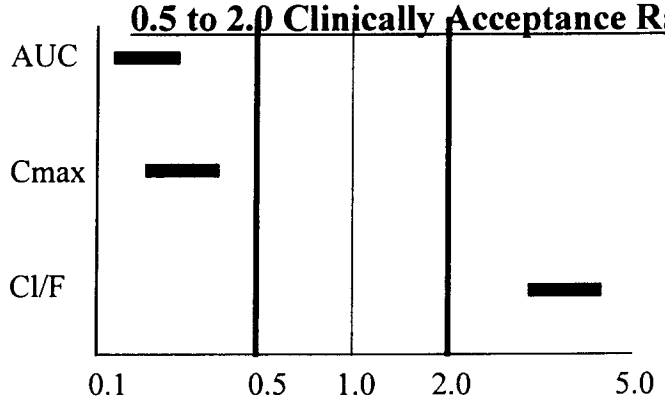
* **Goal post will be determined based on prior knowledge (clinical experiences) or conservative approach (e.g., one-sided,100-125 or 100-150% for inhibition studies or two-sided as shown in the next example)**

STUDY DESIGN/DATA ANALYSIS <Recent Publications/Reviews Utilizing the Equivalence Approach>

- **Cyclosporin and Piroxican**
- **Cyclosporin and Indomethacin**
  - Randomized, two-way crossover (MD for P or I, SD for C)
  - <Kovarik et al, J Clin Pharmacol 37:336-343,1997>
- **Meloxicam on Warfarin**
  - Two-period, sequential treatment; CI used for both PK and PD
  - <Turck et al, Eu J Clin Pharmacol 51 (5): 421-425, 1997>
- **Cimetidine on Compound A**
  - Randomized, two-way crossover (MD for C, SD for A)
  - <CPBB, May, 1997>
- **Rifampin on Nelfinavir** -next slide

DATA ANALYSIS

Case 6: 90% Confidence Intervals (Nelfinavir + Rifampin/Nelfinavir)



<Yuen GJ et al., Clin Pharmacol Ther 61 (2): 147, 1997 (ASCPT 3/97, San Diego, CA)>

POPULATION PK

Hypothesis Generating:

Case 7: Drug B: Not Metabolized; F 23%; C14 study showed majority (94%) in feces as unchanged; <0.6 % unchanged in urine

POPULATION PK

Hypothesis Generating:

Case 7: Drug B: Not Metabolized; F 23%; C14 study showed majority (94%) in feces as unchanged; <0.6 % unchanged in urine

Line Extension Studies (New Formulation) :

Four patients appeared to be outliers

- Low concentrations
- All receiving rifampin
- Clearance increased by about 110%

POPULATION PK

Hypothesis Generating:

Case 7: Drug B: Not Metabolized; F 23%; C14 study showed majority (94%) in feces as unchanged; <0.6 % unchanged in urine

Line Extension Studies (New Formulation) :

Four patients appeared to be outliers

- Low concentrations
- All receiving rifampin
- Clearance increased by about 110%

-- >Specific Studies Confirmed Rifampin Effect -- > Labeling Changes

LABELING

- Selection of Interactants
- When/What to Report in the labeling
- Role and Method of Statistical Evaluation
- Report of Negative Single Dose Studies
- Report of Negative In Vitro Studies
- Report of Positive In Vitro Studies
- Report of Effect on Co-Administered Drugs

EMEA: GUIDELINE FOR DRUG INTERACTIONS

–Page 10, Experimental Design

•<u>Cross-over design</u> usually the first choice Number of subjects ....demonstrate no clinically relevant interactions, ...Type II error, i.e. the risk for not detecting a relevant interaction

–Page 10, Statistical Analysis

•in general ... <u>ANOVA, CI</u> for the estimates of the size if the effects

•To demonstrate <u>the lack of a relevant interaction</u>, the currently accepted bioequivalence approach (... 90% CI for the ratio/difference of the means)

•If this fails, <u>point estimate with the CI</u>... should from the basis for any potential recommendations of dose modifications

WORKING GROUP PROGRESS SUMMARY/NEXT STEPS

- **Identification/Discussion of Issues**
  - (Monthly WG Meetings 1/30/97-present)
- **Early Input from Industry/Academia**
  - Short Course/Seminar/Roundtable Discussions held at the Agency (1997)
    - J. Collins, P. Honig, A. Rahman
    - A. Parkinson, A. Madan, E. LeCluyse, P. Watkins, R. Branch, R. Vestal
    - D. Rodrigues, S. Wrighton, A. Lu
  - Advisory Committee for Pharmaceutical Science Meeting 5/8/97
  - PhRMA/OPS/OCPB Meeting 5/30/97
  - PhRMA Fall Workshop 9/22-23/97
- **Crosstalk with EMEA:** CPMP Guideline -Tomas Salmonson
  - EUFEPS meeting at Nuremberg 11/27-29/97

INPUT FOR ISSUES IN *IN VIVO* DRUG - DRUG INTERACTION

- **In Vitro - In Vivo Relationship:**
  When In Vivo Studies Are Not Necessary
- **Study Design/Data Analysis:**
  Specific Studies and Population Studies
- **Labeling:**
  What In Vitro and In Vivo Data Can Be Used for Labeling

If clinical metabolism-based drug-drug interaction studies are considered necessary, the following general issues should be considered in designing clinical studies.

