CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: PHARMACEUTICAL SCIENCE ADVISORY COMMITTEE

DATE OF MEETING: 12/11-12/97

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AGENDA

ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

DECEMBER 11-12, 1997
QUALITY HOTEL
8727 COLESVILLE ROAD, SILVER SPRING

AGENDA

Day 1: Thursday, December 11, 1997

8:30- 8:45	Call to Order/Conflict of Interest	Robert Taylor, M.D., Ph.D.
8:45- 9:00	Overview and Objectives	Roger Williams, M.D.
9:00-10:15	**Biopharmaceutics Classification System (BCS)**	
	Moderator	Ajaz Hussain, Ph.D.
9:00-9:15	BCS Guidance Development: General Issues	Ajaz Hussain, Ph.D.
9:15-9:30	Permeability Determination in Vivo	Lydia Kaus, Ph.D.
9:30-9:45	Permeability Determination in Vitro	Donna Volpe, Ph.D.
9:45-10:15	Committee Discussion	
10:15-10:30	Break	
10:30-12:00	**Locally Acting Drug Products: Dermatologic Drug Products**	
	Moderator	Vinod Shah, Ph.D.
10:30-10:45	Guidance Development: Overview and Issues	Vinod Shah, Ph.D
10:45-11:00	Clinical Considerations	Howard Maibach, M.D.
11:00-11:10	Dermatologic Perspectives	Joseph McGuire, M.D.
11:10-11:25	Dermatopharmacokinetic Approaches	Hans Schaefer, Ph.D.
11:25-11:30	Lower Strengths	Vinod Shah, Ph.D.
11:30-Noon	Committee Discussion	

Noon-1:00	Lunch	
1:00-2:00	Open Public Hearing	
2:00-5:30	**Narrow Therapeutic Index Drugs**	
	Moderator	Roger Williams, M.D.
2:00-2:20	Overview	Roger Williams, M.D.
2:20-2:30	SUPAC Approach and Issues	Douglas Sporn
2:30-3:00	Individual Bioequivalence	Rabindra Patnaik, Ph.D.
3:00-3:15	Criteria	John Balian, M.D.
3:15-3:45	Break	
3:45-5:30	Committee Discussion	

Day 2: Friday, December 12, 1997

8:30-8:45	Call to Order/Conflict of Interest	Robert Taylor, M.D., Ph.D.
8:45-3:30	**Clinical Pharmacology Section of MPCC**	
	Moderator	Larry Lesko, Ph.D.
8:45-9:00	Overview	Larry Lesko, Ph.D
9:00-Noon	**Drug-Drug Interaction Guidance**	
9:00-9:15	General Issues	Shiew-Mei Huang, Ph.D.
9:15-9:30	Study Design	Peter Honig, M.D., M. P.H.
9:30-9:45	Data Analysis/Interpretation	Shiew-Mei Huang, Ph.D.
9:45-10:00	In Vitro-In Vivo Relationship	Jerry Collins, Ph.D.
10:00-10:20	Break	
10:20-Noon	Committee Discussion	

Noon-1:30	Lunch	
1:30-2:00	Open Public Hearing	
2:00-3:30	**Documentaion of BE Studies During the IND Period**	
2:00-2:05	Introduction	Larry Lesko, Ph.D.
2:05-2:20	General Issues	Dale Conner, Pharm.D.
2:20-2:35	Clinical Perspective	Peter Honig, M.D., M.P.H.
2:35-3:30	Committee Discussion	
3:30-3:45	Break	
3:45-4:30	**Office of Testing and Research Preview**	
3:45-4:00	Phamacology/Toxicology Research Program	James MacGregor, Ph.D.
4:00-4:15	Product Quality Research Initiative (PQRI)	Karl Flora, Ph.D.
4:15-4:30	Committee Discussion	
4:30	Adjourn	

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DATE OF MEETING: 12/11-12/97

SLIDES

Slides for the
A C P S Meeting
on
Dec. 11-12, 1997

Advisory Committee for Pharmaceutical Science
December 11, 1997
Topical Dermatological Drug Products

Guidance Development: Overview and issues	Vinod P. Shah, Ph. D.
Clinical Considerations	Howard Maibach, M. D.
Dermatological Perspectives	Joseph McGuire, M. D.
Dermatopharmacokinetic Approaches	Hans Schaefer, Ph. D.
Lower Strength	Vinod P. Shah, Ph. D.

Committee Discussions

Input requested on two issues:

1. Can dermatopharmacokinetic (DPK) methodology be used for BE determination of all dermatological drug products? For, e.g.,
   - Antiacne (Retinoids)
   - Antiviral
   - Antifungal
   - Antibacterial
   - Glucocorticoids

   If not, then for what classes can it be used.

2. Can in-vitro drug release be used for granting bio-waiver for lower strength?

Bioequivalence Determination

- Clinical:	Difficult, Expensive, Insensitive
- Pharmacodynamic:	Now applicable to only few classes of compounds, e.g., glucocorticoids
- Dermatopharmacokinetics:	Feasible, Logical, Generally applicable
- In vitro method:	Universally applicable Signal of possible inequivalence

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- Glucocorticoids:
  Pharmacodynamics Guidance - Topical Dermatologic Corticosteroids: In Vivo Bioequivalence (June 2, 1995)
- Antifungals:
  Comparative Clinical Studies with Bioequivalence Determination, Draft Guidance (February 24, 1990)
- Antivirals:
- Antiacne:
- Antibacterials

Lower Strength

Oral immediate release drug products:

- BE study at highest dosage strength
- Lower strength products approved based on composition similarity and dissolution profile

Similarly, for

Locally acting dermatological drug products,

- BE study at highest dosage strength
- Approval of lower doses based on composition similarity and in-vitro drug release?

Lower Strength

Assumption:

- Formulations (of two strengths) differ only in the concentration of the active ingredient
- There is no difference in manufacturing process and type of equipment used between the two strengths

Requirements:

- Reference Listed Drug (Innovator) is marketed at both the strengths - Higher Strength (HS) and Lower Strength (LS)
- The generic product is determined to be BE to innovator product using appropriate BE test requirement.

Lower Strength

In Vitro Release:

All release rates should be measured under the same test conditions.

In vitro release rate should be compared between

(1) Reference products at both the strengths (RHS and RLS)

(2) Test (generic) products at both strengths (THS and TLS)

On the basis of comparative in vitro release rate ratio, it is proposed that in vivo BE requirements for lower strength product can be waived.

$$\frac{\text{Release rate of R HS}}{\text{Release rate of R LS}} \sim = \frac{\text{Release rate of T HS}}{\text{Release rate of T LS}}$$

VP Shah, December 11, 1997

Derm

ROUTE OF AGENT APPLIED TO SKIN SURFACE

1. Stratum corneum - inter-corneocyte lamella
2. Microfissures in S.C. related to disease e.g., dermatitis
3. Eccrine glands
4. Pilosebaceous
5. Hair Follicles
6. Changes in integrity of epidermis by prior treatment.

McGuire

AGENT AND TARGET

SC	VEP	P. DERMIS
urea	GCS	GCS
salicylic acid	RA	?RA
∝ OH acid	CPT	?CPT
lactic acid		
emollient		
detergent		

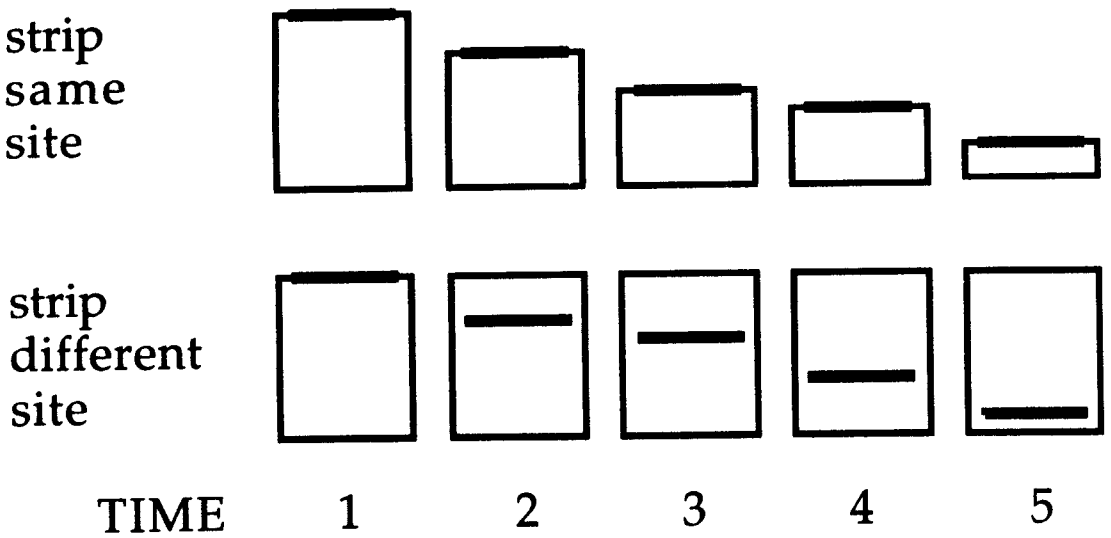
scale
xerosis
UV protection

dermatitis
psoriasis
acne

intracellular lamella
corneocytes
suprabasal
granular cell
basal cell
melanocyte
Langerhan cell
lymphocyte
fibroblast
mast cell
endothelial cell
lymphocyte

TAPE STRIPPING FOR DERM PK

1. Skin site preparation
2. Application of drug
3. Clean site after application
4. Tape strip
5. Successive strippings - same site or different site
   (Stripping changes permeability, induces cytokines)



SUPAC Approach and Issues

- The List
- Generic Drug Scandal 1989-1994
- Regulatory Definition
- Application to SUPAC's

Dr Spoun

SUPAC =

Scale-Up and Post-Approval Changes

Narrow Therapeutic Range Drugs

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

ER - Extended Release
DR - Delayed Release

21 CFR 320.33(c)

- Less than 2-fold difference in median lethal dose and median effective dose values, or
- Less than 2-fold difference in minimum toxic concentrations and minimum effective concentrations in the blood, and
- Safe and effective use of the products require careful titration and monitoring

SUPAC - Examples of Impact (cont.)

MR - Components and Composition - Release Controlling Excipient

Level 2 Change - test documentation varies on whether product considered to have narrow therapeutic range

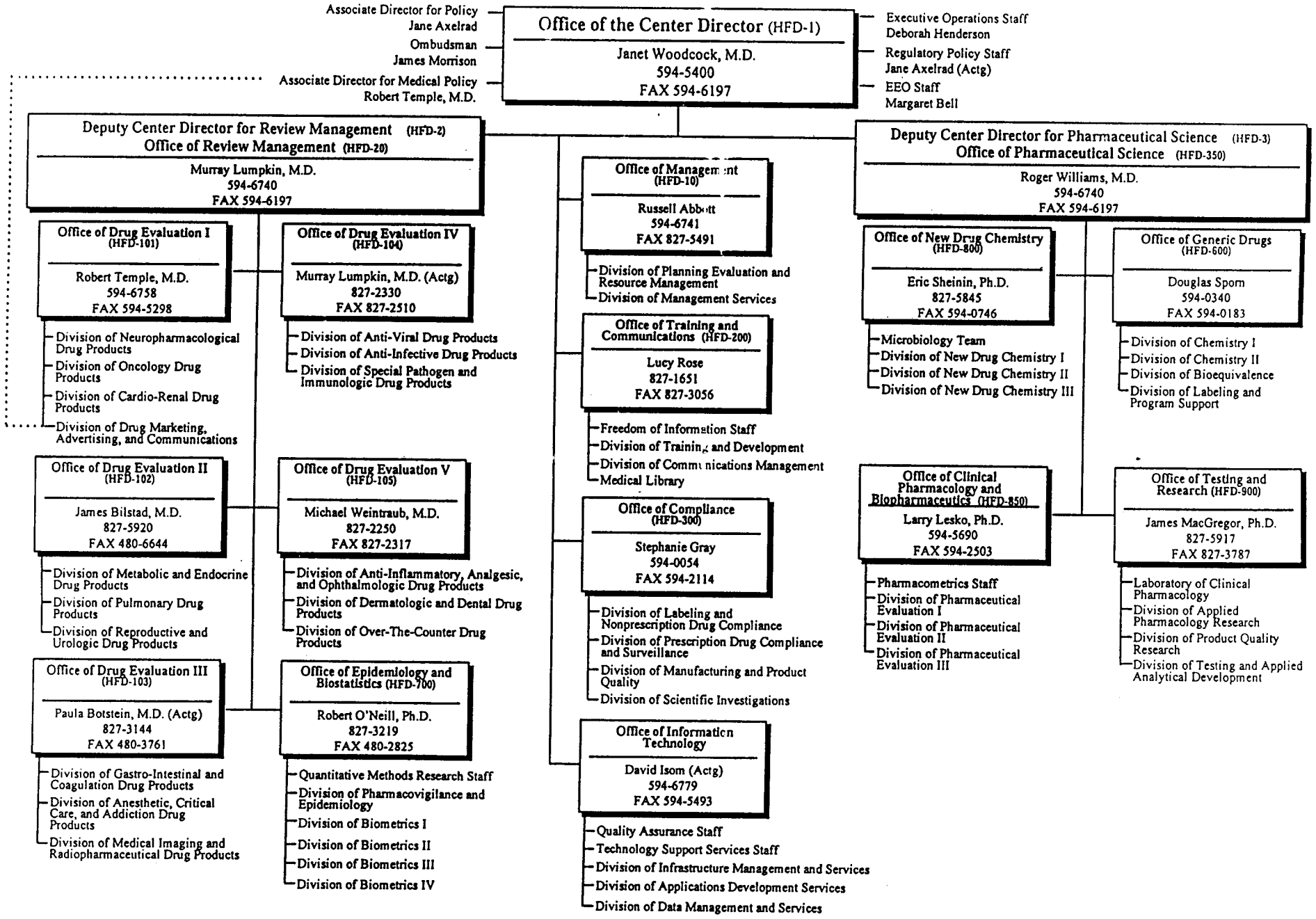
Advisory Committee for Pharmaceutical Science
Quality Hotel
Colesville Road, Silver Spring
December 11, 1997