I. Design of metabolism-based drug-drug interaction studies

A. Study Population

In most cases, clinical drug-drug interactions studies may be performed using healthy volunteer subjects. This strategy is favored for several reasons including ease and cost of recruitment as well as the potential reducing inter- and intra-subject variability due to qualitative, quantitative and temporal differences in concomitant diseases, medications, and other intrinsic (e.g. genetic polymorphisms) and extrinsic sources (e.g. environmental factors) of variability. There may be situations that preclude the use of volunteer subjects. For example, the study of oncolytics may be more appropriate performed in patients. In such situations, care should be taken to control for the sources of variability mentioned above by explicit designation and appropriate use of protocol-defined inclusion and exclusion criteria. In such instances, it may also be helpful to investigate the effect of disease severity on drug-drug interactions by stratifying. In all situations, it would be reasonable to phenotype and genotype participants with regard to genetically determined polymorphisms of metabolism if the drug of interest has been shown to be entirely or partially metabolized by polymorphically distributed enzymes.

B. Choice of Interactants

B.1. Inhibitors/Inducers: Selection of an inhibitor or inducer that is most likely to demonstrate an interaction should be directed by available in vitro metabolism information. For example, if the test substrate is shown to be a substrate of CYP3A4, the logical choice of inhibitor would be ketoconazole. This strategy has the advantage of allowing extrapolation of negative clinical study results to less potent specific inhibitors or inducers of the same metabolic pathway. If the clinical study of the most potent specific inhibitor/inducer is not unequivocally negative and the sponsor wishes to claim no interaction for other less potent specific inhibitors, a clinical study is required.

B2. Substrates: If in vitro studies indicate that the test drug is an inhibitor of

specific metabolic pathways and, likely to occur in vivo, clinical studies may be required to provide proper dosage recommendation. The choice of which drugs to study would, of course, depend on the isoenzyme(s) affected as well as the likelihood of coadministration. For example, if a test drug is being studied in asthma and shown to be an inhibitor of CYP3A4 at achievable plasma concentrations, it would be reasonable to conduct a clinical study with terfenadine but not with alprazolam because benzodiazepines are not routinely administered in asthma. If it was found to be an inhibitor of CYP1A2, it would be necessary to conduct a theophylline interaction study but a tacrine interaction study would not be necessary for the same reasons.

B3. Shared Pathway Drugs: If in vitro studies indicate that the test drug is likely to share and, therefore, compete with coadminstered drugs for specific isoenzymes, clinical studies may be required. Again, the choice of which drugs to study would depend on the isoenzyme(s) affected and on the likelihood of coadministration.

C. Route of administration

C.1 Of test drug: The route of administration of the new drug will, of course, depend on the available formulations as well as the formulations intended for marketing. That is, if only oral dosage forms will be marketed, there is no need to perform studies with an intravenous formulation. However, studies employing both oral and intravenous formulations may be very useful in discerning the relative contributions of alterations in absorption/presystemic gut and liver clearance to the overall effect observed for a drug interaction (e.g. cyclosporin and ketoconazole interaction). On the other hand, if an interaction is expected to occur primarily on the basis of hepatic metabolism (e.g., a substrate of CYP1A2 such as theophylline), use of an intravenous formulation only is acceptable.

C.2. Of Inhibitor/Inducer: The choice of the route of administration of the inhibitor or inducer will, similarly, depend on the available marketed formulations. In the vast majority of cases, this will be by the oral route.

D. Dose Selection

Of test drug and interacting drug: Ideally, the maximum approved dose and shortest approved dosing interval of both drugs should be studied. If adequate safety measures cannot be instituted or patient tolerability precludes the study of

drugs at their highest doses or frequencies, consideration may be given to studying drugs at lower doses provided the sponsor demonstrate that the drug assays are adequate with regard to sensitivity and precision at lower concentrations and the magnitude of the pharmacokinetic interaction, if present, is linear to maximum labeled doses. The latter consideration is particularly important if a claim of no interaction (at less than maximum recommended daily doses) is made based on equivalence criteria as outlined below (see statistical considerations).

E. Study Design

There is no one correct study design for studying drug-drug interactions. The most appropriate and feasible study design depends upon several considerations including: the pharmacokinetic and pharmacodynamic characteristics of the test drug and its major metabolite as well as the nature of the suspected interaction (i.e., competitive versus non-competitive inhibition, stimulation, induction). The study may be open-label unless pharmacodynamic endpoints that are subject to bias (e.g. adverse events, symptoms, etc.) are collected. From a statistical perspective, the most efficient methodology would be to employ a randomized, two-way, two-period, crossover design. The appropriate between-period washout duration would be dependent on the pharmacokinetics and effect kinetics of the interactants. The ideal study design would employ steady-state dosing of test drug and interacting drug and would be necessary if a PK/PD relationship is not established or understood or if single dose does not predict steady-state pharmacodynamics. With such a design single and multiple dose effects may be determined. If, however, the multiple-dose pharmacokinetics of the test drug and its active/toxic major metabolites can be predicted from single-dose pharmacokinetic data, the drug assay has the requisite sensitivity and precision for parent and any major metabolites, and the interaction is purely competitive in nature, the inhibiting/inducing drug may be dosed to steady-state and the substrate may be administered as a single-dose. Occasionally, however, the pharmacokinetics (e.g. very long half-life) of the drug being dosed to steady-state make the use of a cross-over design problematic. In such cases, loading dose strategies may be considered in an attempt to decrease the time to Css. Alternatively, a parallel,one-way crossoverl dosing design may be employed. Parallel group designs are preferred in cases where a sufficient washout period cannot be guaranteed or there is evidence that the exposure to the drug may irreversibly modify the subjects pharmacokinetic handling of the drugs in question (e.g. cancer chemotherapy). In all cases, the inhibiting/inducing drug should be

dosed throughout the dosing interval of the second drug. Since induction effects are dose and time dependent, clinical studies evaluating induction effects may require multiple dosing of the inducer for adequate periods of time at maximum recommended doses. Studies employing the effect of single doses of very well characterized competitive inhibitors (e.g. ketoconazole) on the multiple-dose pharmacokinetics of the test drug may be considered; however, study designs employing single doses of inhibitor and substrate are discouraged.

F. Dosing Duration

After a decision is made to conduct a study employing multiple dosing of test and/or interactant drug, the duration of dosing is an important consideration. For purely competitive inhibition studies, the suspected inhibiting drug should be dosed to steady-state based on the known pharmacokinetic parameters of the drug and, if important, its major metabolites. In such studies, if a multiple-dose strategy for the test drug is also employed, it will be difficult to predefine the dosing duration required to reach new pharmacokinetic steady-state during inhibition. The selection of a dosing duration should be made in the context of the known effects and time course of the inhibitor and its major metabolites (if inhibitors) on other substrates and the magnitude of the inhibition effect seen in vitro. For example, if a study involving a drug likely to be inhibited by fluoxetine were planned, it would not be reasonable to dose fluoxetine to steady-state on the basis of fluoxetine concentrations alone. Norfluoxetine is also an important inhibitor with a longer half-life than its parent and dosing duration must be adjusted accordingly. In any case, such studies require pharmacokinetic sampling that will allow for testing of the hypothesis that pharmacokinetic steady-state has been achieved before and after the inhibition. As such, dosing and sampling should be adequate for serial trough concentration (Cmin) analysis.

For studies involving inducers, the dosing duration is critically important and should be selected using existing knowledge of the time course of the effect. Studies involving pharmacodynamic endpoints present unique problems and dosing duration selection involve the aforementioned pharmacokinetic as well as the time course of additive or synergistic pharmacokinetic effects (see Pharmacodynamic endpoints (H) below).

G. Pharmacokinetic Endpoints

The following pharmacokinetic variables should be determined for both interacting drugs: AUC, Cmax and clearance. Determination of Tmax, F or F/dose, or half life ($t_{1/2}$) by regression of the log-linear segment of the concentration-time curve may be helpful in some circumstances. In multiple-dose studies, trough concentrations (Cmin) before and during maximum interaction effect are also important in demonstrating that the dosing strategies were adequate to achieve steady-state before and during the interaction. Cmax, Tmax, AUC and Cmin should not be modeled and should be calculated using measured data. The study protocol should be designed to insure adequate sampling to capture Cmax and Tmax.

H. Sample Collection and Analysis

The frequency of sampling should be adequate to allow accurate determination of the relevant pharmacokinetic parameters for the parent and, if any, major active or toxic metabolites. Plasma samples should be analyzed for test drug and its major metabolites with known or suspected activity (desired or toxic) as well as the interactant drug. Since the interaction concerned by this guidance are metabolism-based, measurement of total concentration (bound and unbound) is reasonable unless there is evidence to suggest that protein binding is concentration-dependent (e.g. disopyramide).

I. Pharmacodynamic Endpoints:

Occasionally, it will be necessary to incorporate pharmacodynamic endpoints into the study. This would be necessary if the PK/PD relationship for the endpoint of interest is not established or if pharmacodynamic changes do not solely result from pharmacokinetic interactions (e.g, quinidine and tricyclic antidepressants).

J. Sample Size and Statistical Consideration

To demonstrate no interaction, an equivalence approach is reasonable with the 90% CI of the ratio of the PK or PD parameter of interest falling within a prespecified range being necessary. The designation of a pharmacokinetic endpoint or endpoints of interest will depend on the PK/PD relationship of the drugs being studied. If the PD endpoint of concern is most closely related to the

peak concentration (e.g. tachycardia with sympathomimetics), Cmax would be the appropriate primary PK endpoint. Conversely, if exposure is the primary determinant of the pharmacodynamic effect, AUC would be preferred. In any case, the primary PK parameter(s) and the prespecified range within which the 90% CI must fit in order to declare no clinically significant interaction will depend on the PK/PD relationship and therapeutic index of the study drug and should be discussed with the review division. If 'lack of interaction' is not demonstrated, dose modification recommendations will be made on the basis of the point estimate and confidence interval in the context of the therapeutic index of the drug. The sample size should be calculated in the context of the known pharmacokinetic variability of the drug and be adequate to meet the aforementioned criteria.