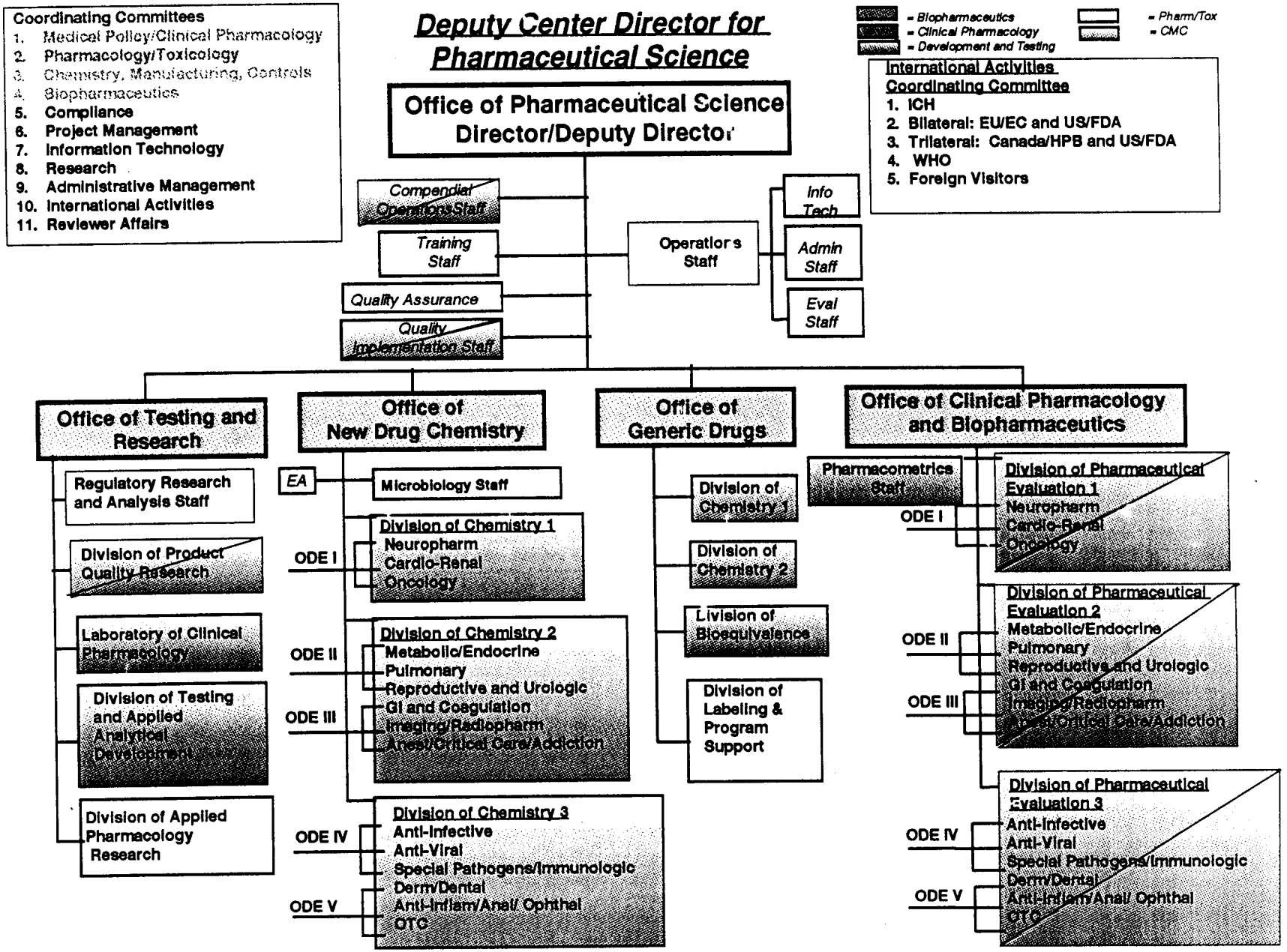
Overview and Objectives

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

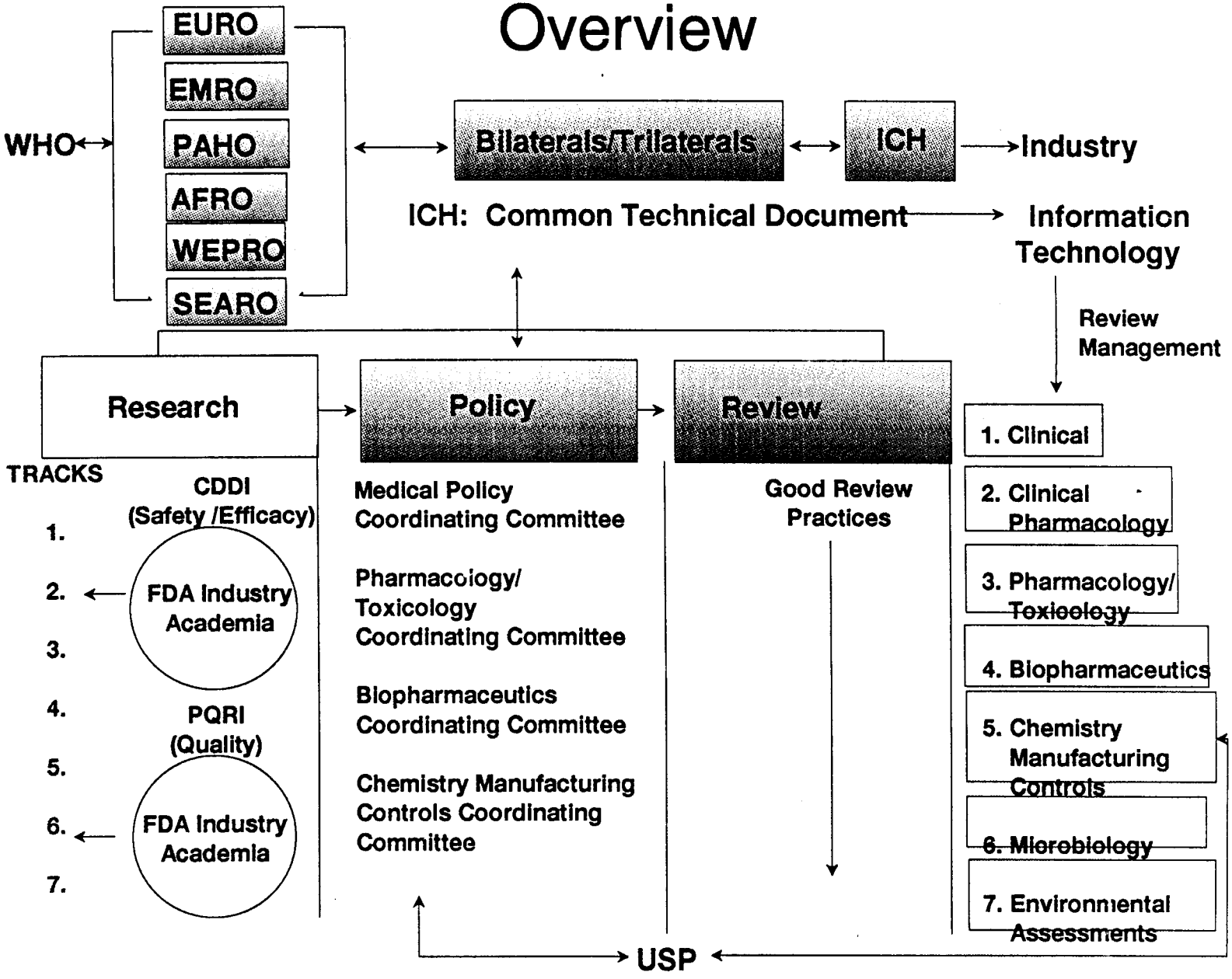
CENTER FOR DRUG EVALUATION AND RESEARCH

AS OF: 10/29/97

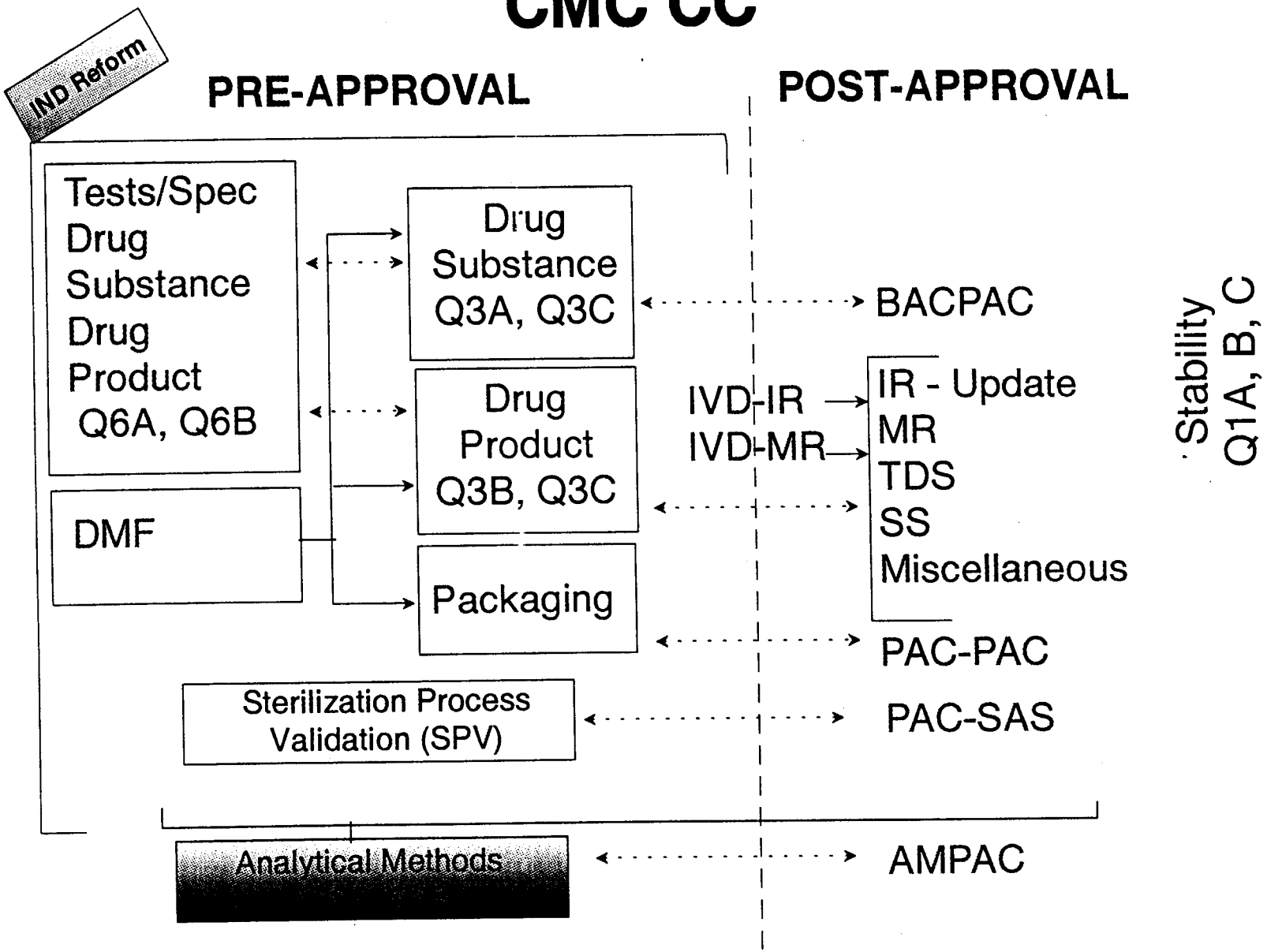


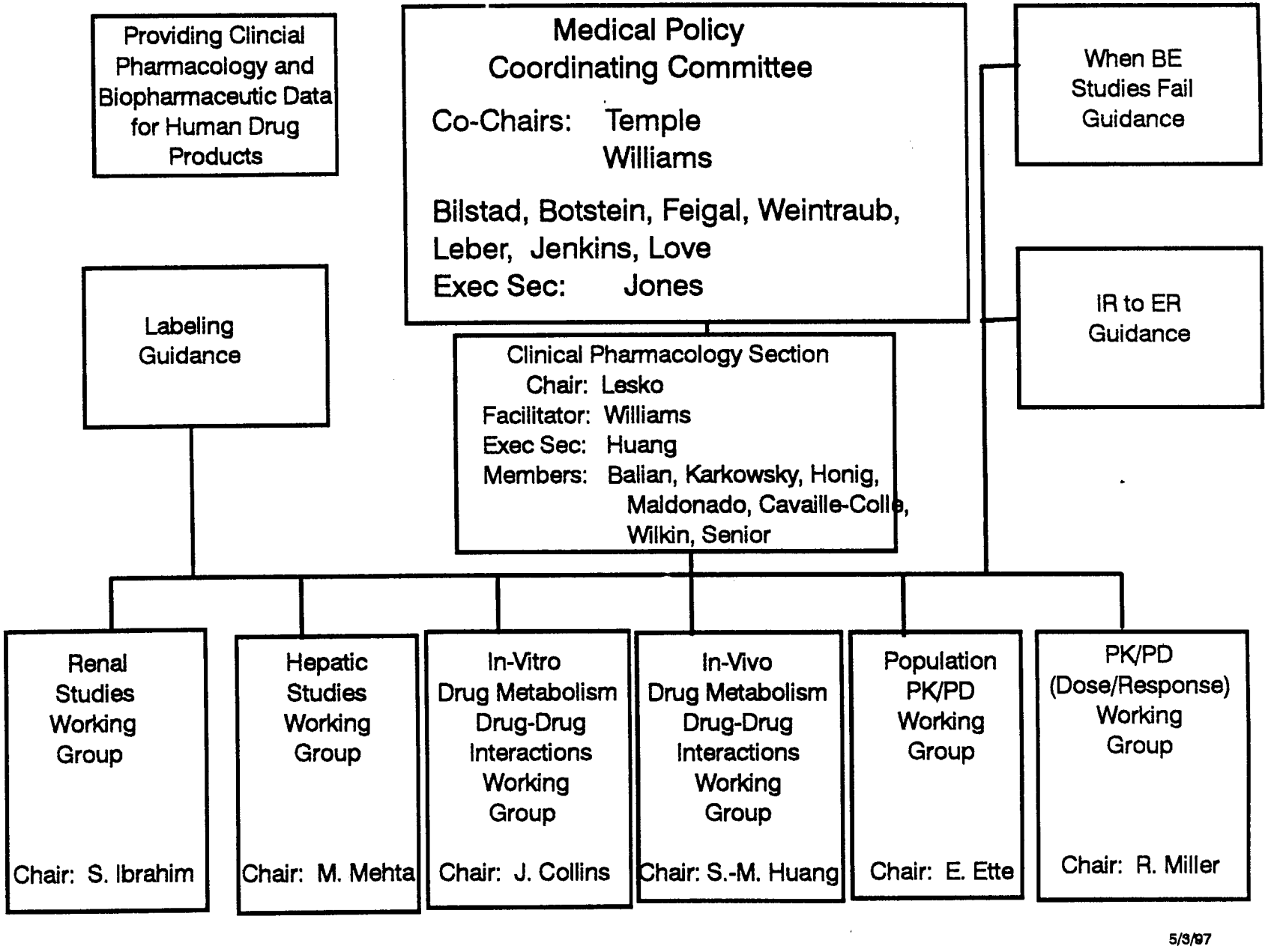

Coordinating Committees
1. Medical Policy/Clinical Pharmacology
2. Pharmacology/Toxicology
3. Chemistry, Manufacturing, Controls
4. Biopharmaceutics
5. Compliance
6. Project Management
7. Information Technology
8. Research
9. Administrative Management
10. International Activities
11. Reviewer Affairs
Deputy Center Director for Pharmaceutical Science
= 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
GI and Coagulation
Imaging/Radiopharm
Anest/Critical Care/Addiction
ODE III
ODE IV
Division of Chemistry 3
Anti-Infective
Anti-Viral
Special Pathogens/Immunologic
Derm/Dental
Anti-Inflam/Anal/ Ophthal
OTC
ODE V
Office of Generic Drugs
Division of Chemistry 1
Division of Chemistry 2
Livision 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
GI and Coagulation
Imaging/Radiopharm
Anest/Critical Care/Addiction
ODE III
ODE IV
Division of Pharmaceutical Evaluation 3
Anti-Infective
Anti-Viral
Special Pathogens/Immunologic
Derm/Dental
Anti-Inflam/Anal/ Ophthal
OTC
ODE V

Overview

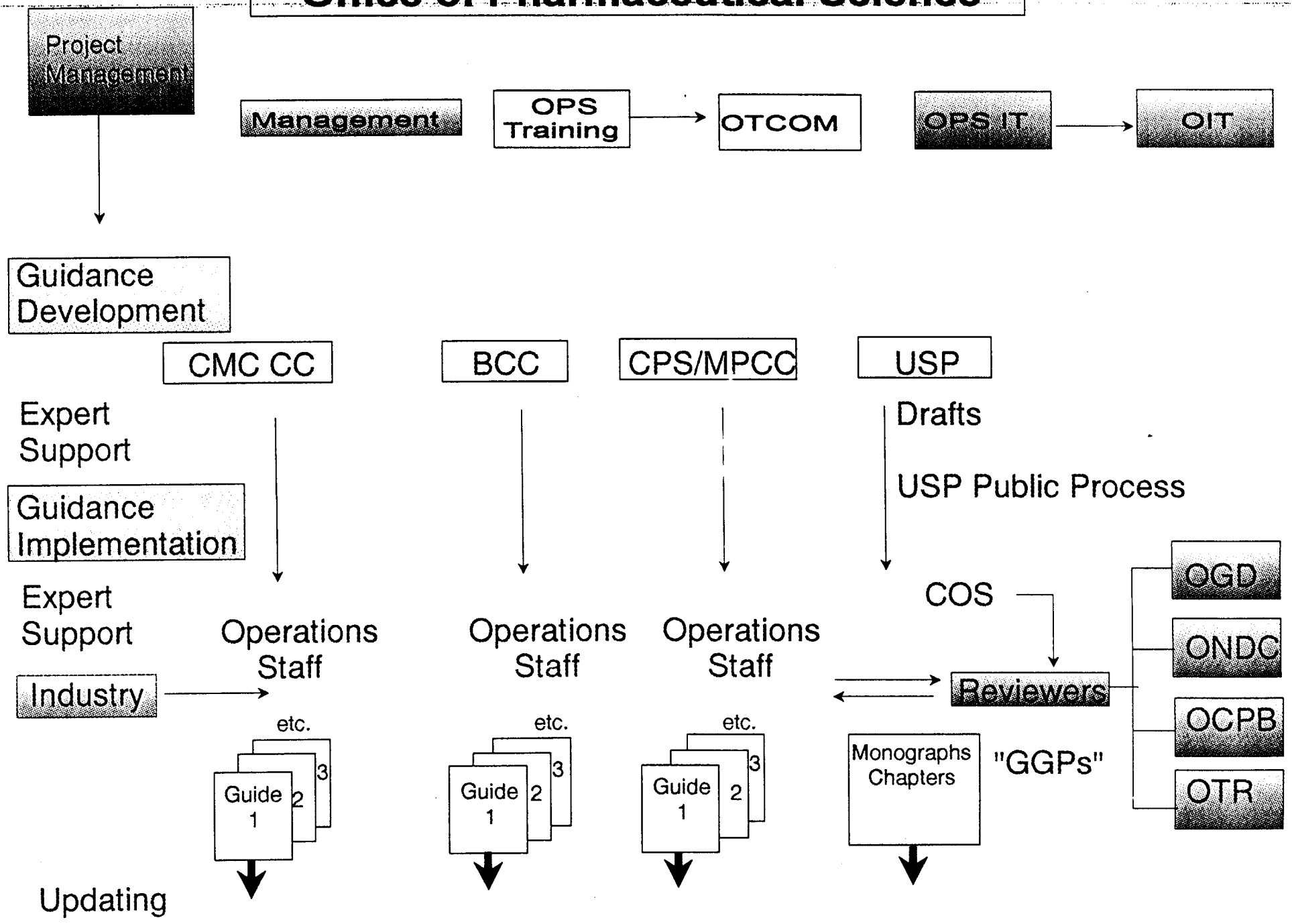

EURO
EMRO
PAHO
AFRO
WEPRO
SEARO
WHO
Bilaterals/Trilaterals
ICH
Industry
ICH: Common Technical Document
Information Technology
Review Management
Research
Policy
Review
TRACKS
CDDI (Safety /Efficacy)
1.
2.
3.
FDA Industry Academia
4.
PQRI (Quality)
5.
6.
7.
FDA Industry Academia
Medical Policy Coordinating 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

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
BACPAC
IVD-IR
IVD-MR
IR - Update
MR
TDS
SS
Miscellaneous
PAC-PAC
PAC-SAS
AMPAC
Stability
Q1A, B, C

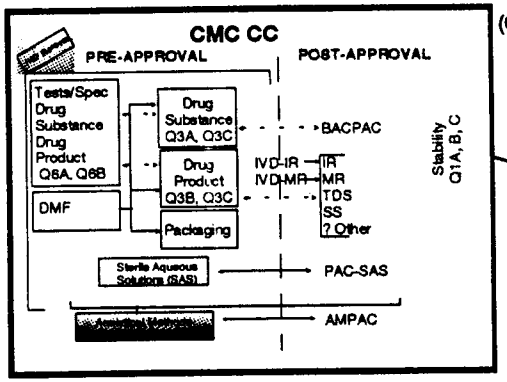

Providing Clincial Pharmacology and Biopharmaceutic Data for Human Drug Products
Medical Policy Coordinating Committee
Co-Chairs: Temple
Williams
Bilstad, Botstein, Feigal, Weintraub, Leber, Jenkins, Love
Exec Sec: Jones
When BE Studies Fail Guidance
IR to ER Guidance
Labeling Guidance
Clinical Pharmacology 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

Office of Pharmaceutical Science



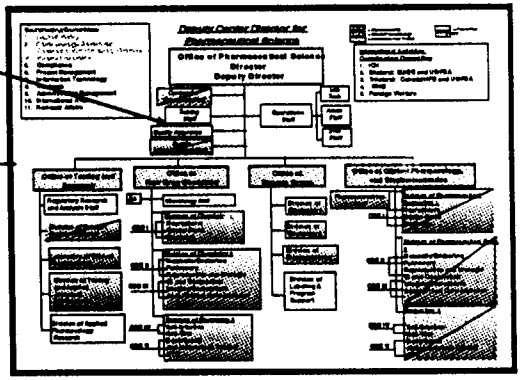
OPS GUIDANCE PROCESS

Guidances



(Clinical Pharmacology Section/MPCC)

Training
Implementation
Management



(2 Years)

(1 Year)

Updating
(1 Year)

Lessons Learned

(3 Years)

CDDI

PQRI

Biopharmaceutics Classification System: Development of Guidance Document

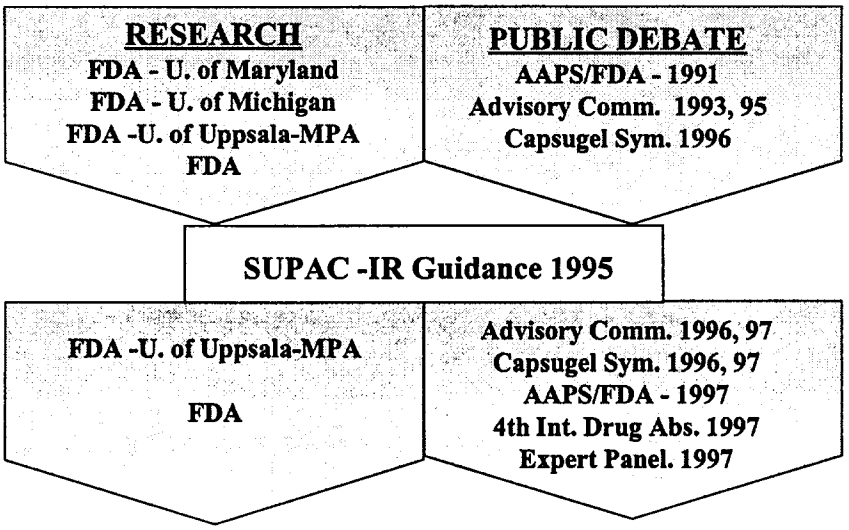
Ajaz S. Hussain, Ph.D.
BCS Working Group
BCC/OPS/CDER/FDA

Guidance: Research - Policy - Review

- **Regulatory tool for improving the effectiveness and efficiency of reviews**
- **Tool, for industry, for optimizing drug development by reducing regulatory uncertainty**
- **Non-binding recommendations**

- **Research**
  - Establishing causal links, understand mechanisms, and creating a framework for rational decision making
- **Policy**
  - Identify areas of agreement between causal links and regulatory decisions
- **Review**
  - Improve effectiveness and efficiency by allowing reviewers to focus on problem areas

BCS: Research - Policy



Purpose of BCS Guidance

- To recommend methods to permit classification according to dosage form dissolution and the solubility and permeability characteristics of a drug.
- To recommend a class of immediate release solid oral dosage forms for which bioequivalence may be assessed based on dissolution tests, *in vitro*.

Working Group

- Lydia Kaus (OCPB): Permeability (human), F Vs. Peff relationship, computer simulation study.
- Ko-Yu Lo (ONDC): Solubility
- Ram Mhatre (OGD): Permeability (animals)
- Vinod Shah (OPS): Link BCS Guidance with the Dissolution Guidance
- Donna Volpe (OTR): Permeability (cell/tissue culture)
- Ajaz Hussain (OTR): Chair; Coordination of all efforts and experimental evidence for "rapid dissolution."

Biopharmaceutics Classification System (BCS)

- Background Information
  - Bioequivalence assessment
  - Biowaivers for oral solutions and immediate release (IR) solid oral dosage forms
  - Role of dissolution tests in bioequivalence assessment, before and after SUPAC-IR
- BCS approach for identifying IR dosage forms for which bioequivalence may be assessed based on dissolution tests

What is BCS?

- A tool, based on drug solubility and permeability, and product dissolution characteristics, for:
  - 1) identifying when an *IVIVC* may be expected for conventional solid oral dosage forms (IR-products)
  - 2) recommending when bioequivalence assessment *in vivo* may not be necessary
    - improving confidence in dissolution tests *in vitro*

High Solubility
(Draft Not for Implementation)

- pH-solubility profile over the pH range of 1-8 at 37 °C is suggested
- Eight or more pH conditions are recommended
- High Solubility: When the volume of each buffer required to dissolve the highest strength in less than or equal to 250 ml
- Solution stability documentation recommended

High Permeability: SUPAC-IR

- "Permeability (P_e, cm/sec) is defined as the effective human jejunal wall permeability of a drug and includes an apparent resistance to mass transport to the intestinal membrane. High permeability drugs are generally those with an extent of absorption greater than 90% in the absence of documented instability in the gastrointestinal tract, or those whose permeability attributes have been determined experimentally."

High Permeability
(Draft Not for Implementation)

- High permeability drugs are expected to be "rapidly and completely absorbed"
- High permeability drugs are generally those with an extent of absorption greater than 90% (lower confidence interval bound of 80%) in the absence of documented instability in the gastrointestinal tract.

BCS Hypothesis

- If two drug products, containing the same drug, have the same concentration time profile at the intestinal membrane surface then they will have the same rate and extent of absorption (Amidon *et. al.*, 1995)
- Similar dissolution profiles ensures bioequivalence of some drug products that undergo minor post approval changes (SUPAC-IR Guidance, Nov. 1995)
- Dissolution tests may be used to assess bioequivalence of rapidly dissolving products of highly soluble and highly permeable drugs (BCS Guidance under development)

Beyond SUPAC-IR: Next Step

	HS/HP	LS/HP	HS/LP	LS/LP
Critical Process	**Gastric Emptying**	**Dissolution**	**Permeability**	**Case by case**
IVIVC	**Not likely**	**Likely**	**Not likely**	**Case by case**
Dissolution	**0.1 N HCl**	**pH 1 - 7.5**	**Compendial**	**Case by case**
Standard	**Single point**	**Multiple profiles**	**Single profile**	**Case by case**
Beyond SUPAC-IR	**(✓)**	**?**	**?**	**?**

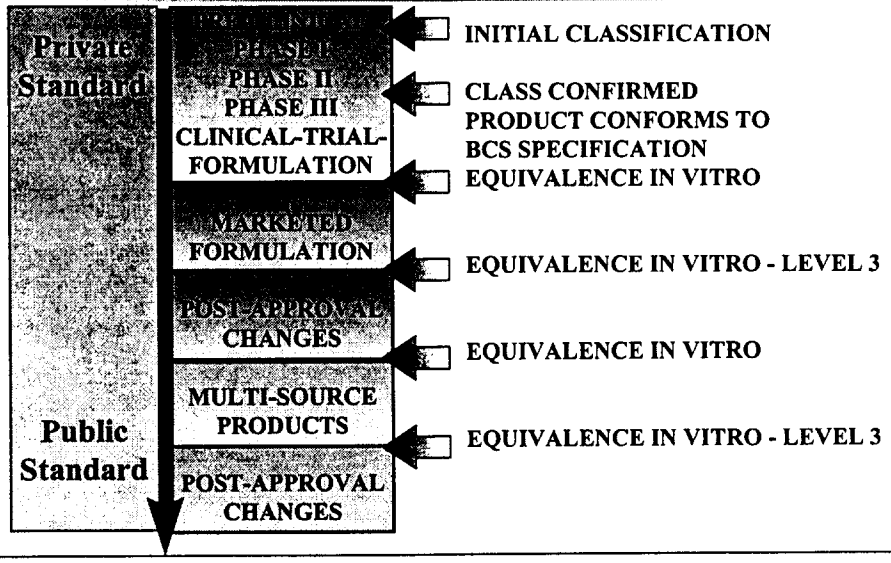
BEST POSSIBLE

Rapidly Dissolving Products of Highly Soluble and Highly Permeable Drugs

- Absorption generally characterized as "rapid and complete"
- When dissolution is rapid in gastric fluid, the rate of absorption is primarily a function of gastric emptying
- High solubility plus high permeability classification ensures extent of absorption
- Dissolution tests may serve as a sensitive tool to ensure rate of absorption

BCS Application Beyond SUPAC-IR

(Draft Not For Implementation)

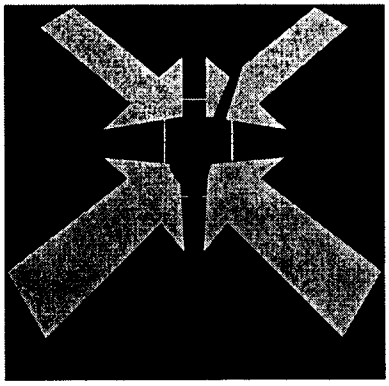


Examples of "Level 3" Changes

- SUPAC-IR
  - Quantitative change in formulation beyond current SUPAC-IR Level 2 Change
    - Change greater than +/- 0.5% for Mg-stearate
  - Qualitative change in composition
  - Change in type of manufacturing process
    - Wet granulation to direct compression
- Other changes
  - Drug Particle size
  - Capsule to Tablet

Pre-defined Dissolution Specification

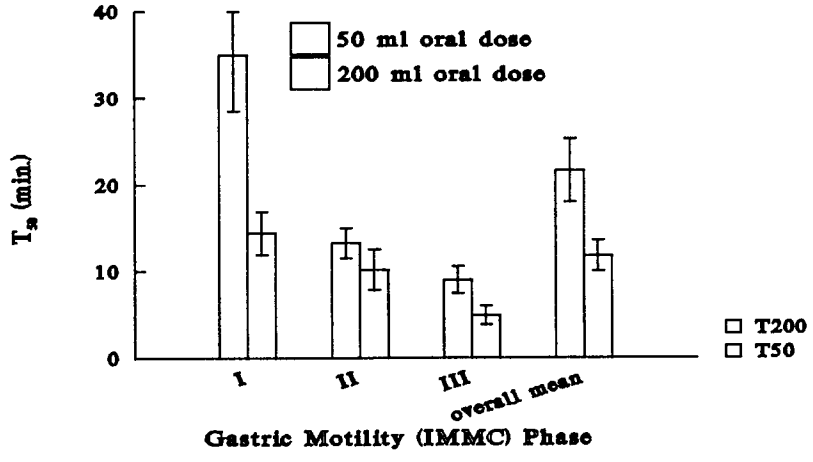
- Immediate release drug products of highly soluble and highly permeable class of drugs manufactured in accordance with cGMP's to meet optimal pre-defined specification for rapid dissolution are likely to be bioequivalent.
- Acceptable SOP's, in-process controls, other specifications, stability, and validation.



Dissolution Test for Bioequivalence Assessment

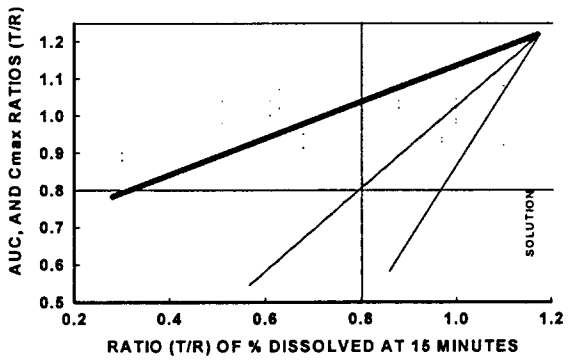
- **Ho:** Two IR solid oral products that meet SUPAC-IR Case A dissolution specification are likely to be bioequivalent.
  - Dissolution of not less than 85% in 15 minutes in 900 ml or less of 0.1 N HCl, at 37°C, when tested using the USP apparatus 1 and 2 at the usual rate of agitation of 100 and 50 rpm, respectively.
  - 15 minutes is based on the average time it takes to empty 50% of 200-250ml water administered to fasting normal healthy human volunteers (literature values range from 6 - 20 minutes).

Human Gastric Emptying Rates: T50



Expected IVIV Relationship

IN VITRO DISSOLUTION AND BIOEQUIVALENCE RELATIONSHIP
RD DRUG PRODUCTS OF HS & HP DRUGS



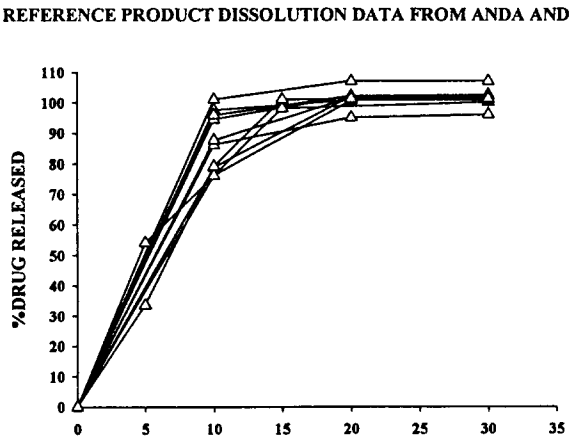
BEST
POSSIBL

Evaluation of Dissolution Tests

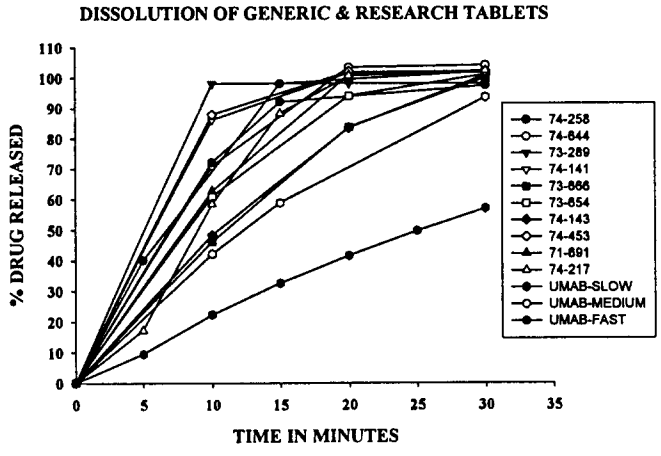
- FDA-UMAB Research Data
- Survey of Literature
- NDA/ANDA Information
- Supportive Simulation Study

BEST POSSIBLE

Metoprolol Reference Product Dissolution Data



Metoprolol Dissolution Data: Multisource and Research Tablets



BEST POSSIBLE

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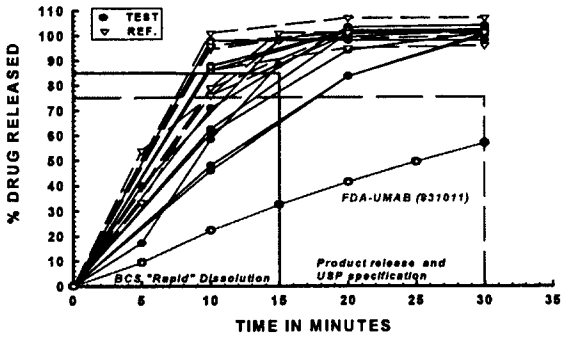
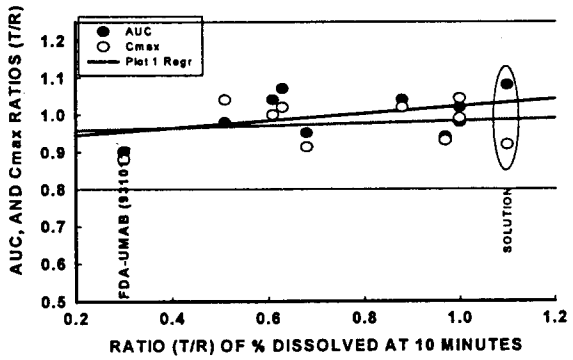
Metoprolol Dissolution

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



IVIV Relationship

IN VITRO DISSOLUTION AND BIOEQUIVALENCE RELATIONSHIP
METOPROLOL 100 mg CONVENTIONAL TABLET



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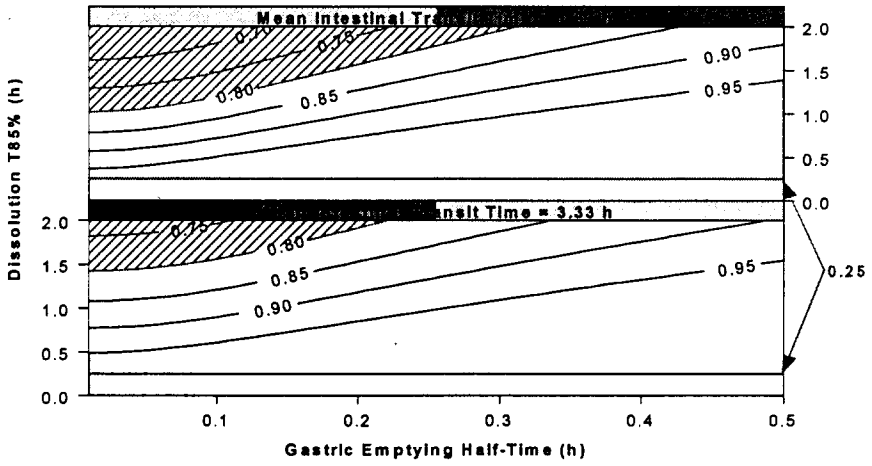
Simulation Study*: Cmax Ratio for Tablet vs. Solution



* L. Kaus, W. Gillespie, A. Hussain, G. Amidon

Bioequivalence Assessment In Vitro

Rapidly dissolving conventional solid dosage forms of highly soluble and highly permeable drugs - equivalence determination based on dissolution tests and assessment of inactive ingredients

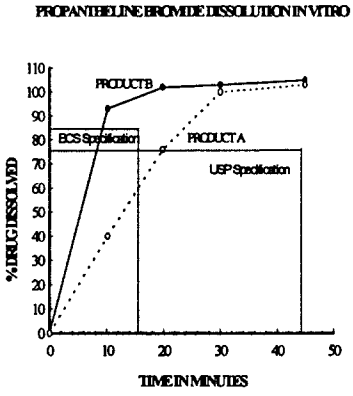
The BCS Approach: Dissolution - Solubility- Permeability

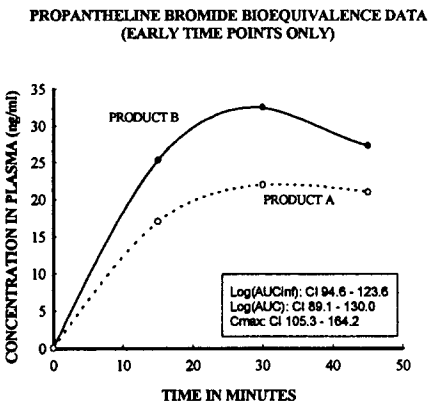
21 CFR 320.33	**The USP Experience**
Criteria and Evidence Actual or Potential Bioequivalence Problems 1. Clinical 2. Physico-chemical 3. Pharmacokinetics	"There are no medically significant bioinequivalence problems with articles where 75% of an article dissolved in water or acid at 37° C in 45 minutes in the official basket or paddle apparatus operated at the usual speed, that is, USP First Case"

BEST POSSIBLE

BEST POSSIBLE

Dissolution Tests: Need for Early Sampling

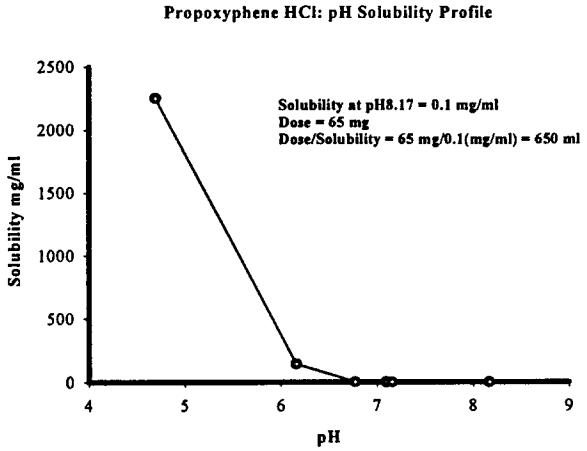




Reported Failures

- Failure: Dissolution test unable to discriminate between "bioinequivalent" products
  - Inappropriate specification
  - Inappropriate test conditions
  - Highly variable products?
- Literature Examples:
  - Propoxyphene HCL capsules (DeSante et al. J. Pharm. Sci. 66: 1713, 1977): Mean AUC ratio for a experimental formulation (dissolution 96.5% in 10 min) was 0.76 compared to the reference (dissolution 89.9% in 10 min). Unknown dissolution media or test conditions.

Propoxyphene HCL



C. Brownell, and G. Shiu. DPQR Lab Data

Survey of New Drugs (CNS)*: Selection Based on Dissolution Specification

NDA	Dosage Form	Dissolution Test	Specification
1	Tablet	USP2, 50rpm, 900ml 0.1NHCl	NLT 85%in 30 min
2	Tablet	USP2, 50rpm, 500ml 0.1NHCl	NLT 80%in 15 min
3	Tablet	USP1, 50rpm, 500ml pH4.5 buffer	NLT 85%in 15 min
4	Tablet	USP2, 50rpm, 900ml water	NLT 80%in 30 min
5	Capsule	USP2, 50rpm, 900ml 0.01NHCl	NLT 80%in 30 min
6	Tablet	USP2, 75rpm, 900ml pH8.5 buffer	NLT 80%in 30 min
7	Tablet	USP2, 50rpm, 900ml 0.1NHCl	NLT 80%in 30 min
8	Tablet	USP2, 50rpm, 900ml 0.1NHCl	NLT 80%in 30 min
9	Tablet	USP1, 100rpm, 500ml 0.1 NHCl	NLT 80%in 15 min
10	Tablet	USP2, 50rpm, 900ml 0.1NHCl	NLT 80%in 15 min
11	Tablet	USP2, 50rpm, 900ml water	NLT 80%in 20 min

*V. Tammara, M. Hossain, H. Malinowski, A. Hussain

BEST POSSIBLE

Solubility and Permeability Characteristics

NDA	Solubility	Permeability	Comments
1	High	Likely to be High	79% in urine, LogP = 5
2	High	?	65% in urine, LogP = 1
3	High	High	91% in urine
4	High	?	73% in urine, LogP = 3
5	Low	?	52% in urine, LogP = 4
6	Low	?	60% in urine
7	(Low)*	High	90% in urine, LogP = 4
8	High	High	95% in urine, LogP=- 2
9	High	?	53% in urine
10	High	High	Bioavailability 90%
11	High	?	70% in urine

* Appears to be borderline. Use of approved dose strength (1/2 of what was used in one BE study) for calculation may result in classification as High. Poor solubility/dissolution in water and simulated intestinal fluid.

Relative Bioavailability, Food Effects, and Metabolism

NDA	Relative Bioavailability	Food Effect	Metabolism	Isozyme
1	1.0, 1.0,1.0 *	1.0, 0.95, 1.1 *	High	CYP2D6 & 3A4
2	0.93, 0.94, 2.1	0.85, 0.85, 1.2	High	NA
3	0.85, 0.88,1.0	0.90,0.77,2.7	High	CYP1A2
4	1.0, 1.0, 1.0	1.2, 1.3, 1.1	High	CYP3A4
5	0.89, 1.1, 1.0	1.1, 0.95, 1.2	High	CYP3A4 & 2D6
6	NA	0.80, 0.50, 2.0	High	NA
7	NA	0.80, 0.70, 2.5	High	CYP1A2
8	1.0, 0.9, 1.6	1.0, 0.8, 2.0	Low	NA
9	NA	1.0, 1.3, 0.4	High	NA
10	0.95, 0.9, 1.0	1.0, 0.60, 3.5	Low	NA
11	0.82, 0.86, 0.5	1.0, 0.84, 3.0	Low	NA

** AUC, Cmax, Tmax Ratios (mean)*

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BEST POSSIBLE

Formulation Changes and Bioequivalence

NDA	Formulation Changes	Bioequivalence
1	Site of manufacture and composition	2 SDF-BE
2	Addition of film coat, ...	2 SDF-BE
3	No change	None
4	Site, particle size,....	3 SDF-BE, 1 MD-BE
5	Tablet to capsule, site,...	4 SDF-BE
6	Site of manufacture	4 SD-BE (bioinequivalence with respect to Cmax in 2)
7	Wet granulation - direct compression, particle size,...	2 SDF-BE (bioinequivalence with respect to Cmax in 2)
8	Addition of film coat, ...	1 SDF-BE
9	No changes	1 SDF-BE (mapping)
10	Addition of film coat, ...	10 SD-FBE, 1 MD-BE (MD study - bioinequivalence with respect to CI of Cmax)
11	No change	2 SDF-BE

SDF-BE: Single dose fasting bioequivalence study; MD: Multiple dose in patients

Failure to Demonstrate Bioequivalence

NDA	Solubility and Permeability	Dissolution Specification	BE Study and Dissolution
6	Low and ?	NLT 80% in 30 min USP 2, 75 rpm, 900ml pH 8.5 buffer	Single dose fasting; Dissolution differences noted
7	(Low) and High	NLT 80% in 30 min USP 2, 50 rpm, 900 ml 0.1 NHCl	Single dose fasting; Disintegration and Dissolution Differences (inverse relation)
10	High and High	NLT 80% in 15 min. USP 2, 50 rpm, 900 ml 0.1 NHCl	Multiple dose in patients to compare low and high strengths

One Case: Need for 5 Minute Dissolution Specification

- The review staff in the OCPB/DPEIII (C. Sahajwalla) provided one example where a five minute specification was necessary to assure bioequivalence with respect to Cmax
  - Change: Capsule to Tablet
  - Reference capsule: 85% in 20 min
  - For tablet: Q=65% at 5 min and Q=85% at 15 min
  - 500 mg tablet - High solubility in pH 1 -3 but lower solubility in pH 4-8 range (approximately 0.03 mg/ml)

Need for 5 Minute Dissolution Specification

	BE		Dissolution	
LOT	AUC	Cmax	5 min	15 min
1	Yes	No	32	94
2	Yes	No	34	95
3	Yes	No	13	67
4	No	No	10	47
5	Yes	No	44	95
6	Yes	Yes	88	99

Dissolution Test: Summary

- Dissolution in vitro of 70-80% in 30 min, in 0.1 N HCl, is a good indicator of rapid dissolution in vivo. Case A specification appears to be conservative.
- Some members of the working group have concerns with borderline High Solubility drugs, especially those that exhibit low solubility/dissolution in pH reflective of intestinal fluids.
  - For bioequivalence demonstration should dissolution data in 2-3 media, with pH in 1-6.5 range, be requested?

Methods for Permeability

- Clinical Methods (Direct)
  - Human pharmacokinetic/mass balance studies
- Clinical (Indirect)
  - In vivo jejunal perfusion methods
- Pre-Clinical Methods
  - Human tissue/cell culture
  - Pharmacokinetic studies or intestinal perfusion in animals

Permeability Determination

- Any method that does not directly estimate the extent of drug absorption in humans will need to be justified and the ability to predict the extent of drug absorption in humans demonstrated
- Impact of absorption mechanism and pre-systemic metabolism need to be considered when selecting experimental method(s)
- Issues: Method selection, standardization (use of "internal standards" to reduce variability)

Pharmacokinetic Studies

- Absolute bioavailability obtained from comparing data after oral vs. intravenous administration
- Mass balance with use of radiolabeled drug
- Mass balance with specific assays

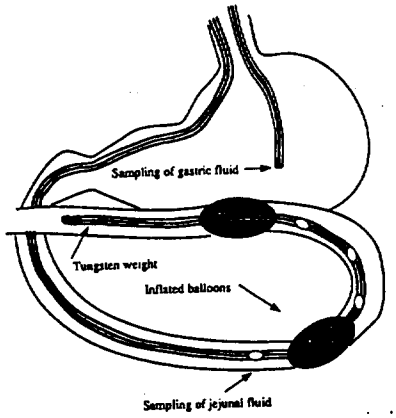
Absolute Bioavailability

- Gives measure of drug available to the systemic circulation, but not necessarily the amount of drug absorbed prior to metabolism
- Intravenous form of drug not always feasible

Mass Balance Studies

- Difficult to account for greater than 80% of drug administered
- Erroneous conclusions drawn if:
  - Drug unstable in gut lumen
  - Metabolism in gut lumen
  - Re-cycling of drug
  - Insufficient time for collection of samples

Jejunal Perfusion Method



- Perfusion of proximal regional jejunal segment in healthy subjects
- Fluids perfused at set rate
- Perfusate samples collected at set intervals
- Non-absorbable markers for fluid flux corrections

Jejunal Perfusion Method (cont.)

- Effective permeability determined from fluid flux corrected drug concentration in exit perfusate
- Shows correlation with fraction absorbed of drugs studied to date
- Can be used for drugs with differing mechanisms of absorption
- Some difficulties encountered with low solubility drugs
- Higher variability in the data compared to in vitro methods

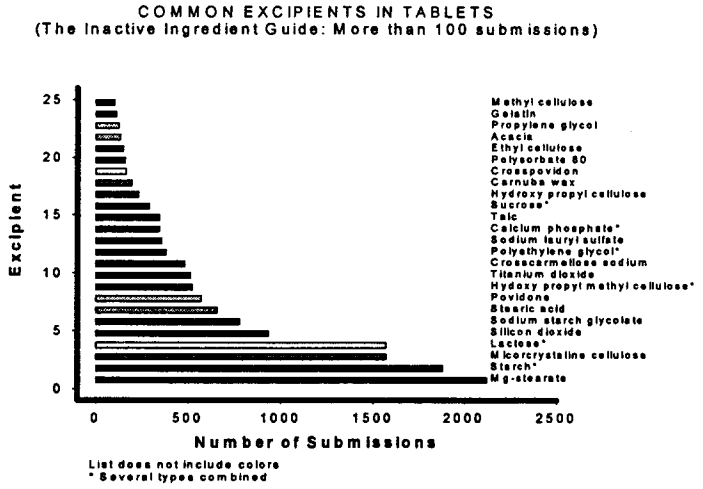
Influence of Inactive Ingredients?

- Detectable *in vitro*
  - Drug-Excipient interactions (chemical)
  - Drug-Excipient interactions (physical)
- Detectable *in vivo*
  - Excipient - GI motility
  - Excipient - Permeability
  - Excipient - Metabolism

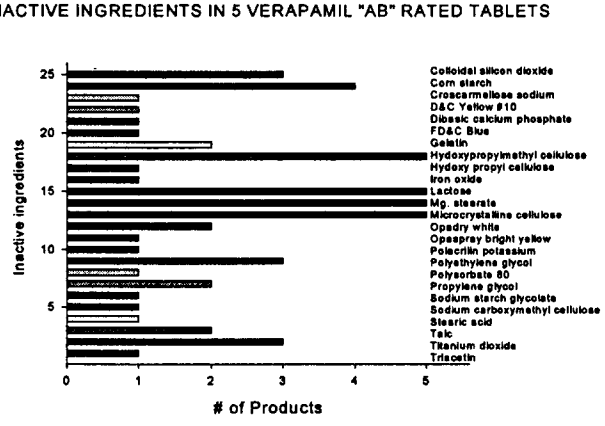
Examples of Potential Excipient Effects on Bioavailability

Excipient	Drug	BE	Mechanism
SAPP	Ranitidine	Reduced	Decreased SITT
Mannitiol	Cimetidine	Reduced	Decreased SITT
Sorbitol	Theophylline	Lower levels	Decreased SITT
Myristic acid	Nitrofurantoin	Increased	Increased gastric emptying time
Polysorbate 80, Cremophor	Pgp substrates	Potential to increase absorption	pgp inhibition, IV and In Vitro
Oleic acid-bile salts	Propranolol	Increased	Lymphatic uptake

Common Excipients in IR Tablets

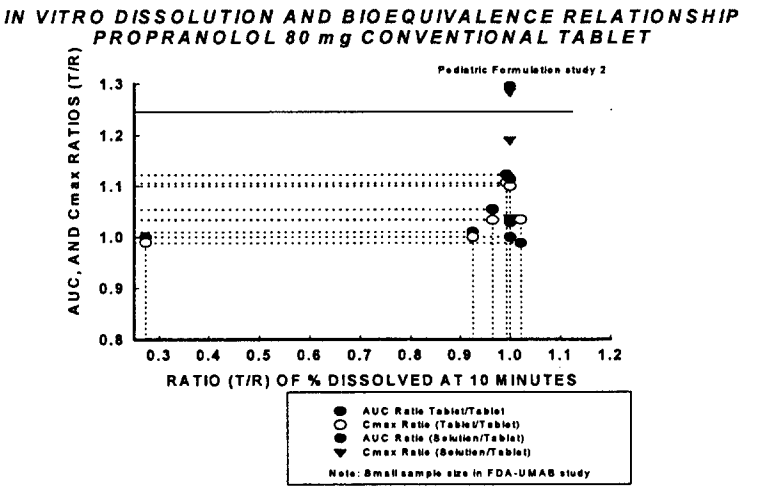


Inactive Ingredients: IR Solid Oral Dosage Forms



BEST POSSIBLE

Propranolol

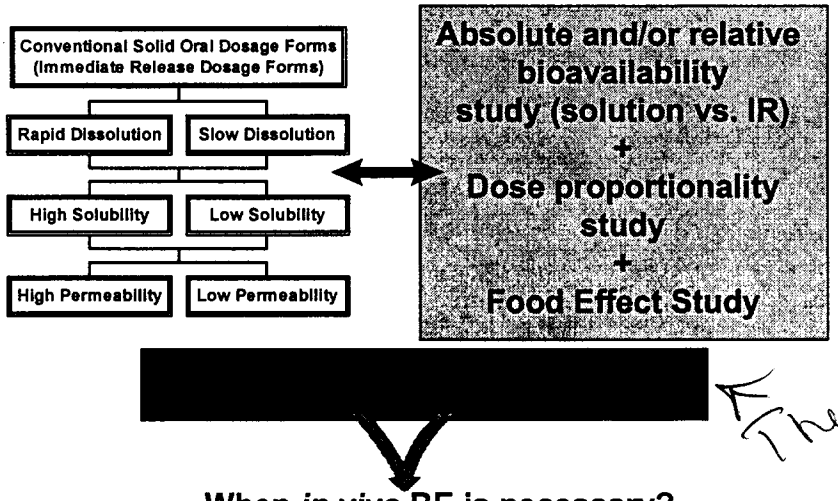


Inactive Ingredients: IR Solid Oral Dosage Forms

- Conventional solid oral products are not intended to alter GI motility, metabolism, etc.
- Disintegration, distribution, and dilution effects reduce the likelihood of excipient interactions
- Excipients in conventional solid oral products are likely to be inert compared to oral liquid products such as syrups and elixirs
- New excipients and/or unusually large quantities in a product would need to be evaluated

BEST POSSIBLE

Regulatory application of BCS



Therapeutic Clinical Considerations

Comments Received

- BCS Research Methods
  - Permeability - high variability
  - F% Vs. Peff relationship
  - Permeability - Absorptive Clearance
  - Fick's Law assumptions not appropriate
- AAPS/CRS/FDA Workshop (April '97)
  - Rapid dissolution - too conservative
  - Why do we need Permeability in BCS?
  - Need to consider a sub-class for drugs exhibiting high first-pass metabolism (excipients may interfere)
  - Overall strong support for this approach

Expert Panel Meeting: Members

- 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)

Expert Panel Meeting: Issues

- What data or evidence should be determined for the classification of a drug as either high or low permeability?
  - 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%?]
  - How should this data be obtained?
  - What assumptions do we need to make?

Expert Panel Meeting: Issues

- 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?
  - Should we define an "intermediate solubility" class (for example, high solubility in pH 3-8)?
- 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?
  - Should a product also meet the "rapid dissolution" specification in a media of higher pH (for example, pH 4.5)?

Expert Panel Meeting: Issues

- What other considerations are necessary when applying the BCS for regulatory decisions?
  - Narrow Therapeutic Index drugs?
  - Dose proportionality study information?
  - Any other considerations?
- When in drug development, can BCS be first applied?
  - Biowaiver for changes in clinical trial formulation?
  - Biowaiver for approving generic drug products?

BIOPHARMACEUTICAL CLASSIFICATION SYSTEM: *IN VITRO* CELL CULTURE SYSTEM FOR DETERMINING DRUG PERMEABILITY

Donna Volpe (DAPR), Patrick Faustino (DPQR), Alan Knapton (DAPR),
Christopher Ellison (DPQR), Karl Flora (DPQR), Ajaz Hussain (DPQR)

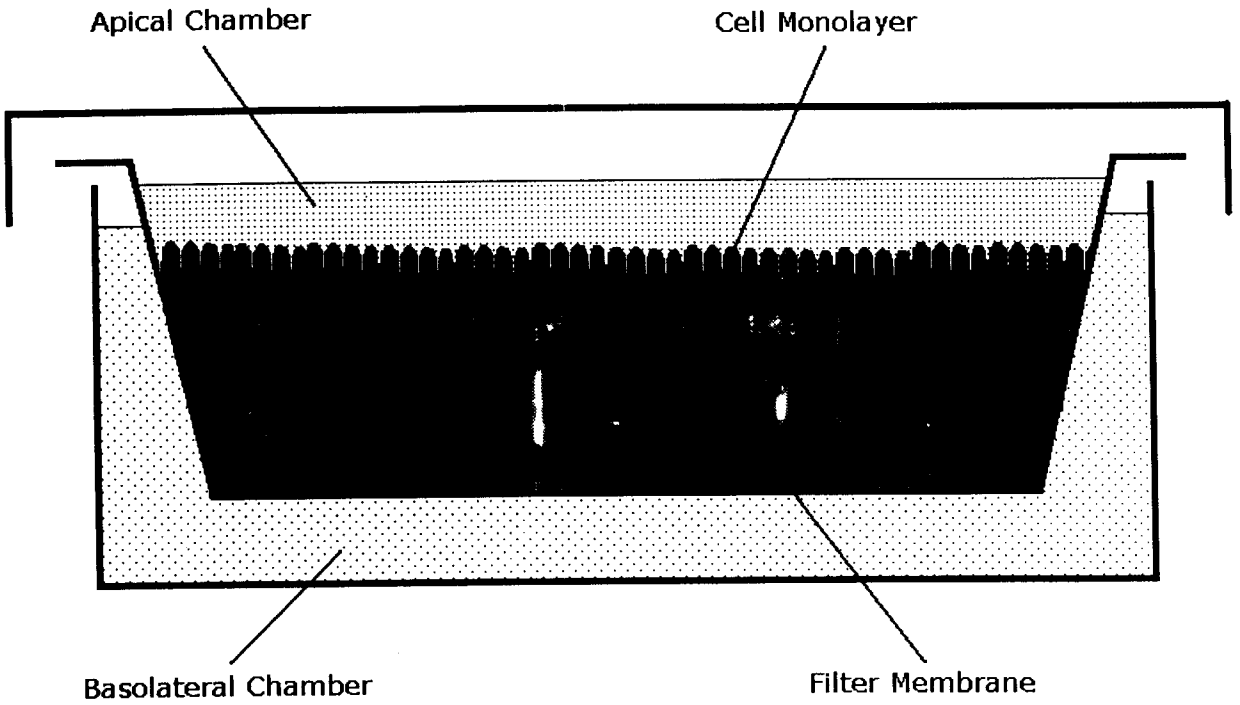
Office of Testing and Research
Center for Drug Evaluation and Research
Food and Drug Administration

ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCES
December 11, 1997

CELL CULTURE METHOD WITH CACO-2 CELL LINE

- *In vitro* model to evaluate drug permeability after oral administration.
- Caco-2 is a human colon adenocarcinoma cell line that undergoes spontaneous structural and functional differentiation.
- Caco-2 cells form confluent monolayers on filters with enterocytic morphology typical of villus cells with tight junctions, brush border enzymes and active transport systems.
- Caco-2 permeability values correlate well with extent of absorption in humans for passively transported drugs.