K. Role of Population Pharmacokinetic Studies

Population pharmacokinetic analyses of data obtained from sparse sampling in large Phase 3 trials may provide valuable information in identifying unsuspected pharmacokinetically determined drug-drug interactions. The observational approaches are less valuable in proving the absence of suspected interactions or in definitively ruling out unsuspected ones; however, they may be valuable in confirming the absence of a clinically significant effect or addressing issues of dose modification recommendations if an effect is observed in more rigorously controlled and prospectively designed drug-drug interaction studies.

II. Labeling

A. Introduction

In-vivo metabolic based pharmacokinetic drug interaction data (in addition to *in-vitro* based drug interaction data) between the subject drug and other drugs should be presented in the Drug-Drug Interaction subsection of the Clinical Pharmacology section of the label in a descriptive manner. In certain cases, information based on human drug interaction studies not employing the labeled drug can be reported with explanation that similar results might be expected for the labeled drug. In order to take this approach, there needs to be strong evidence that the metabolic pathway(s) for the labeled drug is the same and that there are similar effects on metabolizing enzymes which metabolize or are affected by the labeled drug as for one of the drugs in the drug interaction study

being referenced.

The clinical significance of any demonstrated or predicted drug-drug interaction should be addressed. When serious metabolic based drug-drug interactions are shown or predicted, recommendations should be placed in the PRECAUTIONS, WARNINGS, DOSAGE AND ADMINISTRATION, and/or CONTRAINDICATIONS sections of the labeling, depending on the level of hazard.

In cases where *in-vivo* single dose drug-drug interaction studies do not demonstrate an interaction, the extrapolation of this to the chronic dosing clinical situation needs to be considered prior to making labeling statements on no drug interaction.

Any well designed *in-vivo* drug interaction study whether it be conventional or population based can provide evidence for this section of the labeling. The type or types of *in-vivo* drug interaction studies on which statements are based should be clearly identified in the labeling (conventional or population PK in nature-see population PK guidance).

The effect of the subject drug on the co-administered drug should also be reported in the subject labeling (many times, only the effect of the co-administered drug on the subject drug is studied and reported in the labeling) as well as in the interacting drug's labeling.

Variations in metabolism with respect to factors such as age, gender, ethnicity, social (smoking, drinking), concomitant pathology (e.g., renal or hepatic insufficiency), diet, or environment which may lead to differences in metabolic-based drug-drug interaction between different populations should be addressed in this section of the labeling as well as in the special populations section of the labeling. Any need for dosing adjustment, precaution, warning, or contraindication based on the above factors should be included in the respective sections of the labeling.

B. Drug-Drug Interaction Subsection of the Clinical Pharmacology Section of the Labeling:

All relevant *In-vivo* metabolic based drug-drug interaction data (in addition to *in-vitro* based) should be presented in this section of the labeling. Guidance exists on the Format and Content of the Clinical Pharmacology Section of the labeling which will aid in developing the Drug Interaction Suction.

I. Cases and Text Examples: Drug-Drug Interaction Subsection of Clinical Pharmacology Section of Labeling

Below are several different cases of drugs for which varying amounts and types of metabolic based drug interaction information is available. Examples of appropriate labeling for those cases is also presented.

a. Case of a drug for which *in-vivo* drug-drug interaction studies indicated little or no PK effect (metabolic based or otherwise): on

> "Data from a drug-drug interaction study involving _____ and _____ in patients/healthy individuals indicated that the PK disposition of either _____ or _____ was not altered when co-administered."

b. Case of a drug for which *in-vivo* drug-drug interaction studies indicated clinically significant PK (metabolic based or otherwise) interaction: the following statement may be modified as appropriate and in accordance with what is known about the drug (e.g. racemate with different activity of stereoisomers, active or toxic metabolite, etc.) and from the studies performed in accordance with this guidance.

> "The effect of _____ on the pharmacokinetics of _____ was studied in _____ patients/healthy subjects. The Cmax, AUC, half-life and clearances of _____ increased/decreased by ____% in the presence of _____. The dosage should be increased/reduced when _____ is co-administered with _____ (see Dosage And Administration) OR should be administered concurrently with caution with/without dosage adjustment OR should not be administered concurrently (see Precautions, Warnings, Dosage and Administration, or Contraindications sections)."

c. In cases where specific isoenzymes are identified as metabolizing a drug, but no *in-vivo* or *in-vitro* drug interaction studies have been conducted, the label should state this with the appropriate language regarding potential for *in-vivo* PK interactions. .

> "*In-Vitro* drug metabolism studies reveal that drug X is a substrate of the CYP 3A4 enzyme. No drug interaction *in-vitro* or clinical studies were performed to evaluate interactions. Based upon the *in-vitro* metabolism, there is the potential for interaction of the substrates of this enzyme and the

drug leading to PK drug interactions"

d. In cases where neither *in-vivo* nor *in-vitro* drug-drug study has been conducted and there is no significant hepatic metabolism of the drug, the following language should be incorporated into the labeling:

> " In-vivo or in-vitro drug-drug interaction studies have not been conducted. The drug interaction potential is expected to be low because approximately 90% of the recovered dose is excreted in the urine as unchanged drug and, it is not an inhibitor or an inducer of known metabolic pathways."

e. In the case of a drug where *in-vitro* interaction studies are performed but no *in-vivo* studies have been conducted to confirm or refute a finding, it is appropriate to rely on the positive or negative results of the *in-vitro* drug interaction studies to make labeling statements.