CACO-2 MONOLAYER IN CULTURE SYSTEM



IN VITRO - IN VIVO CORRELATIONS

- Good correlation between oral absorption in humans and results in Caco-2 model (R = 0.63, n = 20) [Artursson, Karlsson, 1991]:
  - if F% = 100%, $P_{eff} > 1.0 \times 10^{-6}$ cm/sec
  - if F% = 1-100%, $P_{eff} = 0.1\text{-}1.0 \times 10^{-6}$ cm/sec
  - if F% = < 1%, $P_{eff} \leq 1 \times 10^{-7}$ cm/sec

- Strong correlation between *in vivo* human absorption and *in vitro* P_{eff} (R = 0.78, n = 34) [Yee, 1997]:
  - if %F = 70-100%, $P_{eff} > 1.0 \times 10^{-6}$ cm/sec
  - if %F = 20-70%, P_{eff} $1.0\text{-}10 \times 10^{-6}$ cm/sec
  - if %F = 0-20%, $P_{eff} < 1.0 \times 10^{-6}$ cm/sec

- Caco-2 cells to predict passive drug transport in humans while prediction of carrier-mediated transport may require a scaling factor due to low expression of carrier in cell line [Lennernäs, et al., 1996].

EFFECT OF TRANSPORT/EFFLUX MECHANISMS

- What of highly metabolized drugs or those that are P-glycoprotein substrates?

- What is the role of metabolism and efflux mechanisms in Caco-2 studies?
  - ✦ A number of metabolic enzymes are present in the apical border of Caco-2 cells (e.g., lactase, peptidases, P_{450}, etc.).

  - Can Caco-2 culture system be used for actively transported drugs?
  - ✦ Transport mechanisms for amino acids and peptides, biotin, bile acids, sugars and monocarboxylic acid drugs have been described in Caco-2 cells.
  - ✦ In general, expression of transporters is different in Caco-2 calls as compared to *in vivo* human intestine.

USE OF INTERNAL STANDARD IN CACO-2 PERMEABILITY STUDIES

- Classification of drugs based on comparison to HP and/or LP internal standard(s).

- Selection of internal standards based on:
  - well defined permeability
  - known absorption mechanism(s)
  - chemical/physical compatibility with test compound
  - metabolic/efflux protein compatibility

- Potential standards:
  - Naproxen (HP)
  - Atenolol (LP)
  - Metoprolol (HP)
  - Ranitidine (LP)

- Internal standard(s) to demonstrate monolayer integrity and stability of system within a laboratory over time.

SPONSOR SUBMISSION OF CACO-2 CELL CULTURE EXPERIMENTS

- Integrity of monolayer:
  - ✦ Visual observations - intact, covering filter surface
  - ✦ TEER - direct measure of epithelial resistance to passive ion flow
  - ✦ Membrane leakage - lucifer yellow, mannitol, PEG 4000, inulin, dextran
  - ✦ Permeability of internal standard(s)
- Documentation of transport mechanism:
  - ✦ Passive (paracellular, transcellular) or active (carrier-mediated, transcytosis).
  - ✦ effect of time, drug concentration, energy source, temperature, direction.
- Documentation of drug compatibility of internal standard(s) with test compound.
  - ✦ Simultaneous or sequential addition of test compound and standard to monolayer.

OTR CACO-2 PERMEABILITY STUDY

- Use of internal standard (ISD) with test compound
  - ✦ complex formation
  - ✦ permeability of test compound with and without internal standard
- Chemical parameters
  - ✦ binding of drugs to plate, filter, media components
  - ✦ drug stability (time, temperature)
- Monolayer integrity
  - ✦ TEER
  - ✦ Lucifer yellow
- Effect of stirring on drug permeability
- Collagen-coated vs. uncoated membrane filter
- Permeability of P-glycoprotein substrates

SUMMARY

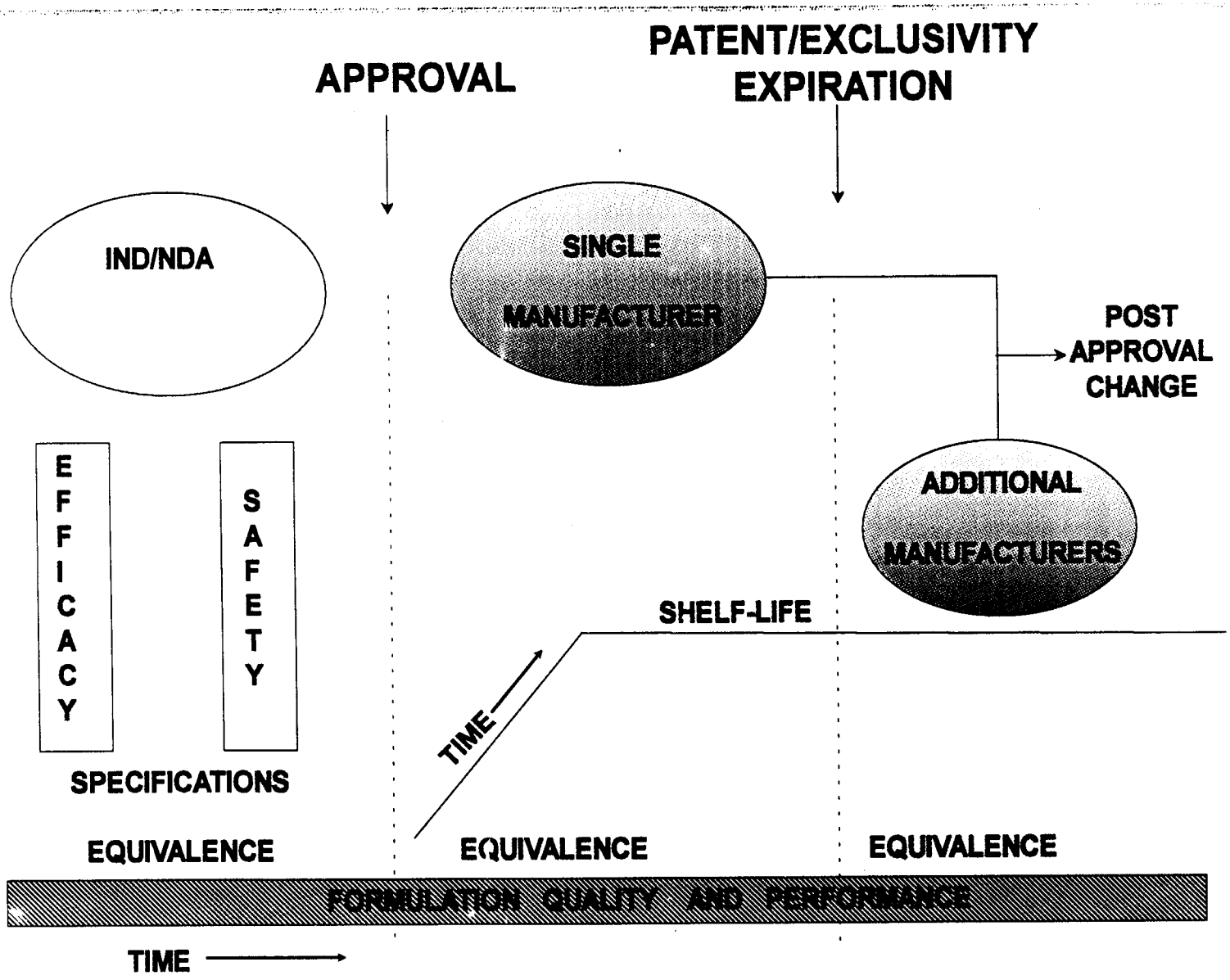
- Conclusions from initial study:
  - ✦ Internal standard can be used when evaluating *in vitro* drug permeability.
  - ✦ Preliminary data shows in vitro/in vivo correlation to human permeability.
  - ✦ Ratio of P_{eff} values for drug/ISD normalizes the data and indicates if drug transport is changed by concentration (complex formation), efflux or metabolism.

- Future studies:
  - ✦ Effect of stirring on drug permeability.
  - ✦ Effect of efflux pump on permeability with P-gp substrates.
  - ✦ Effect of direction on drug permeability.
  - ✦ Evaluate potential for metabolic effects in Caco-2 cells.

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

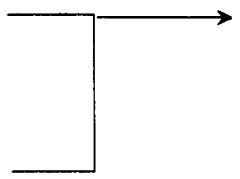
Narrow Therapeutic Index Drugs Overview

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


APPROVAL
PATENT/EXCLUSIVITY EXPIRATION
IND/NDA
SINGLE MANUFACTURER
POST APPROVAL CHANGE
ADDITIONAL MANUFACTURERS
EFFICACY
SAFETY
SHELF-LIFE
TIME
SPECIFICATIONS
EQUIVALENCE
EQUIVALENCE
EQUIVALENCE
FORMULATION QUALITY AND PERFORMANCE
TIME

NDA vs ANDA

BRAND NAME (NDA) Requirements	GENERIC DRUG (ANDA) Requirements
1. CHEMISTRY	1. CHEMISTRY
2. MANUFACTURING	2. MANUFACTURING
3. CONTROLS	3. CONTROLS
4. LABELING	4. LABELING
5. TESTING	5. TESTING
6. PRECLINICAL/CLINICAL STUDIES	6. BIOEQUIVALENCE
7. BIOAVAILABILITY	



Generic Versus Reference Product

PHARMACEUTICAL AND THERAPEUTIC EQUIVALENCE

- **Pharmaceutical Equivalence**
  - Same active ingredient
  - Same strength
  - Same dosage form and route of administration
  - Comparable labeling
- **Bioequivalence**
  - In vivo measurement of active moiety (moieties) in biologic fluid (blood/urine)
  - In vivo pharmacodynamic comparison
  - In vivo clinical comparison
  - In vitro comparison
  - Other

➡THEN: THERAPEUTIC EQUIVALENCE

ORANGE BOOK

"AB" Rating

- Identical active ingredient(s)
- Dosage form
- Route of administration
- Strength
- Bioequivalent
- GMP's
- Comparable Labeling

Narrow Therapeutic Index "NTI"

FDA Statements to Practitioner

1. CFR definition
2. Product labeling

FDA Statements to Pharmaceutical Manufacturers

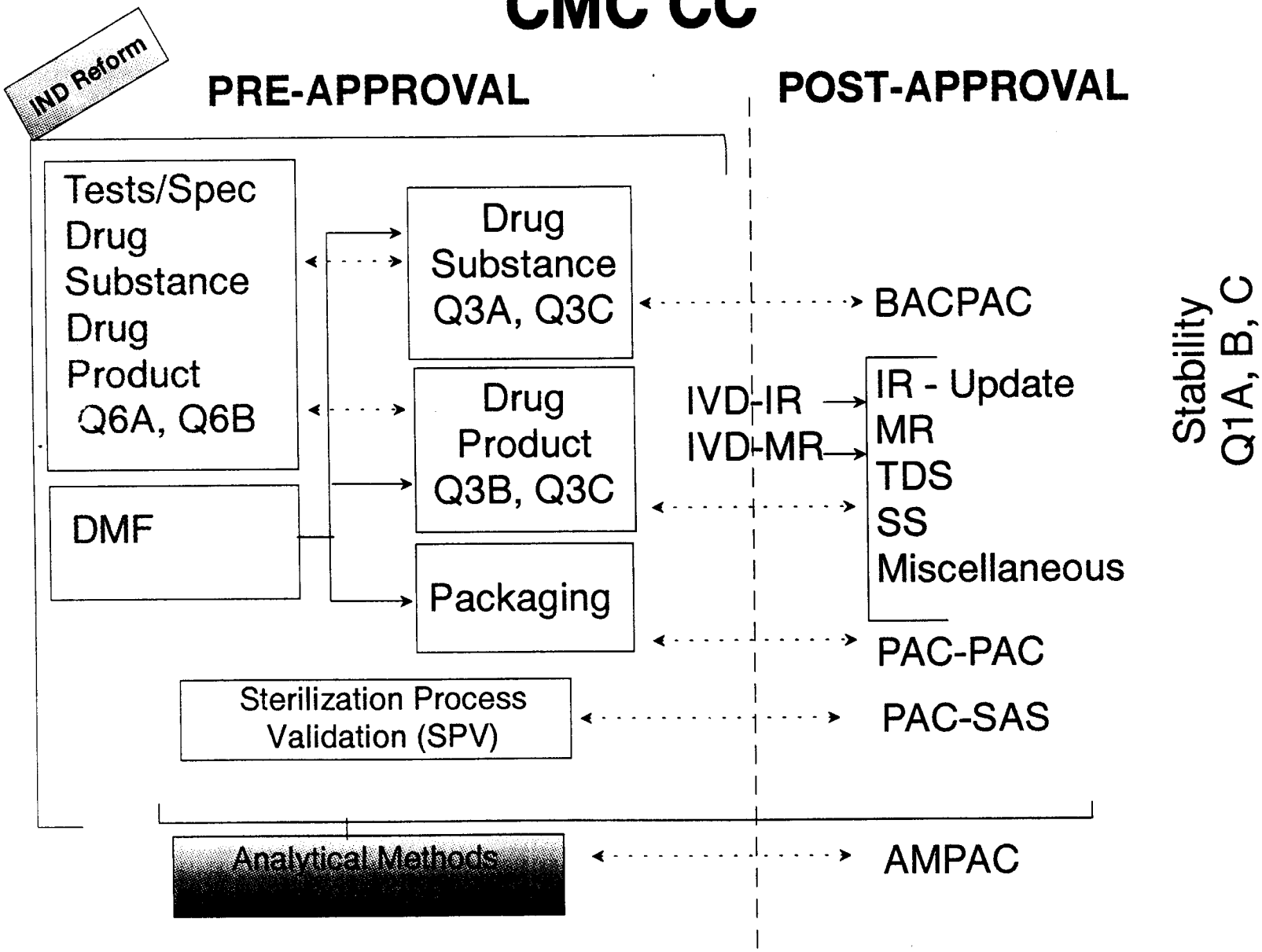
1. SUPAC Approaches
2. CP 7346.832
3. Individual Bioequivalence

COUMADIN

"...a narrow therapeutic range (index) drug, may be affected by factors such as other drugs and dietary Vitamin K. Dosage should be controlled by periodic determinations of prothrombin time (PT)/International Normalized Ratio (INR) or other suitable coagulation tests."

1997 Physicians' Desk Reference
51st Edition, Page 942

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
BACPAC
IVD-IR
IVD-MR
IR - Update
MR
TDS
SS
Miscellaneous
PAC-PAC
PAC-SAS
AMPAC
Stability
Q1A, B, C

Extended Release Solid Oral Dosage Forms Release Controlling Components and Composition

LEVEL	CLASSIFICATION	THERAPEUTIC RANGE	TEST DOCUMENTATION	FILING DOCUMENTATION
I	- ≤5% w/w Change Based On Total Release Controlling Excipient(e.g., controlled release polymer, plasticizer) Content - No other changes	All Drugs	- Stability - Application/Compendial Requirements - No Biostudy	- Annual Report
II	- Change in Technical Grade and/or Specifications - ≤ 10% W/W Change Based on Total Release Controlling Excipeint (e.g., controlled release polymer, plasticizer) Content - No other changes	Non-Narrow	- Notification & Updated Batch Record - Stability - Applicaiton/Compendial Requirements Plus Multi-Point Dissolution Profiles in Three Other Media (e.g., Water, 0.1N HCL, and USP Buffer Media at pH 4.5 and 6.8) until > 80% of drug Released or an Asymptote is Reached[1] - Apply Some Statistical Test (F2 Test) For Comparing Dissolution Profiles[2] - No Biostudy	- Prior Approval Supplement
		Narrow	- Updated Batch Record - Stability - Application/Compendial (Profile) Requirements - Biostudy or IVIVC[1]	- Prior Approval Supplement
III	- > 10% W/W Change Based On Total Release Controlling Excipeint (e.g., controlled release polymer, plasticizer) Content	All Drugs	- Updated Batch Record - Stability - Application/Compendial (Profile) Requirements - Biostudy or IVIVC[1]	- Prior Approval Supplement

[1] In the Presence of an established In Vitro/In Vivo Correlation Only Application/Compendial Dissolution Testing Should Be Performed.
[2] In the Absence of an Established In Vitrol/In Vivo Correlation.

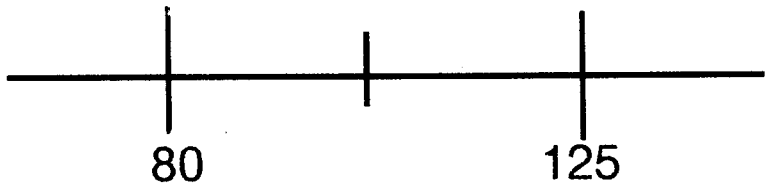
PK/PD METRICS

Statistical Assessment of comparability

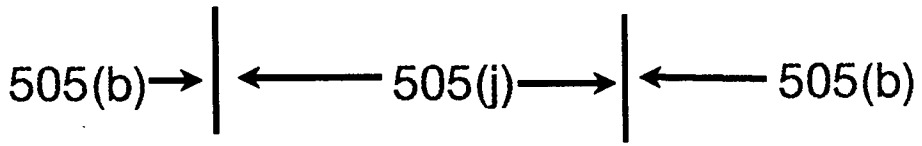
Current

Average response test
within 80-125% reference

$$\ln.8 \leq \mu_T - \mu_R \leq \ln 1.25$$



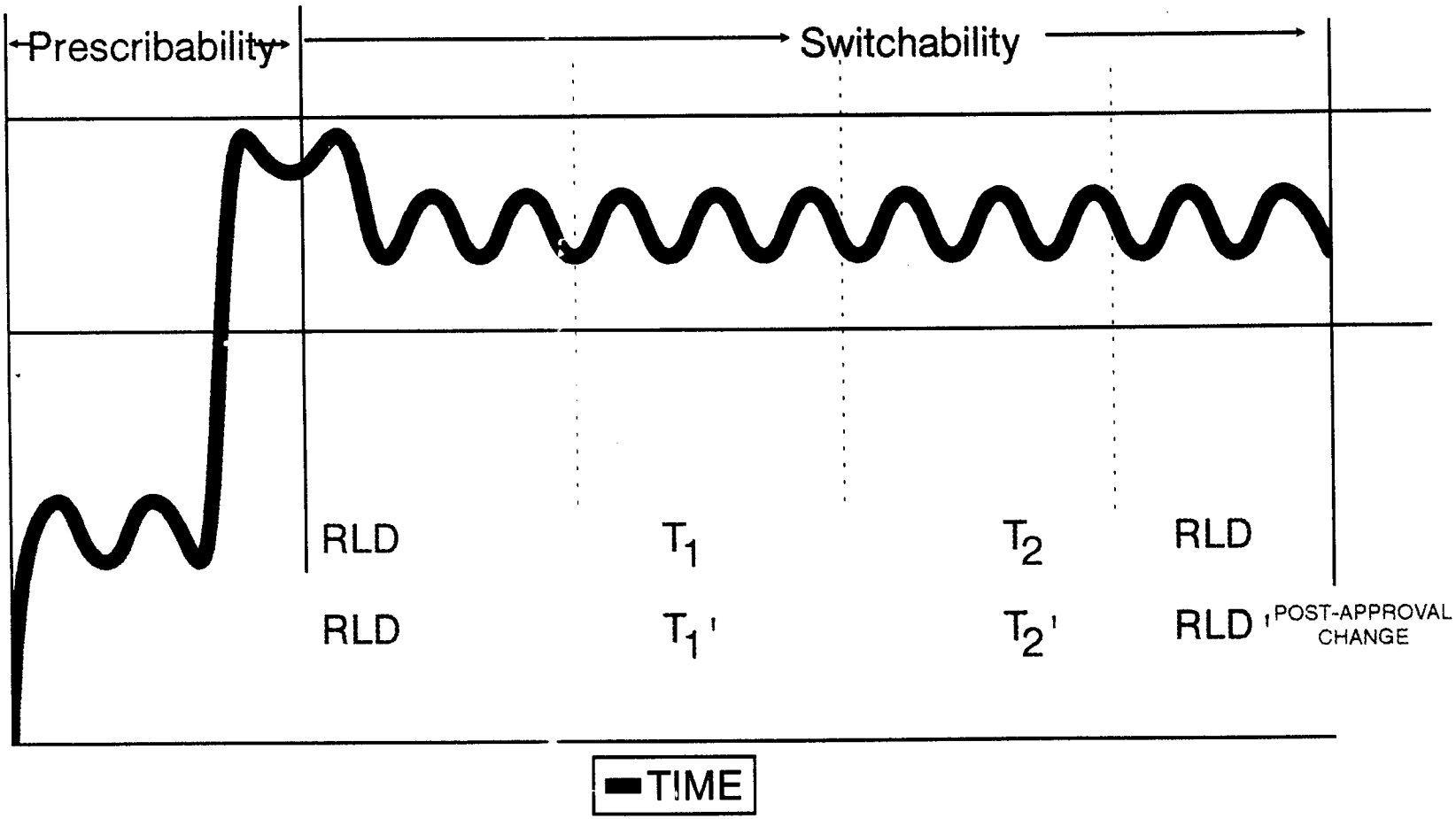
Future



Average BE + Variance terms
Within-Subject Variance Reference

$$\frac{(\mu_T-\mu_R)^2+C_1\sigma_D^2+C_2(\sigma_{WT}^2 - \sigma_{WR}^2)}{\sigma_{wR}^2} \leq \theta_P$$

Prescribability, Switchability, Individual Therapeutic Window



INDIVIDUAL BIOEQUIVALENCE

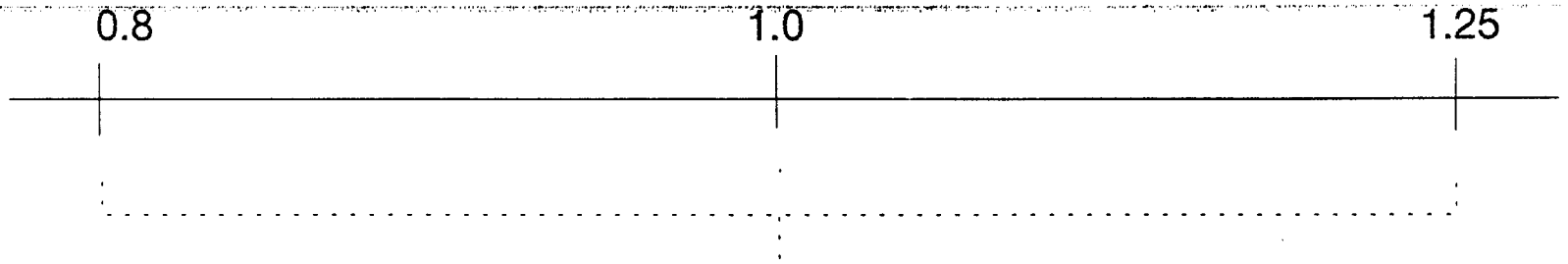
$$\frac{(\mu_T-\mu_R)^2+\sigma_D^2+(\sigma_{WT}^2-\sigma_{WR}^2)}{\sigma_{WR}^2} \leq \theta$$