> *In-Vitro* Interaction Demonstrated
>
> "*In-Vitro* drug interaction studies reveal potent inhibition of the metabolism of drug X by the CYP 3A4 inhibitor ketoconazole. No clinical studies were performed to evaluate this finding. Based upon the *in-vitro* findings, there is strong potential for *in-vivo* interaction of the inhibitors of this enzyme and the drug."
>
> *In-Vitro* Interaction Not Demonstrated
>
> "*In-vitro* drug interaction studies reveal no inhibition of the metabolism of drug X by the CYP 3A4 inhibitor ketoconazole. No clinical studies were performed to evaluate this finding. Based upon the *in-vitro* findings, *in-vivo* metabolic interaction is not anticipated, but cannot be completely ruled out."

ii. Shown below are examples of text with might be placed in the Precautions, Warnings, Dosage and Administration, or Contraindications Sections of the Labeling based on information from the Drug-Drug Interaction Subsection of the Clinical Pharmacology Section of the Labeling:

a. Example- Precautions Section

"Drug_____ /class of drug could cause significant increases in concentrations of drug_____ when co-administered. In certain patients this could lead to <a particular adverse reaction>. If <a particular adverse reaction> occurs, it should be explained to the patient that is usually self limiting and that the concomitant drug administration should not be discontinued. The patient should be instructed to inform the prescriber if <a particular adverse reaction> persists so that dosage can then be modified, or one of the drugs can be discontinued.

b. Example- Warnings Section

"Drug_____ /class of drug could cause significant increases in concentrations of drug_____ when co-administered. In certain patients this could lead to <a particular serious adverse reaction>. If <a particular serious adverse reaction> occurs, immediate consideration should be taken regarding altering dosage or discontinuation of one or both of the concomitantly administered drugs.

c. Example- Dosage and Administration Section

"The effect of drug_____ /class of drug on the pharmacokinetics or of drug_____ is clinically significant; hence, it is recommended that the dose of drug x be decreased by 50% when the patient is also taking drug y.

d. Example -Contraindications Section

"The effect of drug_____ /class of drug on the pharmacokinetics of drug_____ is of high magnitude and can be predicted to lead to serious morbidity or mortality; hence, administration of drug___ to patients on drug_____/class of drug____ is contraindicated."

PhRMA workshop Discussion Summaries (9/22-23/97):

Topic 1: In Vitro-In Vivo Relationships: When in vivo studies are not necessary

Discussion Leaders: Atiqur Rahman, Gerald Miwa, Gary Barnette, John Stubbs

1. When are in vitro drug metabolism/interaction data sufficient to preclude metabolic based in vivo interaction studies?

- o Not an inhibitor/inducer for a known P450 system-would not require clinical confirmation.
- o Narrow TI-In vitro metabolism not adequate
- o Negative in vitro result does not eliminate need for in vivo study

2. Want in vitro metabolism/interaction studies should be considered adequate?

- o Identify/characterize metabolic pathways/enzymes
- o Characterize inhibitory characteristics of NME (Issue: in vitro induction models not robust
- o Need for Metabolically viable system

3. What additional information is required to consider elimination of metabolic based in vivo interactions studies?

- o Consideration of therapeutic index
- o Clinical implication of interaction
- o Concomitant medications

4. Is the in vitro parameter, Ki/I, reliable in predicting a metabolic based in vivo interaction?

- o General agreement with Thummel proposal
- o Ki in vitro vs. Ki in vivo not established

5. For drugs that will be administered in combinations greater than two, would in vitro interaction studies with pairs of compounds be sufficient?

- o In simplest case, with reversible inhibition and single enzyme system pairwise study OK followed by combination in vitro
- o However, general consensus in vivo study necessary

Topic 2: Design of in vivo studies

Discussion Leaders: Peter Honig, Mitch Cayen, Raman Baweja, William Crouthamel

1. Subjects.

It was agreed that normal subjects are easier and less costly to use. However, some drugs can only be tested in patients(for example anti cancer drugs) and in some cases additional information on efficacy can be obtained from patients.

2. Doses.

Many questions can be answered by single dose studies , particularly drugs given as single doses(analgesics). To truly understand a drug interaction the drugs need to be administered in the same way which they are used in the therapeutic setting. This usually requires multiple doses of at least one of the drugs and often both drugs.

3. Inhibitor/inducer drugs:

When the CYP 450 isozyme which is responsible for the potential interaction is identified there is usually general agreement regarding the choice of inhibitor. The choice is usually the drug having the greatest chance of showing an interaction at a dose that will produce an interaction if it is present.

4. Design.

The most appropriate design will depend on the pharmacokinetics characteristics of the drug, and its clinical use. Although a crossover design may be appropriate in some cases, a sequential parallel study design will usually be the one chosen.

5. Population Pharmacokinetics.

Plasma drug concentration monitoring and population pharmacokinetics are powerful tools to detect interactions particularly in patients. To understand the interaction more extensive studies are usually required. Population Pharmacokinetics will be particularly important in studying drugs under the new proposed rule for studies in pediatric patients

Topic 3: Labeling: What in Vitro and In Vivo Data Can be Used for Labeling

Discussion Leader: John Balian, Michael Lamson, Funmi Ajayi, William Robinson

1. What drug interaction information should appear in the label?

- o Ask what is the purpose of the label and who is audience (physician needs vs

<In Vitro Data>

- o Need for identifying the P450 isoenzymes that mediate the metabolism of the sponsor's drug
- o Want clear interpretive "bottom line" information only; not really interested in Km or Vmax data, possible Ki but only as it relates to a precautionary statement
- o Questions were raised about the reproducibility of in vitro dat
- o No methodology (experimental conditions) should appear in the label; only want in vitro conclusions

< In Vivo Data>

- o All information (unless deemed by FDA to be seriously flawed)
- o Journal references may be useful when more information is available

- o No interest in forcing pharmaceutical companies to report the results of another company's drug interaction data unless compelled by safety to do so.

2. What Studies should be included in the label?

- o Most clinically-relevant studies should be described in label
- o In vivo data (classical PK or population PK) should always supersede in vitro data
- o Both pharmacodynamics and pharmacokinetics data are welcome
- o Generally the hurdle is higher for studies a sponsor wants to promote
- o In vitro conclusions are welcome in the absence of in vivo data

3. What information from in vitro studies should appear in the label?

- o Specific P450 isoenzymes and conclusion only
- o Speculation about drug interactions only with respect to cautionary statements

- o Qualitative language only with respect to multiple metabolic pathways, i.e., CYP3A4>>CYP2D6 is preferred over CYP3A4 (60%), CYP 2D6 (40%)
- o Negative results from in vitro studies are OK if the potential for interaction is low

4. Should there be a standardized presentation of drug interaction information in the label?

- o Expansion of the clinical pharmacology or proposed drug interaction section of the PDR is fine
- o However, the precautions/warning/contraindication section should include "bottom line information about (+) interactions" only and "bottom line information about (+) interactions" only and
- o The dosage and Administration Section should recommend only " a course of action"
- o The latter sections should be made user friendly

5. What drug interaction documentation should be required by FDA to support a sponsor's labeling claims?

- o For Safety Concerns multiple case reports or an abstract is fine
- o Claims by the sponsor will require full documentation- prior to NDA approval this means a clinical trial report (CTR): following approval this means a CTR or peer reviewed journal article

DRAFT

Documentation of Bioequivalence Studies During the IND Period

Background

In our role as expert consultants to the medical review divisions in CDER, OCPB is responsible for the review of bioequivalence (BE) studies submitted in NDAs. These studies may be early developmental studies for formulation optimization or pivotal studies for approval. Sponsors carry out pivotal studies for several different purposes or objectives. These objectives may include, bridging the information developed with the clinical trial formulation(s) to the to-be-marketed formulation, comparing and bridging a new modified release formulation to an approved immediate-release formulation, or comparing the performance of a combination product to the individual ingredients given together or separately. To date, we conclude bioequivalence when there is 90% confidence that the ratios (test over reference) of the geometric means of log-transformed AUC and C_{max} are within 80-125%.

Different formulations in an NDA are not required to meet these rigid BE criteria as they are in an ANDA. However, the different formulations need to be clinically (based on safety and efficacy evaluations) comparable. What information (clinical safety and efficacy, biopharmaceutic, clinical pharmacology) is needed to take an appropriate regulatory action on a submission when the BE study fails to demonstrate bioequivalence? The review team (mainly ODE medical officers and OCPB Clinical Pharmacology reviewers) makes the decision using the collective data from the NDA. This decision-making process is not always consistent or well understood by industry or FDA staff. Current efforts are underway to delineate this process in an organized decision map and guidance to aid in understanding and to promote consistency of the regulatory procedures.