- Addresses the correct question (switchability)
- Considers subject by formulation interaction
- Incentive for less variable test product
- Scaling based on variability of the reference product both for highly variable drugs and for certain agency-defined narrow therapeutic range drugs
- Encourages use of subjects more representative of the general population

AAPS Workshop

Narrow Therapeutic Index and Individual Bioequivalence

March 16-18, 1998



BIOEQUIVALENCE INTERVAL
(GOAL POSTS)

$$\text{Point Estimate} = \frac{\text{Average Observed Response of Generic}}{\text{Average Observed Response of RLD}}$$

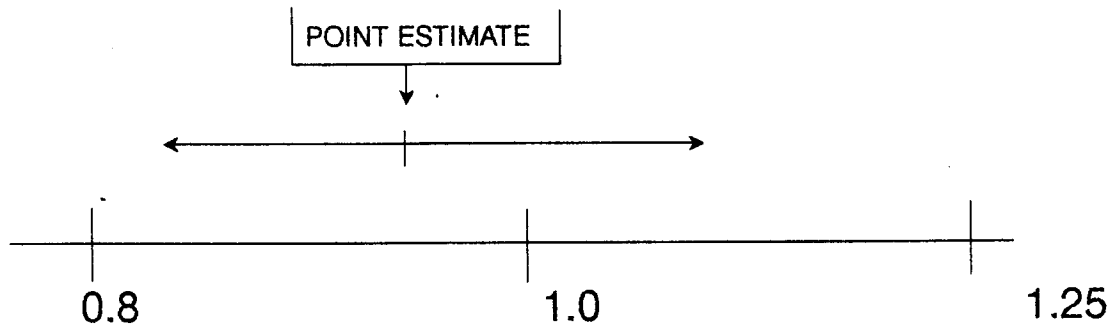
Response = AUC, C_{max}

Study Yields Observed CI and Must Fall Within Goalposts

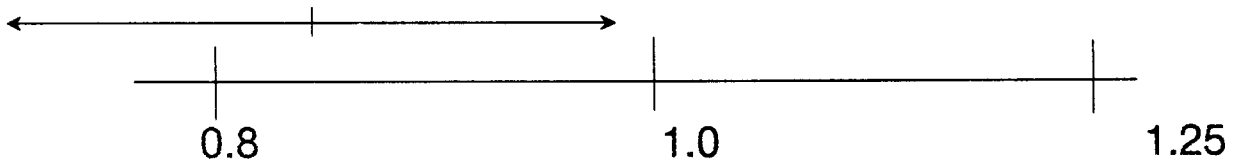
To Document Bioequivalence

90 % CI for Point Estimate Must Fall Within 80 - 125 %

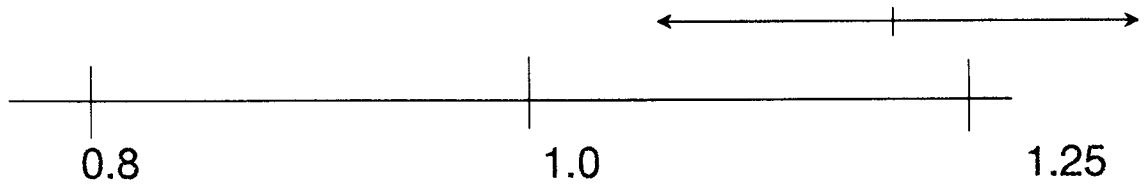
CASE I: Test Product Shown To Be Bioequivalent



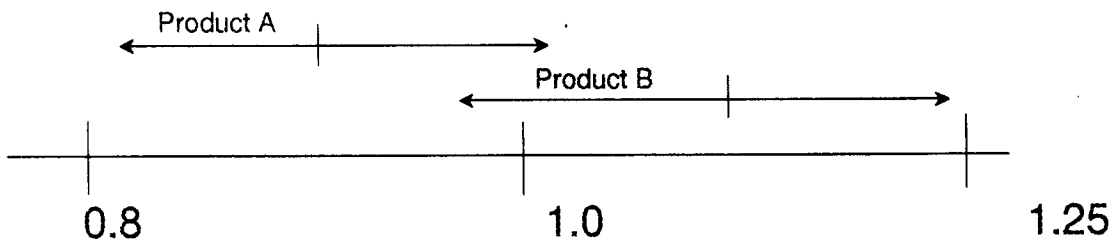
CASE II: Test Product Not Shown To Be Bioequivalent



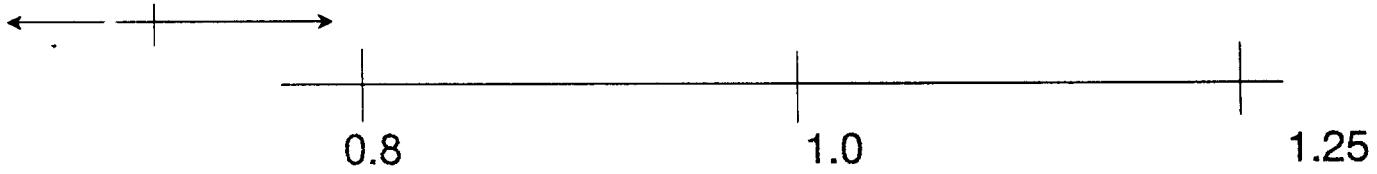
CASE III: Test Product Not Shown To Be Bioequivalent



CASE IV: Comparison of Two Bioequivalent Generic Products



CASE V: Test Product Bioinequivalent



Bioequivalence Studies

- -20 + 25 does not = > 40% range
- Actual performance = < 5%
- Additional tests not required upon product switch
- Therapeutic equivalence

"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."

James Benson
Acting Commissioner of
Food and Drugs
October 1, 1990

STATISTICAL ISSUES
(Continued)

4. Current

    1. Two one-sided tests procedure
       (also called the 90% confidence interval approach)

    2. Logarithmic transformation
       - 90% confidence intervals for AUC and C^{max}
       - Bioequivalence interval: 80-125%

    3. Deletion of outlier subject values
       - Clinical basis
       - Pharmacokinetic basis

July 1, 1992, Statistical Procedures Guidance

STATISTICAL ISSUES

1. Mean product performance

   - Early 1970'S
   - Mean AUC and C^{max} values of test product within ± 20% of the reference product
   - Plasma concentrations not significantly different at most or all individual sampling times

2. Power Approach

   - Early 1970's
   - Applied to AUC and C^{max}
   - Consisted of two tests

3. 75/75 (also called the 75/75-125) rule

   - Late 1970's
   - Applied to AUC and C^{max}
   - Mean product performance also considered
     a. a test of the null hypothesis of no difference between formulations
     b. evaluation of the power of the test to detect a 20% mean difference in treatments
   - Often used in conjunction with the power approach
   - Use of these methods discontinued by the Division of Bioequivalence in 1985

Advisory Committee For Pharmaceutical Science

Quality Hotel, Silver Spring, Maryland

December 11, 1997

Individual Bioequivalence

RABI PATNAIK, PH.D.
DIVISION OF BIOEQUIVALENCE
OFFICE OF GENERIC DRUGS
OFFICE OF PHARMACEUTICAL SCIENCE

Considerations For Assessment of Bioequivalence of Drug Products

* Prescribability and Switchability
* Reference Variability
* Therapeutic Index

Regulatory Concerns

* **Average Bioequivalence**
  * Focuses on Population Averages of Test and Reference
  * Ignores Distribution of Metric Between Test and Reference
  * Ignores Subject-By-Formulation Interaction

* **"Prescribability" vs. "Switchability"**

* **One Size Fits All?**
  * Highly Variable Drugs
  * Narrow Therapeutic Index Drugs
  * Others

* **Incentives for Manufacturing Less Variable Formulations**

Individual Bioequivalence Criterion

Characteristics

$$\frac{(\mu_T - \mu_R)^2 + (\sigma^2_{WT} - \sigma^2_{WR}) + \sigma^2_D}{\sigma^2_{WR}} \leq \theta_I$$

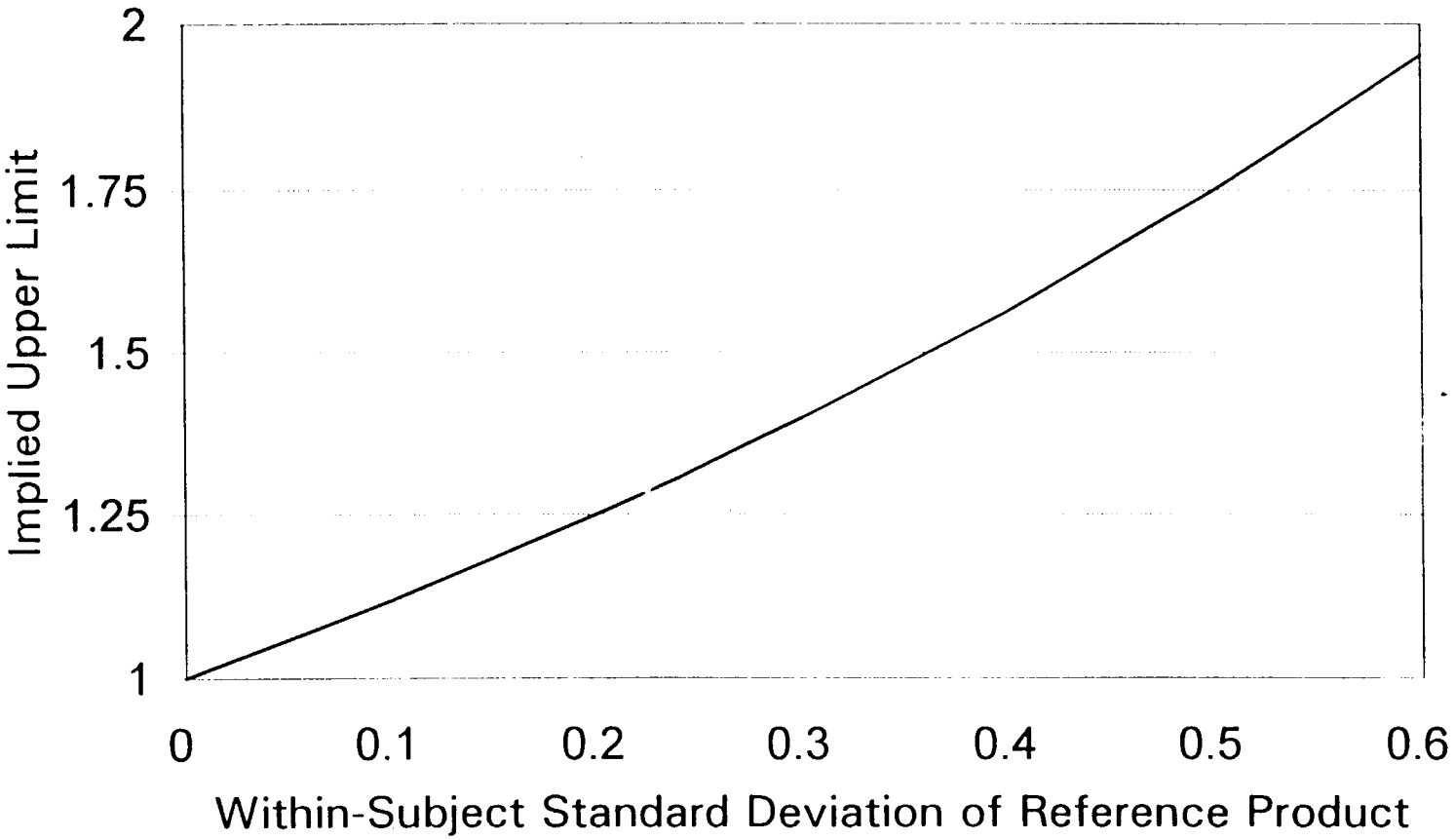
* Moment-Based Approach
* Aggregate Criterion
* One-sided Test
* Scaling Method

Individual Bioequivalence Criterion

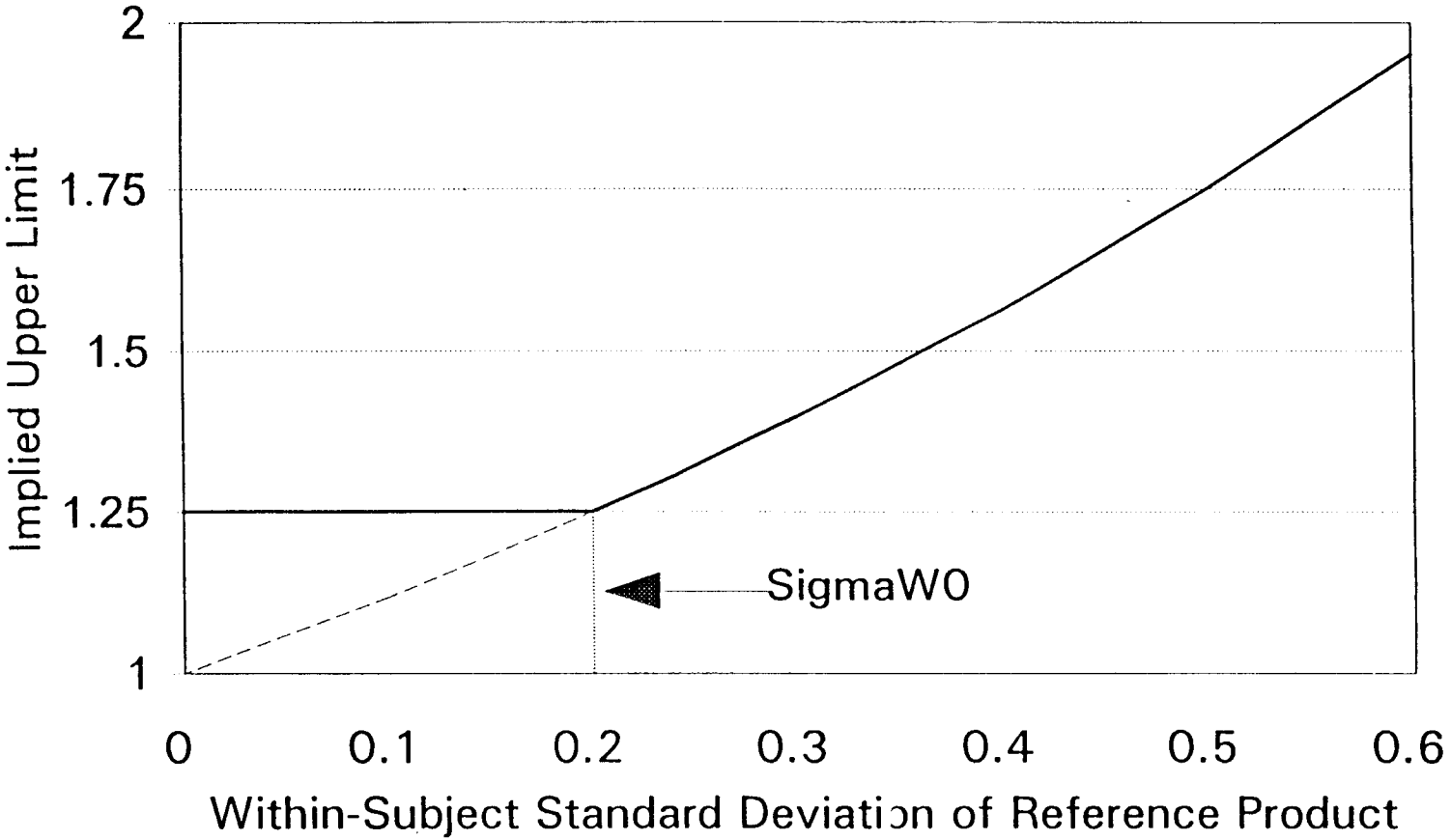
$$\frac{(\mu_T - \mu_R)^2 + (\sigma^2_{WT} - \sigma^2_{WR}) + \sigma^2_D}{\sigma^2_{WR}} \leq \frac{(\ln 1.25)^2 + \varepsilon_I}{\sigma^2_{WO}}$$

$(\mu_T - \mu_R)^2$:	Difference in Averages
$(\sigma^2_{WT} - \sigma^2_{WR})$:	Difference in Within-Subject Variabilities
σ^2_D:	Subject-by-Formulation Interactions
σ^2_{WR}:	Reference Within-Subject Variability
$(\ln 1.25)^2$:	Average Bioequivalence Limit
ε_I :	Variance Allowance
σ^2_{WO} :	Reference Variability Limit

Reference-Scaled Criterion



Reference-Scaled Criterion
With Limited Narrowing



Data Analysis

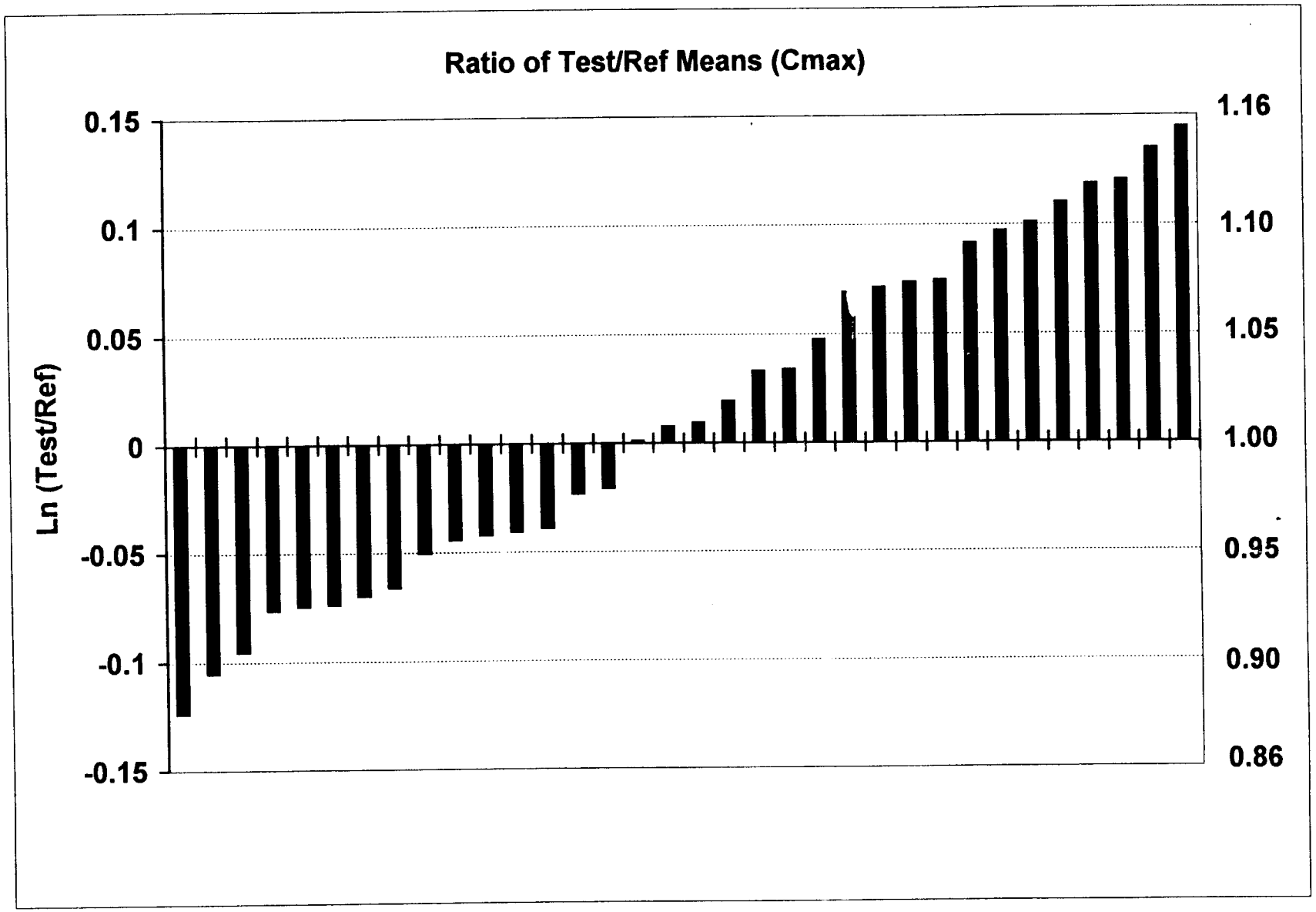
Background of Data Sets

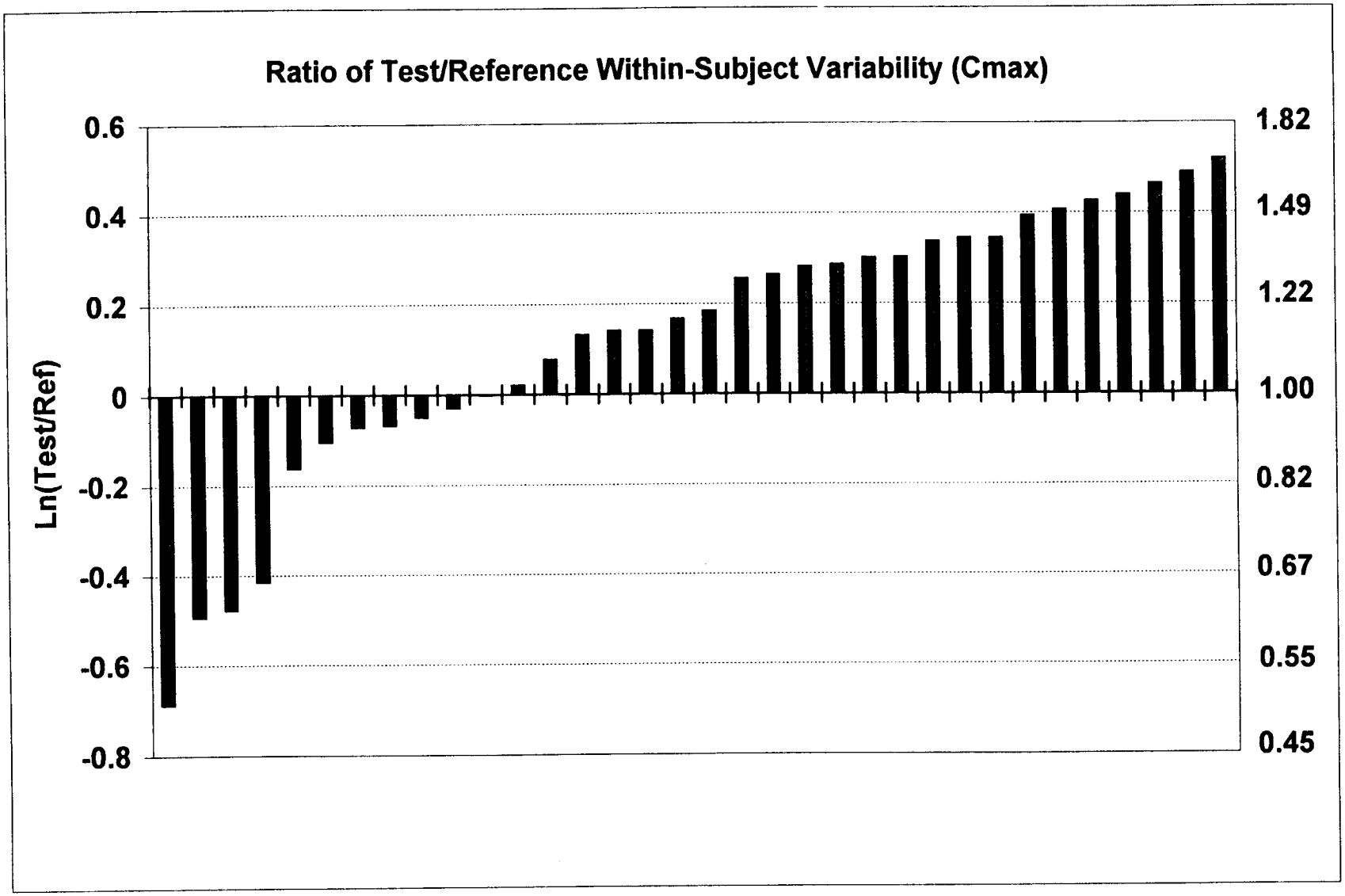
* 12 Studies from FDA Files with 34 Analyses for Each of Two Pharmacokinetic Parameters (AUC, CMAX).
* Replicate Design Studies with Four Periods and Four and Six Sequences.
* Study Designs Chosen by Sponsors; not Recommended by Agency.
* Studies Conducted on Healthy Subjects and Some on Target Population.
* Studies Conducted on Different Dosage Forms.