Operational Paradigm

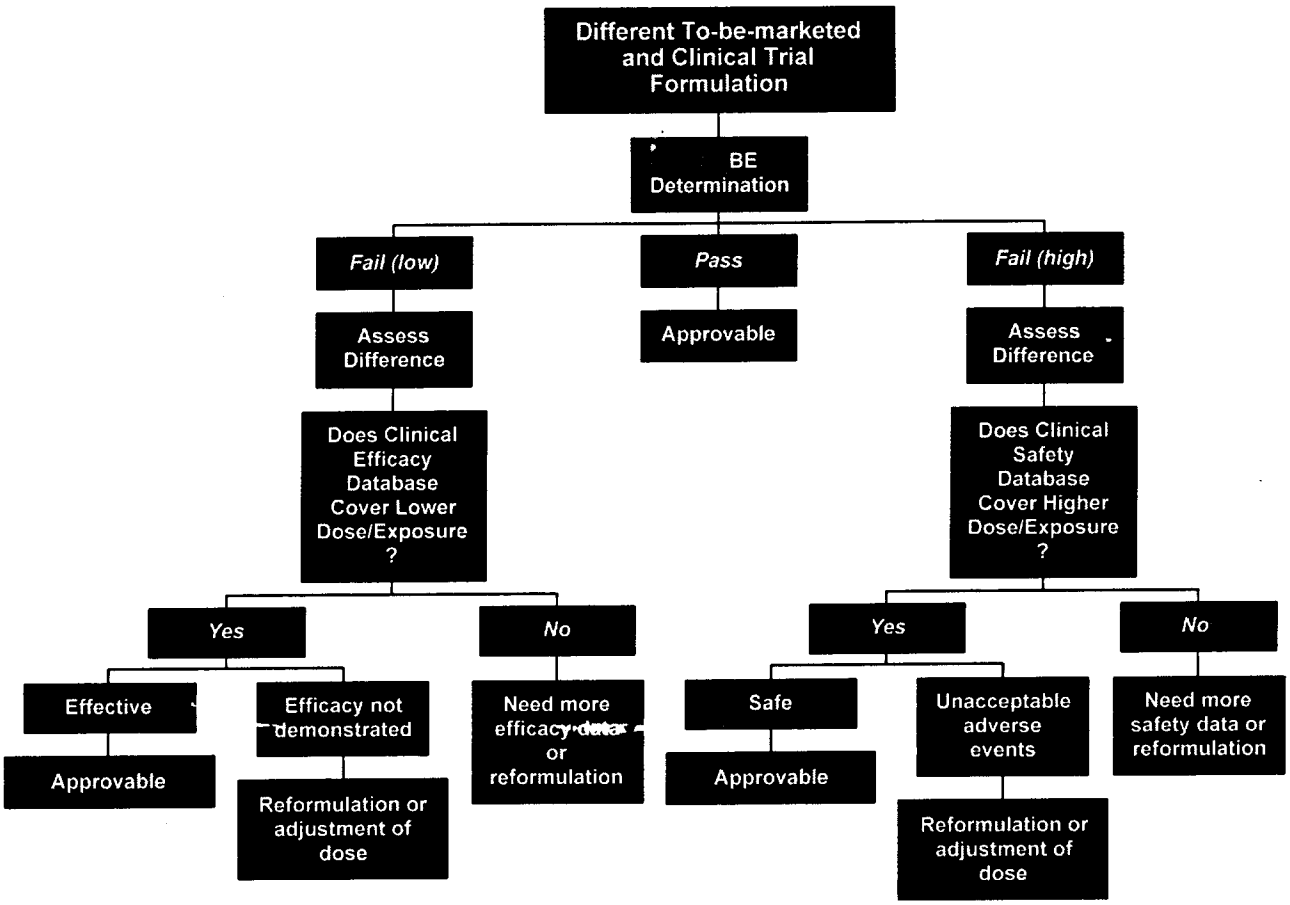
In most cases bioequivalence studies remain the most cost-effective method of determining clinical comparability between different formulations. Alternatives, such as clinical trials, are costly and time-consuming as well as lacking sensitivity in determining equivalence or difference between formulations. We should continue to encourage the conduct of pivotal BE studies, when appropriate, that are well controlled and designed to meet the currently accepted methods for demonstrating bioequivalence. Currently these are crossover studies with confidence interval criteria of 80-125%.

On occasion, the results of an appropriate bioequivalence study fail to demonstrate equivalence between the formulations tested. The data from this study as well as other

data available in the NDA must be used to make a regulatory decision for or against approval of the application. Available data on which to base a regulatory action includes Clinical Pharmacology and clinical safety and efficacy data from the clinical trials

Items 6 and 8 of the NDA submission include Clinical Pharmacology data. The data, which may support a regulatory action, include plasma level response data associated with safety and efficacy, the magnitude and direction (higher or lower) of the difference in formulations based on the BE studies, and information on the therapeutic index of the drug(s). The clinical data may include information on the safety (for higher relative bioavailability) and/or efficacy (for lower relative bioavailability) sufficient to cover the difference in systemic exposure to the drug. Additional questions are: what is the significance of a bioavailability difference to special populations (pediatric, elderly, organ dysfunction, etc.) and potential drug interactions; and has the proper bridge between to-be-marketed and clinical data been made or must new clinical (efficacy or safety) studies be done with the new formulation.

The following flowchart is a diagram of the decision process involved with testing formulations, such as to-be-marketed with the clinical trial formulation, for comparability. It involves the initial BE study(ies) and the decisions following a finding of equivalence, high failure or low failure. As can be seen from the flowchart, the final regulatory decision is a team effort involving the medical officers, OCPB Clinical Pharmacology reviewers and other team members. The information to make the final regulatory decision is drawn from the total information provided in the NDA.



APPEARS THIS WAY ON ORIGINAL

Summary

There is no regulatory requirement for bioequivalence in the NDA review and approval process. Regulatory actions are taken based on the weight of the total evidence presented in the NDA. Clinical, biopharmaceutic and Clinical Pharmacology data all contribute to the regulatory decision and must support safety and efficacy of the drug(s) in the to-be-marketed formulation(s).