Data Analysis

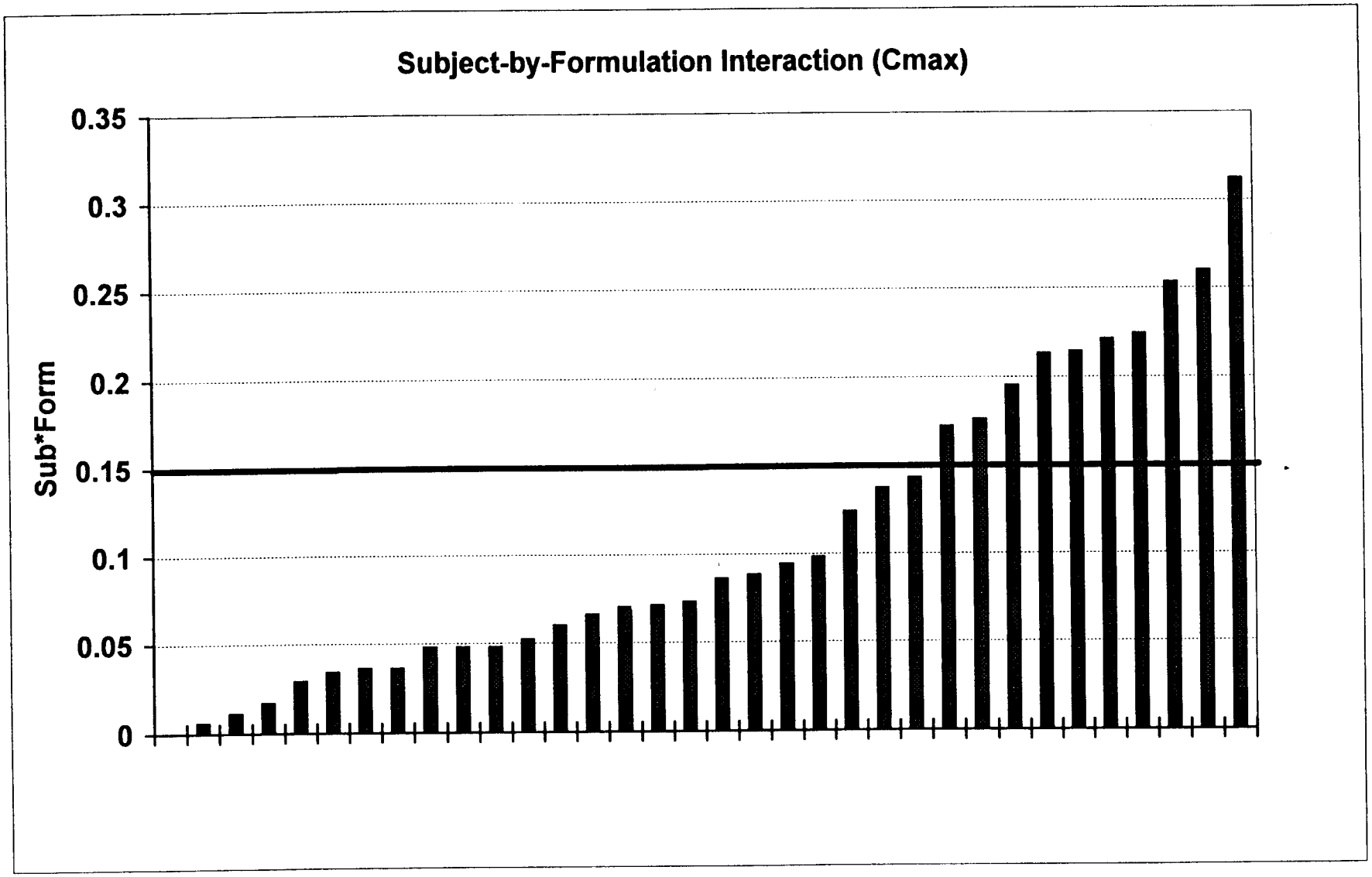
Cmax

* Difference Between Test and Reference Means
* Difference Between Test and Reference Within-Subject Variabilities
* Subject-By-Formulation Interaction
* Reference Within-Subject Variability


Ratio of Test/Ref Means (Cmax)
Ln (Test/Ref)
0.15
0.1
0.05
0
-0.05
-0.1
-0.15
1.16
1.10
1.05
1.00
0.95
0.90
0.86



CMSVSORT.XLS



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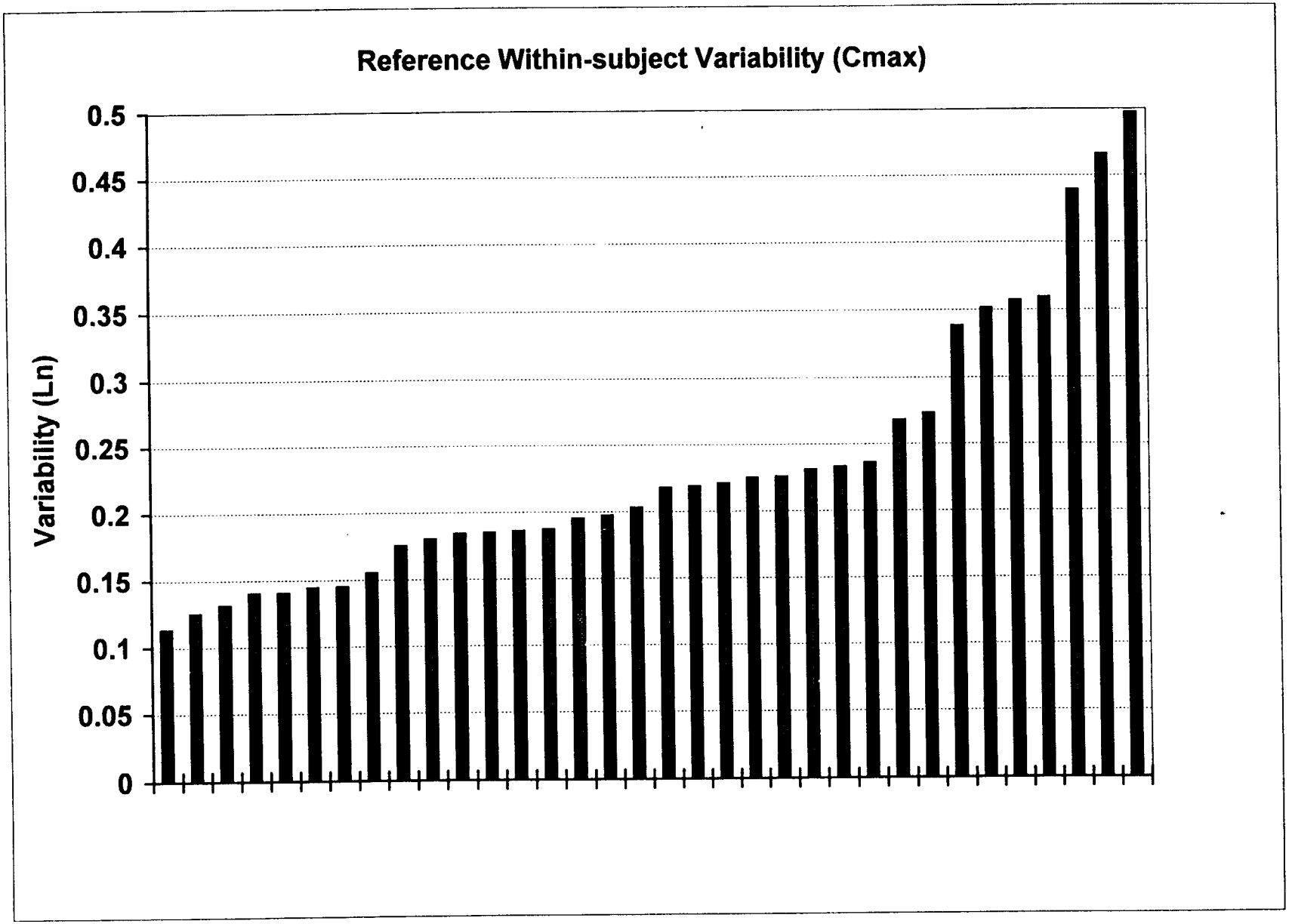

Reference Within-subject Variability (Cmax)
Variability (Ln)
0.5
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0

Summary of Pertinent Parameters

Metric	WSV (Ref.) (>0.2)	WSV Ratio (Test/Ref.) Range	Subject*Formulation (>0.15)
AUC	8/34 (24%)	0.5 - 2.0	8/34 (24%)
CMAX	18/34 (53%)	0.6 - 1.7	10/34 (29%)

WSV = Within-Subject Variability

Individual Bioequivalence

* Addresses the Correct Question (Switchability)

* Considers Subject-By-Formulation Interaction

* Incentive for Less Variable Test Product

* Scaling Based on Variability of the Reference Product, Both Highly Variable Drugs and for Certain Agency-defined Narrow Therapeutic Index Drugs

* Encourages Use of Subjects More Representative of the General Population

Preliminary Draft Guidance

"In Vivo Bioequivalence Studies Based on Population and Individual Bioequivalence Approaches."

* Federal Register Notice

* Available for Public Comments

Narrow Therapeutic Drugs: Definition

John D. Balian, MD
Associate Director For Clinical Pharmacology
Office Of Clinical Pharmacology And Biopharmaceutics
OPS/CDER/FDA

ACPS 12/11/97

NTD Issues

- Scientifically defined criteria are useful in the drug development, review, and prescribing process
- NTD is frequently mentioned in several MPCC and BCC guidances
- It is a true Clinical Pharmacology issue of concentration vs. effect
- Bioequivalence of test and reference drug products (NME and generics)
- More rigid and extensive testing procedures for drugs with NTR?
- Formulation changes and SUPAC-IR (provides a list of NTRDs)
- Drug-drug, drug-food, and drug-disease interactions
- Special populations (age, gender, ethnicity, disease states) requiring tighter control
- An issue considered to determine whether a drug may go OTC

Narrow Therapeutic Drug

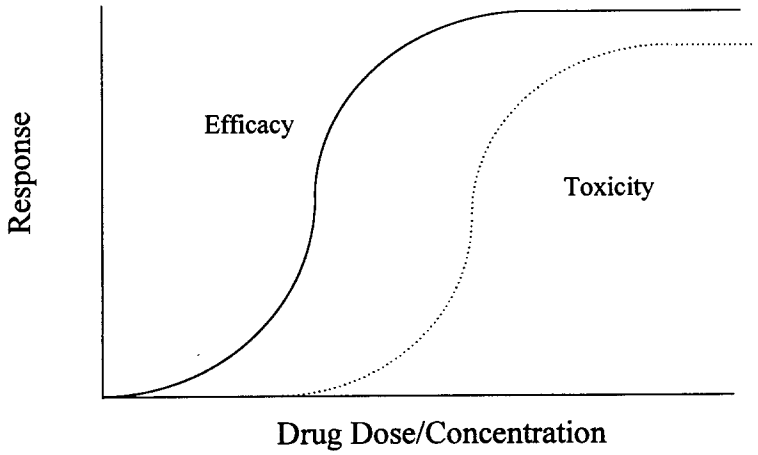
- An NTD is a drug that commonly exhibits adverse effects which limit its therapeutic use in doses close to those needed for therapeutic effect
- Terminology
  - Narrow: range or window
  - Low: index or ratio

Regulatory Definition

- CFR 320.33(c)
  - < 2-fold difference in MLD (median lethal dose (LD50)) and MED (median effective dose (ED50)) values
  - < 2-fold difference in MinToxicC and MinEffecC in the blood
  - For safe and effective use dosage titration and therapeutic monitoring necessary
- Criticism
  - MLD/MED and MTC/MEC are animal data, rarely available, and not very meaningful. Also LD50 is not a requirement anymore.
  - Dosage titration and monitoring is very widespread

Proposed Definition

The degree of the overlap between effective doses/concentrations and doses/concentrations which cause unacceptable toxicity define a narrow therapeutic drug



Considerations

- < 2-fold difference in MinToxicC and MinEffecC in the blood
- Non-Linear kinetics over the therapeutic range
- High inter- and intra-subject variability
- Special populations needing tighter control of therapy
- Therapeutic drug monitoring
- Saturable protein binding
- Accumulation and cumulative toxicity
- Therapeutic category
- Therapeutic indication

Objectives

- A clinically relevant and scientifically defensible definition of NTDs
- Outline criteria/characteristics for assessing products as NTDs
- Next Steps
  - Document (guidance, review article, or white paper)
  - Revisit CFR

Working Group

Members

John D. Balian, MD, Chair
Dennis Bashaw, PharmD
Sayed Al-Habet, PhD
Iftekhar Mahmood, PhD

Internal Consulants

Lawrence Lesko, PhD
Roger Williams, MD
Dale Conner, PharmD
Mark Vogel, PhD

Advisory Committee for Pharmaceutical Science
December 11-12, 1997

In Vivo Metabolism-Based Drug-Drug Interactions: General Issues

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 Metabolism-Based Drug-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: 14 oral NME's; total drug-drug interaction studies reviewed: 87**

< Huang, SM, Balian, J, Marroum, P, Mehta M, Lesko, LJ, " Assessment of the Quality and Quantity of Metabolism-Based Drug-Drug Interaction Studies in NDA Submissions", to be presented at the American Society for Clinical Pharmacology and Therapeutics, 99th Annual Meeting, New Orleans, LA March 1998 >

Clinically Significant Drug-Drug Interactions

- 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 Interactions

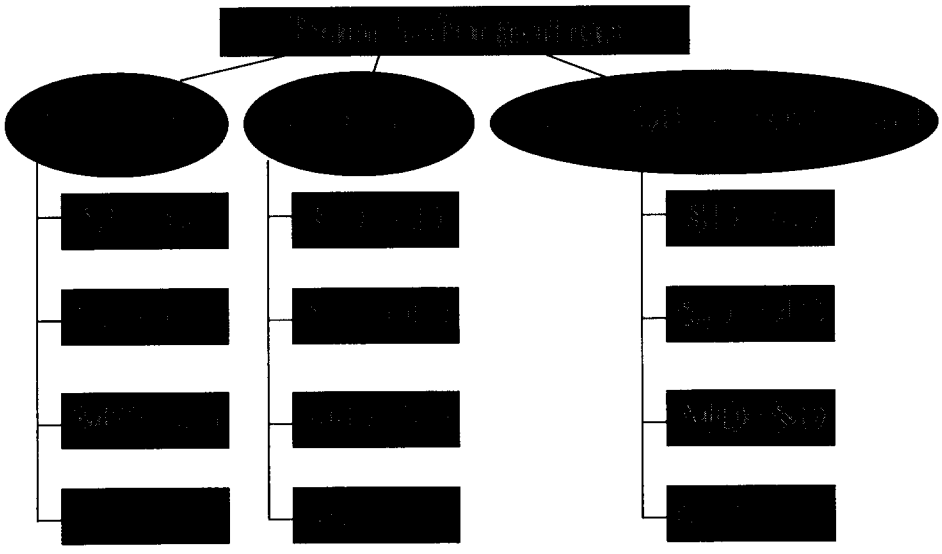
- <u>In Vitro - In Vivo Relationship</u>:
  When In Vivo Studies Not Necessary
- <u>Study Design/Data Analysis</u>:
  Specific Studies and Population Studies
- <u>Labeling</u>:
  What In Vitro and In Vivo Data Can Be Used for Labeling

Inducer/Inhibitor/Subject Drugs 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; 14 oral NME's; total drug-drug interaction studies reviewed: 87 >

Study Design



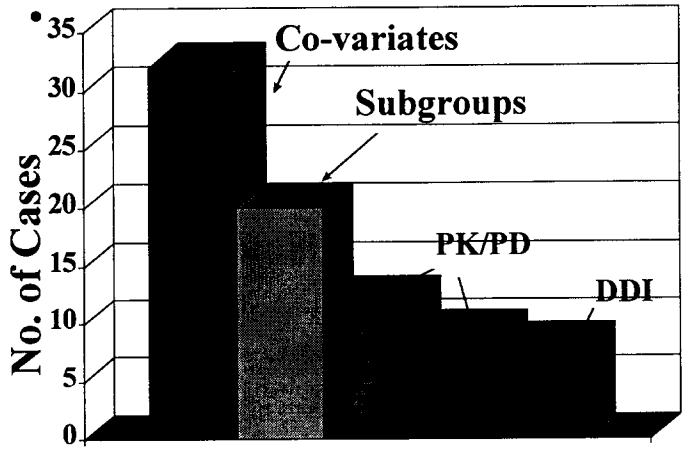
Data Analysis

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

FDA Experiences in Population PK 1995-1996

- Impact on the Labeling (39 out of 47)



<Ette EI, Miller R, Gillespie WR, Huang, SM, Lesko, LJ, Williams, RL, The Population Approach: FDA Experiences, COST meeting, Geneva, 2/97>

Labeling

- **When/What to Report in the labeling**
  (Extrapolation; Class 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 (Cross-Labeling)**

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)**
    - **Collins, Honig, Rahman; Rodrigues, Wrighton, Lu**
    - **Parkinson, Madan, LeCluyse, Watkins, Branch, Vestal**
  - **Advisory Committee for Pharmaceutical Science Meeting : 5/8/97, 12/12/97**
  - **PhRMA/OPS/OCPB Meeting 5/30/97; PhRMA workshop 9/22-23/97**
- **Crosstalk with EMEA: CPMP: Tomas Salmonson**
  - **EUFEPS meeting at Nuremberg 11/27-29/97**
- **Guidance for Industry: draft in preparation**

Questions for the Advisory Committee

- What assumptions are we willing to make in extrapolating data obtained from specific studies conducted in normal subjects to patients
  - that the concentration-response relationships remain unchanged between normals and the target populations (and in special population groups)
  - that the dosage adjustment data derived from the studies in normals can be extrapolated to the target populations (and the special population groups)

13

Questions for the Advisory Committee

- What is the role of population PK in the evaluation of drug-drug interactions?
  - Can data derived from the population PK analysis be confirmatory for lack of interactions?
  - Can data derived from the population PK analysis be used for dosage adjustments?

Questions for the Advisory Committee

- **How do we translate the data to informative labeling language?**
  - **What statistical method/analysis results be included in the labeling**
  - **To what extent do we extrapolate the *in vitro* or *in vivo* results to other drugs (class labeling)**
  - **When should the same labeling language for the study drug appear on the labeling for the interacting drugs (cross-labeling)**

Design of Clinical Drug-Drug Interaction Studies

Peter K Honig, M.D., M.P.H.
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Design of Clinical DDI Studies

- Subjects: Normals versus Patients
  - Convenience
    - Practicality
  - Necessity
    - scientific
    - ethical
    - statistical (variability)

Design of Clinical DDI Studies

- General Considerations
  - Mechanism of interaction
    - Inhibition:
    - Induction:
    - 'Non-metabolic' contribution of changes in absorption
  - Therapeutic indices of subject drugs
  - Likelihood of coadministration
  - Bidirectionality

Design of Clinical DDI Studies

- Choice of interactants
- Route of administration
- Dose and Dosing duration
- Crossover versus parallel design
  - Drug characteristics (PK, intrapatient variability)
  - Patient stability issues
- Single versus multiple dosing
  - Reality
  - Convenience: Assumptions must be met
  - Clinical relevance

Design of Clinical DDI Studies

Test Drug	Interactant* (inhibitor/inducer)
Single Dose	Single Dose
Single Dose	Multiple Dose
Multiple Dose	Single Dose
Multiple Dose	Multiple Dose

*Interactant may be the new drug

Design of Clinical DDI Studies

- PK endpoints (Cmax, AUC, Cl)
- Cmin to demonstrate Css
- Sampling strategies
- Assay
  - Sensitivity
  - Metabolites
  - Bidirectionality
- Pharmacodynamic endpoints

Design of Clinical DDI Studies

- Role of Population PK
  - Identification of unsuspected interactions.
  - Confirming absence of clinically significant, potential interaction.
  - Less valuable in ruling out or quantifying suspected or likely interactions.

Documentation of BE Studies During the IND Period

Clinical Perspective

Peter K Honig, M.D., M.P.H.
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

- The Fact: Sponsor has changed formulation
- The Dilemma: Bioequivalence between the new (TBM) formulation is/cannot be demonstrated
- The MO thought process to resolve the issue
    - -hard line
    - -look at the data

Clinical Considerations

- What are safety concerns for drug of interest?
  - Indication?
  - Significant versus trivial?
  - Frequent versus rare?
  - Monitorable?
  - Therapeutic index
    - Position on efficacy dose-response curve
    - Position on safety dose-response curve
  - Labeling versus approvability issue

Clinical Considerations

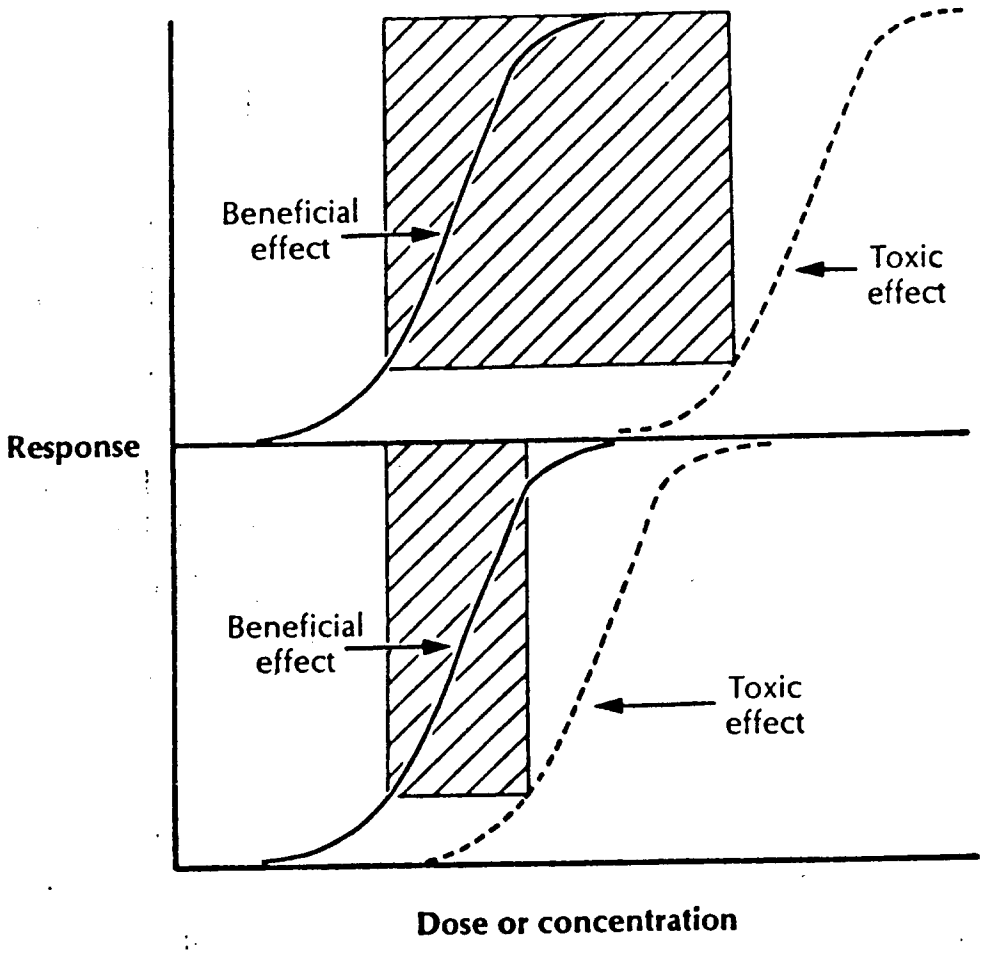
- Best understanding of PK/PD relationship for efficacy and safety
  - Efficacy driven by AUC or Cmax
  - Safety driven by AUC or Cmax
- Look at BE study and see "how" it failed (i.e. diagnosis).
- Extent of safety and efficacy database
  - Dose ranging trials for efficacy
  - Safety database (dose and duration)

Clinical Considerations

- Look at point estimates and variability around clinical study batches to see if there is 'coverage'.
- Operating under the assumption that there was an approvable range of dosing in first place and now that range is limited.
- If no 'coverage', approvability comes into question.

Clinical Considerations

- Look at point estimates and variability around clinical study batches to see if there is 'coverage'.
- Operating under the assumption that there was an approvable range of dosing in first place and now that range is limited.
- If no 'coverage', approvability comes into question.
- In such instances, a described PK/PD relationship for concern (efficacy/safety) may be critical to making the difference in PK clinically interpretable.