Advisory Committee for Pharmaceutical Sciences
Background Information, November 13, 1997

Pharmacology/Toxicology Research Program
Office of Testing and Research, OPS, CDER

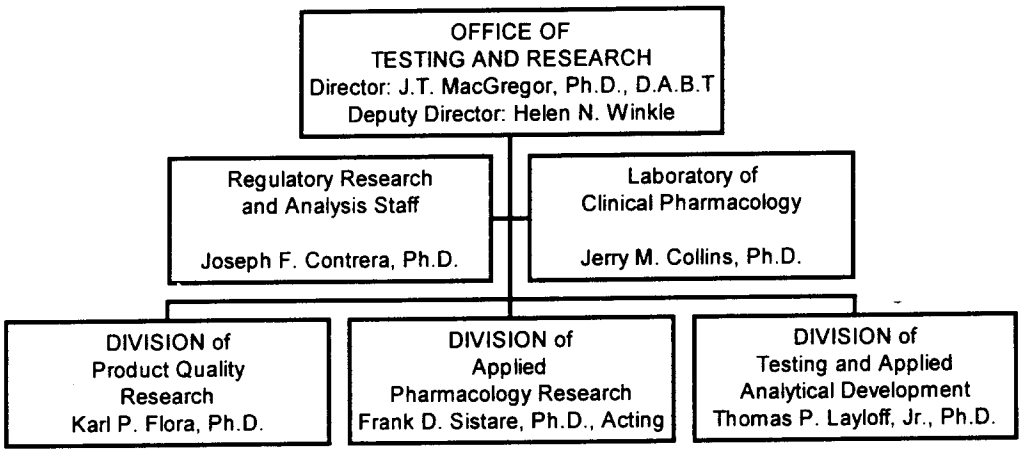
During the Fall of 1997 a series of program retreats were held to refocus the goals and objectives of the programs within the Office of Testing and Research (OTR). Key outcomes of this process will be presented, with emphasis on the pharmacology and toxicology programs.

The mission of the Office is to:

- Advance the scientific basis of regulatory policy
- Assure that regulatory policy and decision making are based on the best available science
- Provide scientific and laboratory support for review, postmarketing surveillance, and compliance activities

The Office is organized into five program groups which are supported by the Immediate Office staff. The organizational structure is illustrated in the following chart:

OTR Organization



APPEARS THIS WAY ON ORIGINAL

Each of the five programs collaborate in a number of key multidisciplinary focus areas that address important aspects of CDER's regulatory mission. These are:

- Nonclinical/clinical linkage: Improved linkage of nonclinical with clinical studies and improved predictability of clinical outcomes by nonclinical studies

- Product quality: Improved methodology for assurance of product quality with analytical test support

- Database availability and monitoring, including analysis of the performance of regulatory methodology and nonclinical and clinical effects of product classes

- Regulatory analytical support to CDER and the Agency, including methods validation and product testing

COLLABORATIONS:

OTR is involved in a number of collaborations in an effort to continue to expand their resources in an environment of shrinking appropriated funds. The main collaborations currently being effected are the Collaboration on Drug Development Improvement (CDDI) and the Product Quality Research Initiative (PQRI).

CDDI is designed to advance the development process for pharmaceuticals and biopharmaceuticals (medicinal products). The information developed by the Collaboration will be used to support guidance documents for industry sponsors on efficient, scientifically sound approaches for development of an investigational medicinal product. The Laboratory for Clinical Pharmacology (LCP), the Division of Applied Pharmacology Research (DAPR), and the Regulatory Research and Analysis Staff (RRAS) are participating in CDDI. Staff from the LCP, DAPR, and the Immediate Office of OTR are involved in the organization of CDDI and in the development of research projects.

The current proposal for PQRI is to form a collaboration in which the FDA, the pharmaceutical industry and academia can collaborate on research projects to support regulatory policy in the area of product quality. The Division of Product Quality Research (DPQR) in OTR has been the main force behind this initiative, working closely with the trade associations and professional associations to development an effective collaboration. It is envisioned that the Division of Testing and Applied Analytical Development (DTAAD) will also participate in this initiative.

OTR also is involved in a number of other collaborations including those with National Institutes of Health (NIH), National Center for Toxicological Research (NCTR), National Institute of Environmental Health Science (NIEHS) and other government organizations, as well as with academia.

Pharmacology and Toxicology Program Plans

The current and emerging program plans in the DAPR, LCP, and RRAS will be presented.

The Division of Applied Pharmacology Research (DAPR) focuses on nonclinical pharmacology/toxicology research to establish the best models and endpoints for accurately predicting the clinical effects of pharmaceutics. DAPR seeks to implement objective research strategies utilizing state-of-the-art technologies and scientific insight, relying on CDER databases to (1) support the evolution of CDER policies and guidelines that will economize the drug development and review process while maintaining the current high standards for drug efficacy and safety, and (2) solve well-defined regulatory problems in a timely manner. The research focus is on bridging preclinical studies from laboratory models to the clinical development and assessment phases of new drug candidates.

The Laboratory of Clinical Pharmacology (LCP) is focused upon the development of a strong scientific basis for regulatory decisions and broader initiatives, such as guidelines based upon the principles of clinical pharmacology, which can lead to more efficient drug development and approval.

The Regulatory Research and Analysis Staff (RRAS) uses the unique CDER databases of nonclinical and clinical outcomes to: (1) support the regulatory review process; (2) assess current practices for toxicology testing and related guideline development; (3) identify information gaps to aid in setting research priorities; and (4) evaluate computer assisted toxicology predictive modeling systems and the enhancement of these systems.

A key element of each program is the bridging of new scientific information and emerging technologies into regulatory practice. Examples of areas of science that currently present opportunities for improved testing methodologies and testing paradigms will be given.