Beneficial effect
Toxic effect
Response
Beneficial effect
Toxic effect
Dose or concentration

In Vitro - In Vivo Relationships

Jerry M. Collins, Ph.D.
Laboratory of Clinical Pharmacology

Guidance for Industry

Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro

GOAL:

Increase confidence in product safety by avoiding undesirable drug-drug interactions

EXPLOSION OF DATA IN VITRO:

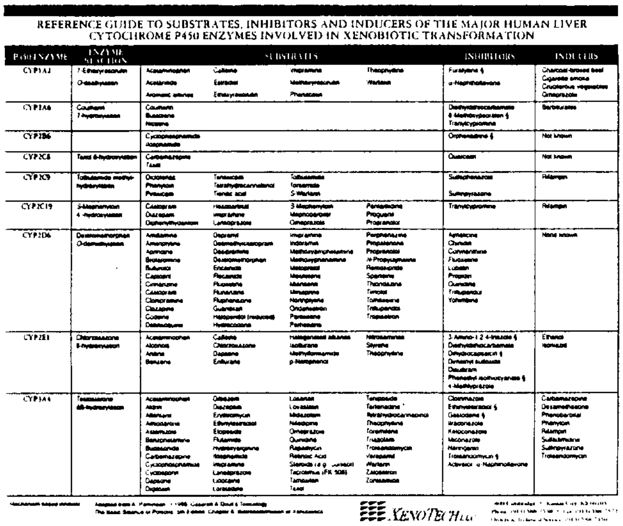
FDA now receives an avalanche of data

The literature has lots of data

The INTERNET has even more data

****

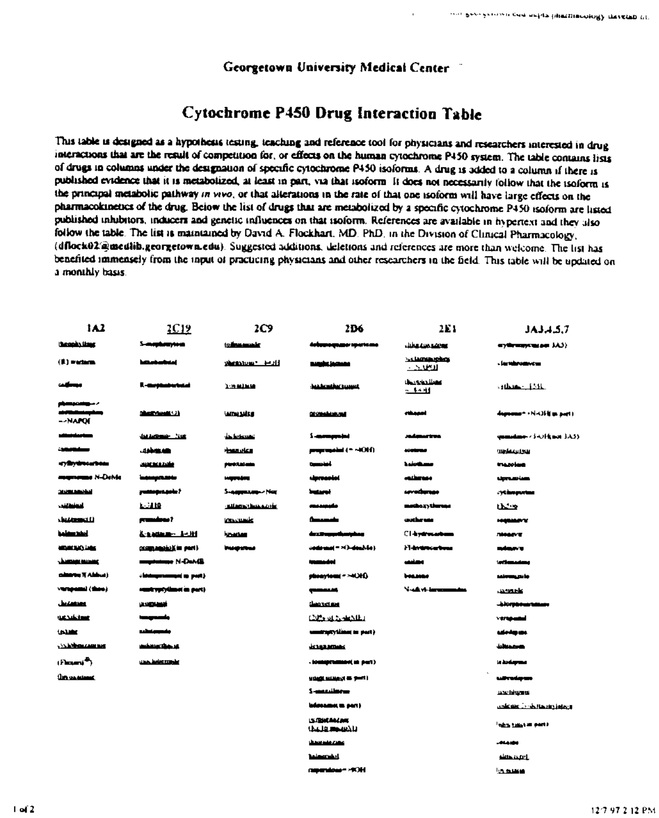
Unless they are predictive of results in vivo, we have no interest in these data.



REFERENCE GUIDE TO SUBSTRATES, INHIBITORS AND INDUCERS OF THE MAJOR HUMAN LIVER CYTOCHROME P450 ENZYMES INVOLVED IN XENOBIOTIC TRANSFORMATION

P450 ENZYME	ENZYME REACTION	SUBSTRATES	INHIBITORS	INDUCERS
CYP1A2	[illegible]	[illegible]	[illegible]	[illegible]
CYP2A6	[illegible]	[illegible]	[illegible]	[illegible]
CYP2B6		[illegible]	[illegible]	Not known
CYP2C8	[illegible]	[illegible]	[illegible]	Not known
CYP2C9	[illegible]	[illegible]	[illegible]	[illegible]
CYP2C19	[illegible]	[illegible]	[illegible]	[illegible]
CYP2D6	[illegible]	[illegible]	[illegible]	None known
CYP2E1	[illegible]	[illegible]	[illegible]	[illegible]
CYP3A4	[illegible]	[illegible]	[illegible]	[illegible]

XenoTech LLC



Georgetown University Medical Center

Cytochrome P450 Drug Interaction Table

This table is designed as a hypothesis testing, teaching and reference tool for physicians and researchers interested in drug interactions that are the result of competition for, or effects on the human cytochrome P450 system. The table contains lists of drugs in columns under the designation of specific cytochrome P450 isoforms. A drug is added to a column if there is published evidence that it is metabolized, at least in part, via that isoform. It does not necessarily follow that the isoform is the principal metabolic pathway *in vivo*, or that alterations in the rate of that one isoform will have large effects on the pharmacokinetics of the drug. Below the list of drugs that are metabolized by a specific cytochrome P450 isoform are listed published inhibitors, inducers and genetic influences on that isoform. References are available in hypertext and they also follow the table. The list is maintained by David A. Flockhart, MD, PhD, in the Division of Clinical Pharmacology, (dflock02@medlib.georgetown.edu). Suggested additions, deletions and references are more than welcome. The list has benefited immensely from the input of practicing physicians and other researchers in the field. This table will be updated on a monthly basis.

1A2	2C19	2C9	2D6	2E1	3A3,4,5,7

1 of 2 12/7/97 2:12 PM

No Information

*

*

*

*

*

*

Only Studies
In Vivo

No Information

"Guided" In Vitro

Only Studies
In Vivo

CENTRAL THEME:

****

For cases in which we agree that data *in vitro* predict the situation *in vivo*, no need for clinical studies

Defining the boundaries of "agreement" will be a constantly-improving process.

Where are we TODAY?

Where Are We Today?

Most Common Finding Is No Interaction

**Major Success:

Drug "X" Inhibition of Other Drugs?

What Drugs Inhibit Metabolism of "X"?

Rule Out (In) Genetic Polymorphism

** Consensus:

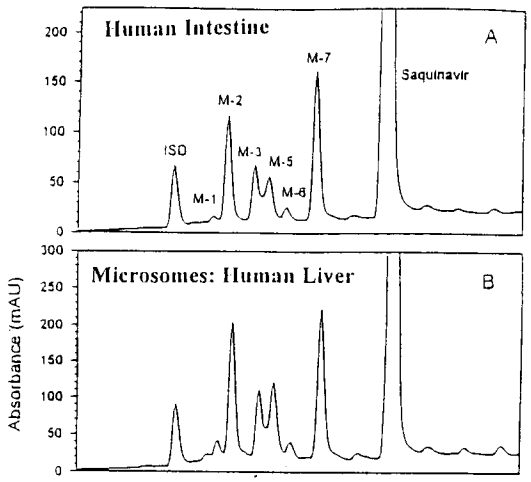
Drugs Which Are Model Compounds for Specific Pathways, either as Substrates or Inhibitors

---

Judging Success/Value/Progress?

Correlation In Vitro - In Vivo

Revolutionary?
Is It Perfect?
Generally Reliable?
Improvement Over Past?
Special Problems?



Areas for Improvement:

Induction Data Not Yet Fully Arrived

****

"Borderline" Cases: C_u / K_i Ratio

****

If Inappropriate Conditions *In Vitro*
- - - > No Confidence in Predictions *In Vivo*

****

Plea For More Data Publication by Industry: We've Already Seen It!

Not Every

Drug-Drug Interaction

Is Metabolism-Based

Seize The Moment!

Advisory Committee on Pharmaceutical Science
December 12, 1997

In Vitro - In Vivo Relationships

Jerry M. Collins, Ph.D.
Laboratory of Clinical Pharmacology

Guidance for Industry

Drug Metabolism/Drug Interactions Studies in the Drug Development Process: Studies In Vitro

Officially Released via World Wide Web
April 1997

GOAL:

Increase confidence in product safety by avoiding undesirable drug-drug interactions

Table of Metabolism/Drug Interaction Data

A.Parkinson chapter in:
Casarett & Doull's Toxicology, 5th Edition, 1996

Example of Metabolism/Drug Interaction Data Available Via World Wide Web: Professor David Flockhart, Georgetown Univ.

www.dml.georgetown.edu/depts/pharmacology/davetab.html

EXPLOSION OF DATA IN VITRO:

FDA now receives an avalanche of data
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The INTERNET has even more data

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No Information

*

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Only Studies *In Vivo*

No Information

"Guided" In Vitro

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In Vivo

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****

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** Consensus:
Drugs Which Are Model Compounds for Specific Pathways, either as Substrates or Inhibitors

Saquinavir Data:
Comparison of Metabolic Profiles for Human Intestinal and Human Hepatic Microsomes

Figure from:
M.E.Fitzsimmons, J.M.Collins. Selective biotransformation of the HIV protease inhibitor saquinavir by human small intestinal cytochrome P450 3A4: potential contribution to high first-pass metabolism. Drug Metab Disposit 25:256-266, 1997.

Areas for Improvement:

Induction Data Not Yet Fully Arrived

****

"Borderline" Cases: Cu / Ki Ratio

****

If Inappropriate Conditions *In Vitro*
- - - > No Confidence in Predictions
In Vivo

****

Plea For More Data Publication by Industry: We've Already Seen It!

Not Every Drug-Drug Interaction Is Metabolism-Based

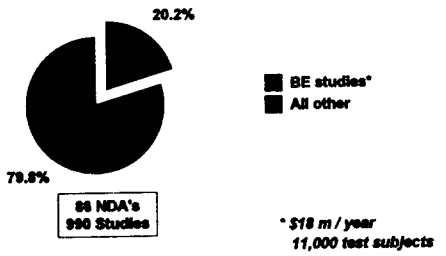
Lawrence J. Lesko, Ph.D.
Director, Office of Clinical Pharmacology and Biopharmaceutics
OPS/CDER/FDA

Documentation of BE Studies During the IND Period

Advisory Committee for Pharmaceutical Science
Quality Hotel
Silver Spring, Maryland
December 12, 1997

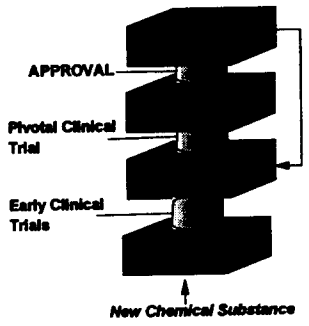
Survey of NDA's for 1995-96

Clinical Pharmacology and Biopharmaceutics Studies



** $18 m / year*
11,000 test subjects

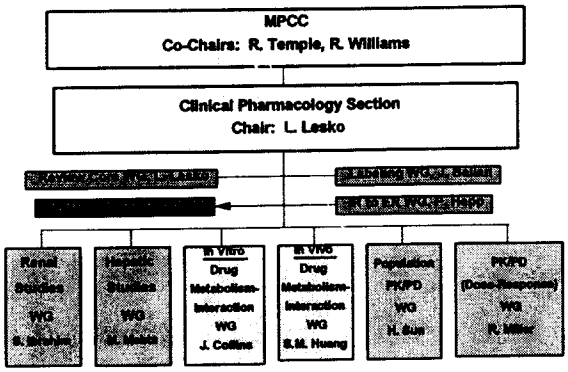
BE Studies During IND Period



CHANGE → EQUIVALENCE?

Pivotal BE Study:
- method of assessment
- acceptance criteria

Policy Development



I.N.D. BE WG

- Dale Conner (Chair)
- Peter Honig (ORM)

OCPB

V. Tammara
D. Wang
D. Bashaw

PhRMA

W. Robinson

What is the Question?

- Prescribability

Will patients who are prescribed the marketed formulation, experience essentially the same safety and efficacy as those who received the clinical trial formulation?

How Sure Do We Want To Be?

- **Method of Assessment**
  - average BE (current)
  - population BE (draft guidance)

- **Acceptance Criteria**
  - strict BE standards (80-125)
  - case-by-case
    - joint clinical pharmacology/clinical decision
    - formal PK/PD relationships
    - safety/efficacy dose-response database
    - totality of evidence

Advisory Committee for Pharmaceutical Science

Office of Testing & Research

Jim MacGregor, Ph.D., D.A.B.T.
Director

December 12, 1997

Organization & Programs

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

Mission

- 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

How can OTR make a difference?

- High ROI projects (In areas of excellence)
  - Focus on implementation of new science
- Leverage
  - Consortia (PQRI, CDDI)
  - Collaboration (NIEHS, NCTR, universities, NTP, other Centers & Agencies)
- Use unique resources (CDER database)
- Support of regulatory functions & training

Our Niche

- Scientific and laboratory support for regulatory activities
- Interface between new science & regulation (applied R&D)

DIVISION OF PRODUCT QUALITY RESEARCH
(Karl Flora, Director)

- **PRODUCT QUALITY RESEARCH INITIATIVE (PQRI)**
  - FDA/industry/academia
- **PRE-FORMULATION RESEARCH**
  - Drug substance/excipient (e.g. BACPAC)
- **FORMULATION RESEARCH**
- **DRUG PRODUCT/DELIVERY SYSTEM REGULATION** (e.g. SUPAC's)
- **BIOPHARMACEUTICS RESEARCH PROGRAM**
  - BIOPHARMACEUTICAL CHARACTERISTICS (e.g. In Vitro BE Tests, BCS)

Division of Applied Pharmacology Research

(Frank D. Sistare, Acting Director)

Programs:

- Cardiopulmonary Pharmacology
- Molecular Toxicology and Carcinogenesis
- Neuropharmacology
- Preclinical Chemotherapeutics

Initiatives:

- Collaboration for Drug Development Improvement (CDDI)

Laboratory of Clinical Pharmacology
(Jerry Collins, Director)

Programs:

- Analytical methods-biofluids
- Drug metabolism/interactions
- Conjugated estrogens
- Nucleoside analogs

Initiatives:

- CDDI

Division of Testing & Applied Analytical Development
(Tom Layloff, Director)

- Testing
  - NDA Method Validation
  - USP Reference Standard Candidate Program
- Applied Analytical Development
  - Uniformity of complex molecules
  - NIR calibration & qualification standards

Regulatory Research and Analysis Staff (Joe Contrera, Director)

- **Data Base Compilation; Distribution**
  - Carcinogenesis
  - Reproductive and Developmental Tox
  - Genetic Toxicity

- **Predictive Modeling Systems Development**
  - CDER Carcinogenesis Module CRADA
  - Reproductive and Developmental Toxicology

Issues in Health Protection

- Important health effects that are difficult to associate with exposure: cancer, reproductive, CV, stroke, neurological effects
  - Clinical testing insensitive and retrospective
  - Quantitative extrapolation of nonclinical data uncertain
- Assurance of product "sameness"

Issues in Development

- Process lengthy (15 yrs), costly ($400M), failure-prone (80% of INDs)
- Advances in discovery are dramatic
  - Combinatorial chemistry/HTS; rational design; genomics
- Animal tox & bioavailability are bottlenecks
- Improved predictive paradigms for tox & bioavailability can improve health protection and have major cost/time impact

Some Opportunities

- New tools for predicting & monitoring health outcome
  - Mechanism-based biomarkers (genomics)
  - Inducible responses to classes of damage
  - Noninvasive techniques
- Human cells & humanized animal models
  - Metabolism, oncogenes, disease models
- Analytical and biological "fingerprinting"

CDER Research Coordinating Committee

- Research Managers
- Coordinating Committee Reps
- Office of Science
- Annual External Review
  - Public/Industry/University

Where should OTR focus?

- Improved predictivity of nonclinical tests and nonclinical/clinical interface
- Effective use of CDER's unique nonclinical and clinical databases
- Better methods & regulatory paradigms for product identity/quality/testing

Office of Testing and Research

Office of Pharmaceutical Science
Center for Drug Evaluation and Research
Food and Drug Administration

Director: James T. MacGregor, Ph.D.

Return to CDERnet HomePage

Comments to: weaver@cder.fda.gov

Return to OPS HomePage

Last Revised: September 1997

Office of Testing and Research

Organizational Structure

Division of Applied Pharmacology Research Acting Director: Frank Sistare, Ph.D.

The Division of Applied Pharmacology Research focuses on nonclinical pharmacology/toxicology research that will establish the best models and endpoints for accurately predicting the clinical effects of therapeutics.

Division of Product Quality Research Director: Karl Flora, Ph.D.

The Division of Product Quality Research conducts intramural and collaborative research to provide a scientific basis for guidance development and regulatory decision making to ensure high standards of product quality and performance.

Division of Testing and Applied Analytical Development Director: Thomas P. Layloff Jr., Ph.D.

The Division of Testing and Applied Analytical Development develops analytical methods, performs testing of drugs where surveillance is required, and evaluates testing methods for new drugs.

Laboratory of Clinical Pharmacology Director: Jerry Collins, Ph.D.

The Laboratory of Clinical Pharmacology develops new analytical methods, conducts research on human tissue metabolism, including collaborative clinical trials, and *in vitro*,or animal studies relevant to human drug utilization.

Regulatory Research and Analysis Staff Director: Joseph Contrera, Ph.D.

The RRAS staff extracts toxicology information from FDA files and develops databases in areas such as carcinogenesis, reproductive and developmental toxicology and genotoxicity that are useful for regulatory decision support and guidance development. The RRAS is also engaged in applying toxicology information to develop improved computer assisted toxicology prediction software for pharmaceuticals.

Immediate Office Staff

The IO staff provides administrative and planning support for all OTR functions.

Division of Applied Pharmacology Research

Carcinogenesis & Molecular Toxicology Program

Overview

Mission

Program Personnel

Research Projects

External Web Sites

Return to DAPR HomePage

Comments to: weaver@cder.fda.gov

Return to DAPR Program List

Last Revised: August 1997

Division of Applied Pharmacology Research

Carcinogenesis & Molecular Toxicology Program:

External Web Sites

- Cancer Facts: Risk Factors
- Cancer Information Service: NCI
- IARC Homepage
- Lab of Cellular Carcinogenesis & Tumor Promotion, NCI, NIH
- Laboratory of Human Carcinogenesis, NCI, NIH
- NTP Home Page
- NCI Comprehensive Cancer Database
- Molecular Carcinogenesis: IRC
- METI: Cellular & Molecular Toxicology
- Carcinogenic Potency Project {Gold Database}
- IARC p53 Mutation Database
- Issues in Carcinogenesis
- Lab of Comparative Carcinogenesis, NCI, NIH
- CancerNet
- OncoLink
- Tumor Pathology
- ITRI Life Sciences
- SRI Mammalian Toxicology

Return to DAPR Program List

Comments to: weaver@cder.fda.gov

Return to DAPR Carcinogenesis

Last Revised: October 1997

PRODUCT QUALITY RESEARCH INITIATIVE (PQRI)

DIVISION OF PRODUCT QUALITY RESEARCH
OFFICE OF TESTING AND RESEARCH
OFFICE OF PHARMACEUTICAL SCIENCE
CDER

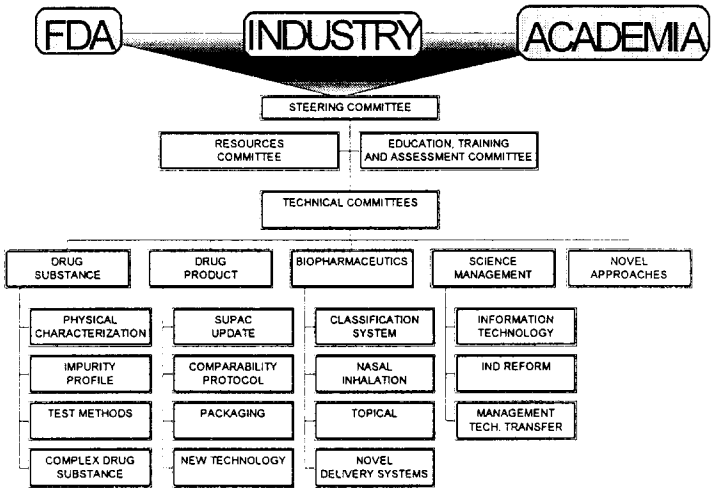
KARL P. FLORA, Ph.D., DIRECTOR
AJAZ HUSSAIN, Ph.D. DEPUTY DIRECTOR

DECEMBER 12, 1997

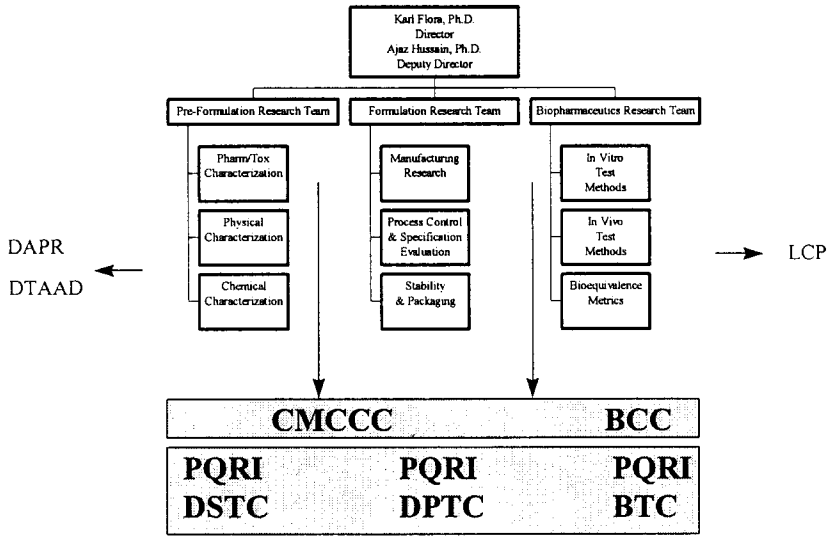
PQRI

- A process for industry, academia and the FDA to collaborate on focused research and policy development projects designed to meet the challenges associated with product quality aspects of drug development and evaluation
- Is a proposal being developed in collaboration with several trade associations

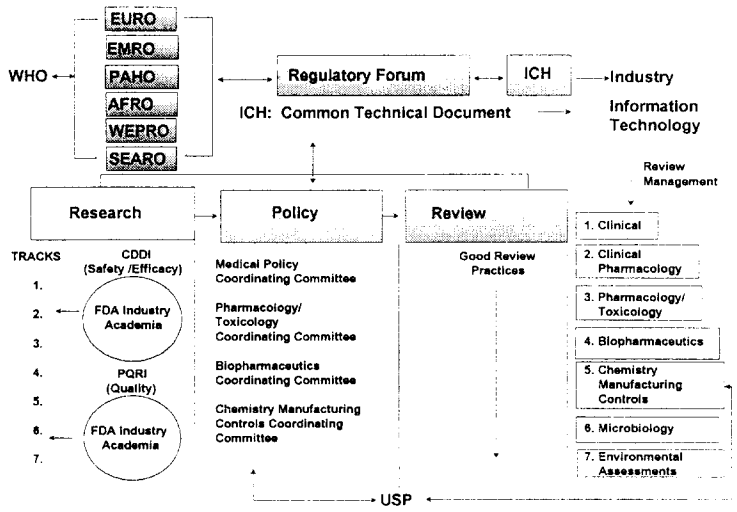
PQRI Proposed Structure



DIVISION OF PRODUCT QUALITY RESEARCH



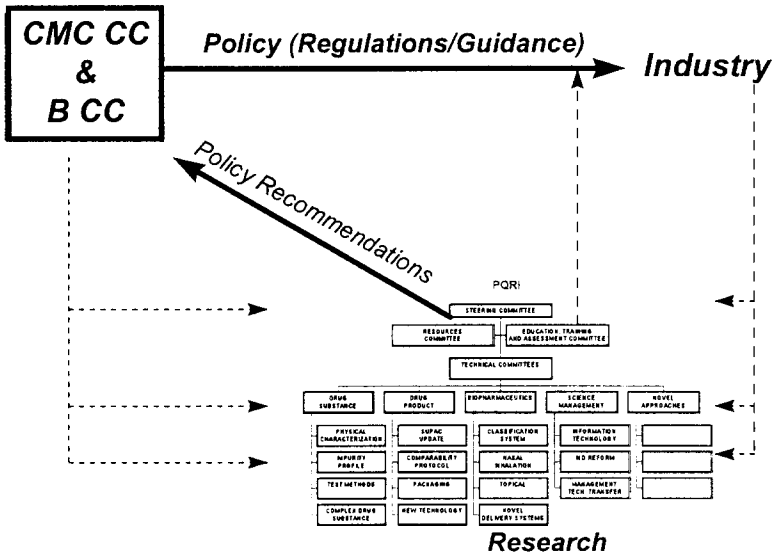
Research-Policy-Review



PQRI Development Efforts

- *December 1995: First draft of concept paper*
- *January 1996: First meeting with GPIA, NAPM, NPA, PDA, and PhRMA.*
- *March 1996: Second meeting*
- *April 1996: Third meeting*
- *September 1996: Fourth meeting*
- *December 1996: PQRI Steering Committee meeting with invited guests - Technical Committees proposed*
- *February 1997- Technical Committees start the process of identifying research projects*
- *March, December 1997- Steering Committee meetings*
- *December 1997 - Technical Committee meetings*
- *February 1998 Introductory Meeting*

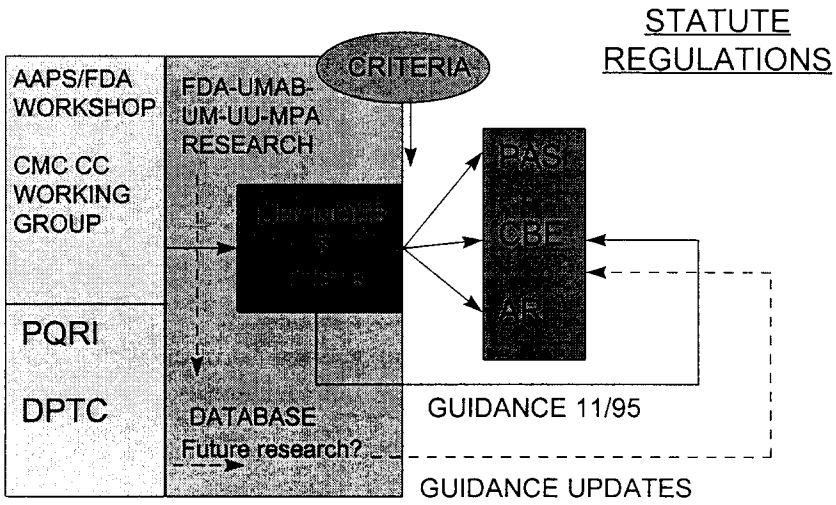
Research - Policy



Technical Committees

- Functions
  - Define applied regulatory research topics
  - Establish priorities for execution of identified topics
  - Evaluate research proposals
  - Select Working Group members to focus on specific programs/projects
  - Evaluate regulatory impact of research programs

The SUPAC Approach



The SUPAC Approach

Outcome/Impact:

- SUPAC guidance documents developed for solid oral (immediate and modified release) and semi-solid topical dosage forms
- SUPAC-IR has been viewed by the pharmaceutical community as a "Paradigm Shift" in the right direction
- Cost savings are projected to be in "hundreds of million dollars" by a panel of scientific leaders (Pharm. Res. 14: 958-966, 1997). Projected cost savings by a FDA contractor are about $ 50 million per year

Return on Investment

- For every dollar spent on this research, the US economy is expected to save $ 10 or more every year
- The estimated cost for the research portion (excluding training and database development) over a three year period was about $ 5 million.
- The return on investment is expected to increase with an revised SUPAC-IR under development
- The FDA-UMAB research contract was the major source of research data to support/validate SUPAC-IR recommendations

DPTC: "Proposed Hypothesis"

- Sidney Goldstein
- Frederick Gustafson
- Colin Gardner
- Dave Gill
- Albinus D'Sa
- Ajaz Hussain
- Larry Augsburger

- DPTC Research Hypothesis: Adherence to established product specifications are sufficient to approve drug products that undergo pre- and post approval changes in:
  - 1. Manufacturing: scale, site, equipment and process
  - 2. Composition and components
  - 3. Packaging

DPTC: "Proposed Demonstration Projects"

- Update of SUPAC-IR
  - Ho: Adherence to product specifications is sufficient to justify any change in component level.
  - Ho: Adherence to product specifications are sufficient to approve multiple changes (site + scale + equipment + process + composition).
- Update of other SUPAC's and "Make your own SUPAC"
  - Hypotheses defined under SUPAC-IR may be tested for other products.
  - Consider granting regulatory relief to companies with well- studied and well-defined processes where critical parameters of unit operations are understood and changes will not impact product performance.

DPTC: "Proposed Demonstration Projects"

- Container/Closure
  - Ho: Solid oral dosage that meet stability specifications under a semi-permeable packaging protocol may be considered to be inherently stable. Additional stability testing may not be necessary for post approval changes in container/closure of such dosage forms.
- Excipients
  - Ho: Adherence to product specifications is sufficient to approve different technical grade or a different source of the same technical grade of an excipient.
  - Corollary: Compliance with USP/NF monograph specifications for excipients assures their functional equivalence.

DPTC: "Proposed Demonstration Projects"

- Introduction of New Technology
  - Ho: Near-IR and other non-destructive probes to test in process blending can provide appropriate assurance of final blend uniformity and permit the establishment of rational standards unconfounded by the complications of sampling and handling of such samples.
  - Ho: The use of alternate manufacturing technology (for example: Barrier Manufacturing Technology for Parenteral Products) based upon equivalent finished product testing and an acceptable product quality history may be approved by the field investigators and reported in an Annual Report submission.

DSTC: "Proposed Hypothesis"

- Ira Berry
- Daniel Gold
- Max Lazar
- John Smith
- Kasturi Srinivasachar
- Karl Flora
- Stephen Byrn

- DSTC Research Hypothesis: Adherence to established final drug substance specifications should be sufficient to approve drug substances that undergo pre- and post approval changes in:
  - Manufacturing: scale, site, equipment , controls and process
  - Route of synthesis
  - Packaging
  - Supplier of drug substance

BTC: "Proposed Hypothesis"

- Dale Conner
- Arnold Repta
- Elizabeth Lane
- Hank Malinowski
- Ajaz Hussain
- Gordon Amidon

- "Umbrella" hypothesis: End product specifications based on physico-chemical characterization and non-clinical data can ensure bioequivalence.

Science Management Technical Committee

- Robert Kasubick
- Floyd Benjamin
- Dennis Casey
- Dave Savello
- Ken Loving
- Charles Hoiberg
- Ajaz Hussain
- Thomas Allen

- Goal: Manage strategies to maximize the effectiveness and efficiency of the total drug development and post-approval regulatory review process.

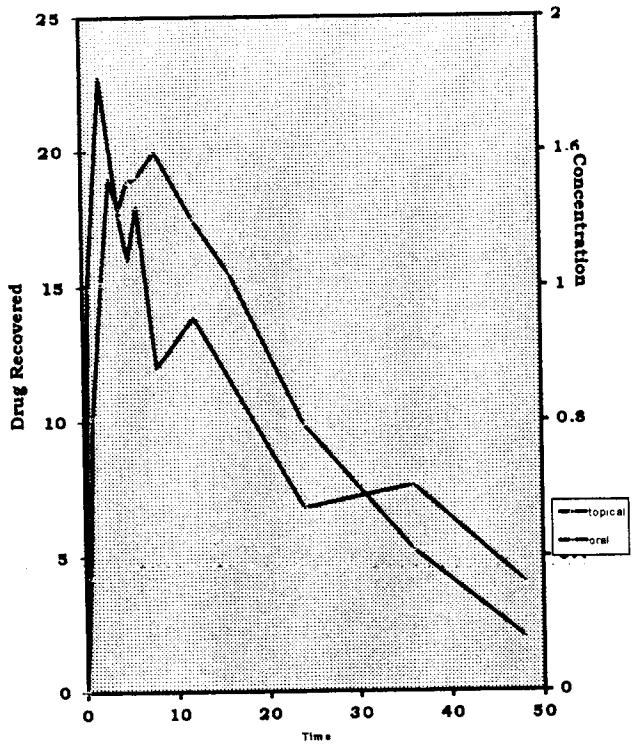
Sources of Variation in Tape Stripping Assay

Carl M. Metzler, Ph.D.
NUTWOOD ASSOCIATES

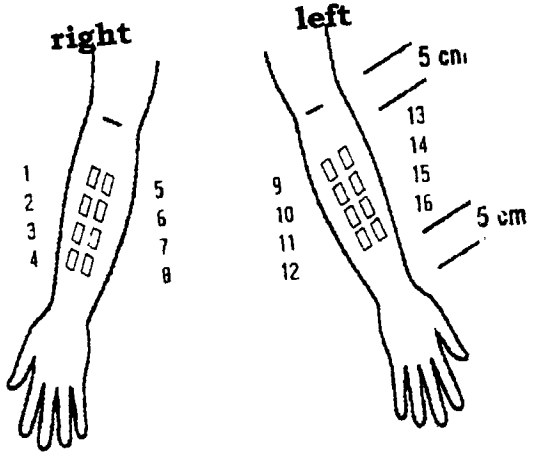
Data from
Dermatopharmacology Laboratory
Department of Dermatology
Univ of Arkansas for Medical Sciences

Financial Support from
ALPHARMA USPD

Oral and Topical Bioavailability



Layout of Drug Application Sites



thumb side is "laterial"

little digit side is "medial"

Sources of Variation in Tape Stripping

Fixed:

- ⇨ **arm**
- ⇨ **side**
- ⇨ **site**

Random:

- ⇨ **subject**
- ⇨ **subject*arm**
- ⇨ **subject*side**
- ⇨ **subject*site**

Experimental Design for Experiments to Estimate Sources of Variation

- 6 subjects
- both right and left arms
- both laterial and medial sides
- 4 sites numbered from elbow to wrist
- 22 tape strips 4 hours after applying drug
- strips 17 to 22 assayed

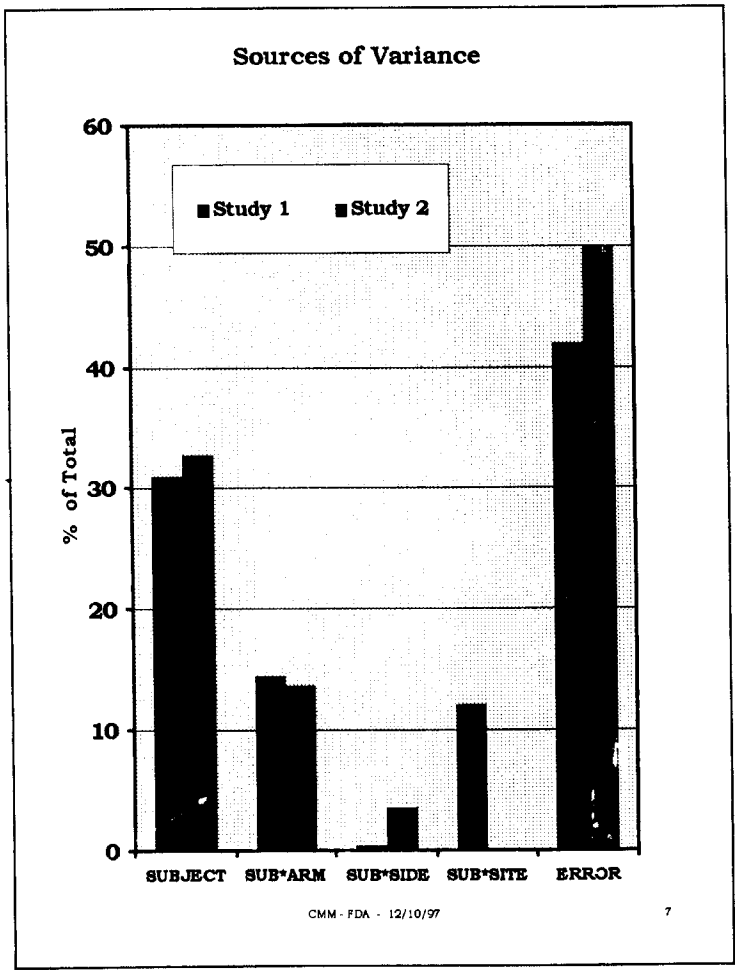
Estimation of Variance Components

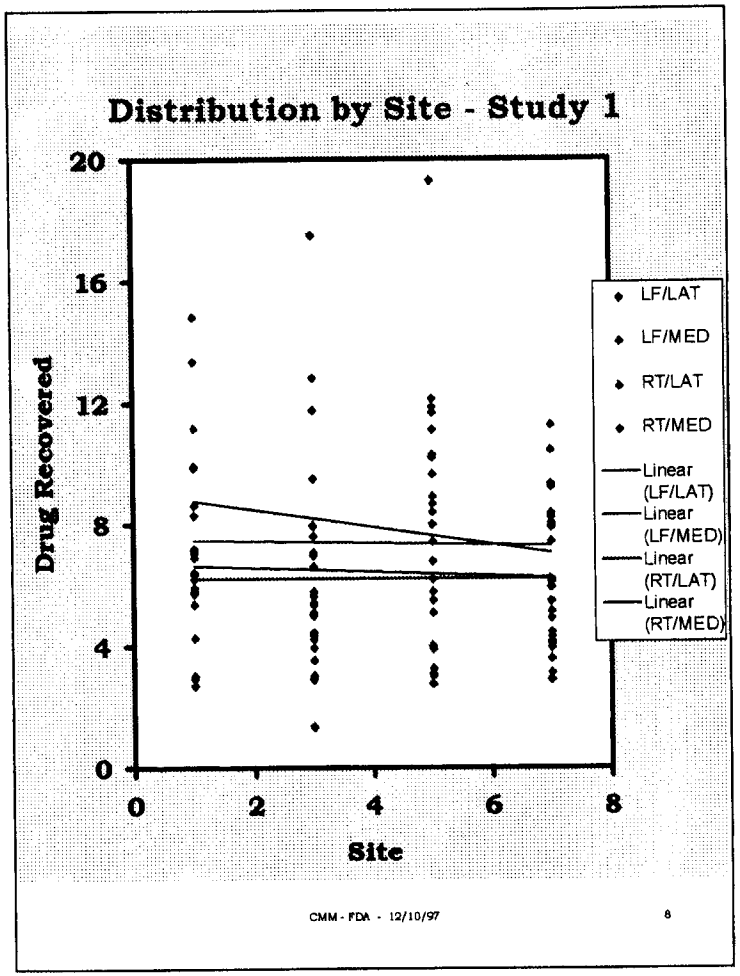
Study One

Variance Component	Estimate
subject	3.692
subject*arm	1.547
subject*side	0.408
subject*site	0.0
error	5.620

Study Two

Variance Component	Estimate
subject	11.115
subject*arm	5.678
subject*side	2.448
subject*site	0.865
error	20.029


Sources of Variance
60
50
40
30
20
10
0
% of Total
Study 1
Study 2
SUBJECT
SUB*ARM
SUB*SIDE
SUB*SITE
ERROR
CMM - FDA - 12/10/97
7


Distribution by Site - Study 1
20
16
12
8
4
0
Drug Recovered
0
2
4
6
8
Site
LF/LAT
LF/MED
RT/LAT
RT/MED
Linear (LF/LAT)
Linear (LF/MED)
Linear (RT/LAT)
Linear (RT/MED)
CMM - FDA - 12/10/97
8

Conclusions from Estimating Variances in Tape Stripping Studies

- Subjects are major source of variation and design should permit removing subject effects
- Subject x Arm interaction is second major effect, arms are not random
- Subject x Site is third largest effect, but sites may have non-random effect

Implications for Design of Tape Stripping Studies which Test Bioequivalence

- Test both formulations simultaneously in each subject (no period effect)
- Randomize formulations to arms
- Assign sampling times to sites in a nonrandom manner

TRANSPORT OF DRUGS IN CACO-2 CELLS

Concentration (μM)	15 min	30 min	60 min	120 min	240 min
Ranitidine 10 μM	0.11±0.03 (1.08%)	0.20±0.10 (1.99%)	0.35±0.15 (3.46%)	0.61±0.29 (6.07%)	1.14±0.47 (11.39%)
Ranitidine 25 μM	0.56±0.10 (1.13%)	2.00±1.16 (3.99%)	2.15±0.42 (4.30%)	3.64±0.13 (7.29%)	4.46±3.08 (8.92%)
Ranitidine 50 μM	2.11±0.36 (0.84%)	2.07±1.90 (0.83%)	5.34±2.29 (2.14%)	9.30±3.52 (3.72%)	20.82±7.68 (8.33%)
Naproxen 10 μM	0.50±0.19 (4.97%)	1.05±0.05 (10.54%)	1.54±0.14 (15.36%)	2.24±0.05 (22.37%)	2.64±0.27 (26.39%)
Naproxen 50 μM	2.44±0.39 (4.88%)	5.43±0.65 (10.86%)	8.05±1.04 (16.11%)	11.36±0.98 (22.72%)	14.04±1.46 (28.08%)
Naproxen 250 μM	13.45±1.36 (5.39%)	24.14±2.36 (9.66%)	38.93±2.05 (15.57%)	53.73±3.67 (21.49%)	67.32±5.05 (26.93%)

Naproxen and Ranitidine tested in presence of ISD (50 μM Metoprolol)
Concentration of test compound in basolateral chamber over time
Mean ± SD of three wells
(Percent drug transported)

IN VITRO PERMEABILITY VALUES

	Peff (× 10^{-4} cm/sec)
Naproxen	3.1
Metoprolol	0.38
Ranitidine	0.064

Mean ± SD of three wells

$$P_{eff} = \frac{V_R}{A \times C_0} \times \frac{\Delta C}{\Delta t}$$

P_{eff} = Permeability, V_R = volume in receiver chamber, A = filter surface area (cm^2), C_0 = initial concentration in donor chamber, and $\Delta C/\Delta t$= initial slope of plot of receiver concentration with time.

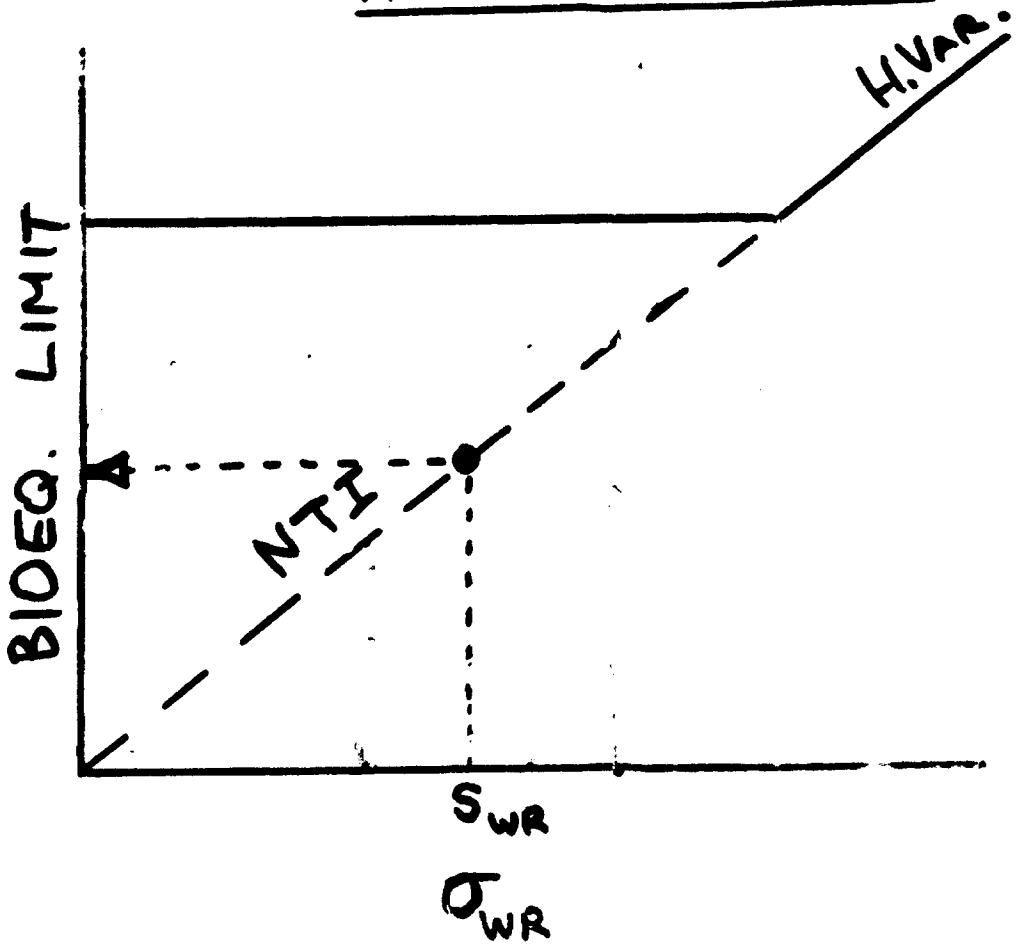
RATIO OF PERMEABILITY VALUES

P_{eff} Values ($\times 10^{-4}$ cm/sec)	Drug	Drug/ISD Ratio
Ranitidine 10 μM	0.008 ± 0.002	0.22 ± 0.05
Ranitidine 25 μM	0.008 ± 0.001	0.21 ± 0.08
Ranitidine 50 μM	0.006 ± 0.001	0.14 ± 0.01
Naproxen 10 μM	2.94 ± 1.32	9.48 ± 1.92
Naproxen 50 μM	2.99 ± 0.54	10.29 ± 1.01
Naproxen 250 μM	3.78 ± 0.47	10.51 ± 0.81

Drugs tested in presence of ISD (50 μM Metoprolol)
Mean ± SD of three wells

In vivo P_{eff}: Ranitidine = 0.43×10^{-4} cm/sec
Metoprolol = 2.0×10^{-4} cm/sec
Naproxen = 8.0×10^{-4} cm/sec

VARIABILITY OF NTI CRITERION



ESTIMATED VARIANCES ARE UNCERTAIN

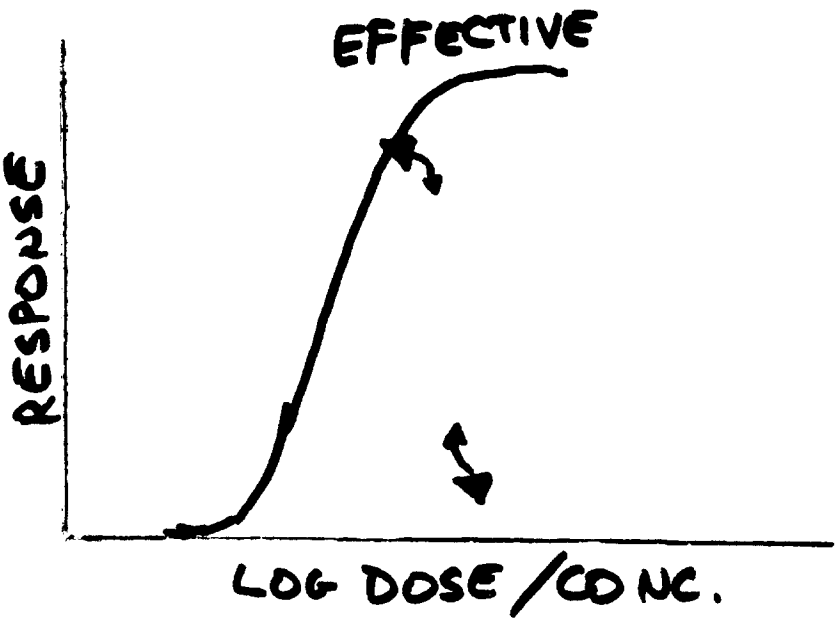
→ ESTIMATED BIOEQ. LIMITS ARE UNCERTAIN

INDICES OF TOXICITY

21 CFR 320.33(c):

TD50/ED50 ●

TDmin/EDmin Δ



SUGGEST; E.G.:

TD10/ED90

NATIONAL PHARMACEUTICAL ASSOCIATION
December 11, 1997

FDA ADVISORY COMMITTEE MEETING: NARROW THERAPEUTIC INDEX DRUGS

Marvin C. Meyer, Ph.D.
University of Tennessee

Lane J. Brunner, Ph.D.
University of Texas

ORIGIN OF THE NTI LIST:

In 1989 the list was developed to identify drugs that should receive priority for FDA testing and inspections resulting from the "Generic Drug Scandals"

Recently included as Appendix A in the SUPAC-IR Guidance.

Purpose - identify drugs that will require in vivo testing if certain "substantial" changes occur in a dosage form of a generic OR innovator firm.

NEVER INTENDED AS A NEGATIVE FORMULARY TO PROHIBIT SUBSTITUTION.

NARROW THERAPEUTIC RANGE DRUGS

Aminophylline Tablets, ER Tablets

***Carbamazepine Tablets, Oral Suspension

Clindamycin Hydrochloride Capsules

Clonidine Hydrochloride Tablets

Clonidine Transdermal Patches

Disopyramide Phosphate Capsules, ER Capsules

Divalproex, Sodium DR Capsules, DR Tablets

***Dyphylline Tablets

Ethinyl Estradiol/Progestin OC Tablets

Guanethidine Sulfate Tablets

Isoetharine Mesylate Inhalation Aerosol

Isoproterenol Sulfate Tablets

Lithium Carbonate Caps, Tabs, ER Tabs

Metaproterenol Sulfate Tablets

Minoxidil Tablets

Oxtriphylline Tablets, DR Tablets, ER Tablets

***Phenytoin, Sodium Capsules (Prompt or Extended), Oral Suspension

Prazosin Hydrochloride Capsules

***Primidone Tablets, Oral Suspension

Procainamide Hydrochloride, Caps Tabs, ER Tablets

Quinidine Sulfate Capsules, Tablets, ER Tablets

Quinidine Gluconate Tablets, ER Tablets

***Theophylline Caps, ER Caps, Tabs, ER Tabs

Valproic Acid Capsules, Syrup

***Warfarin, Na Tablets

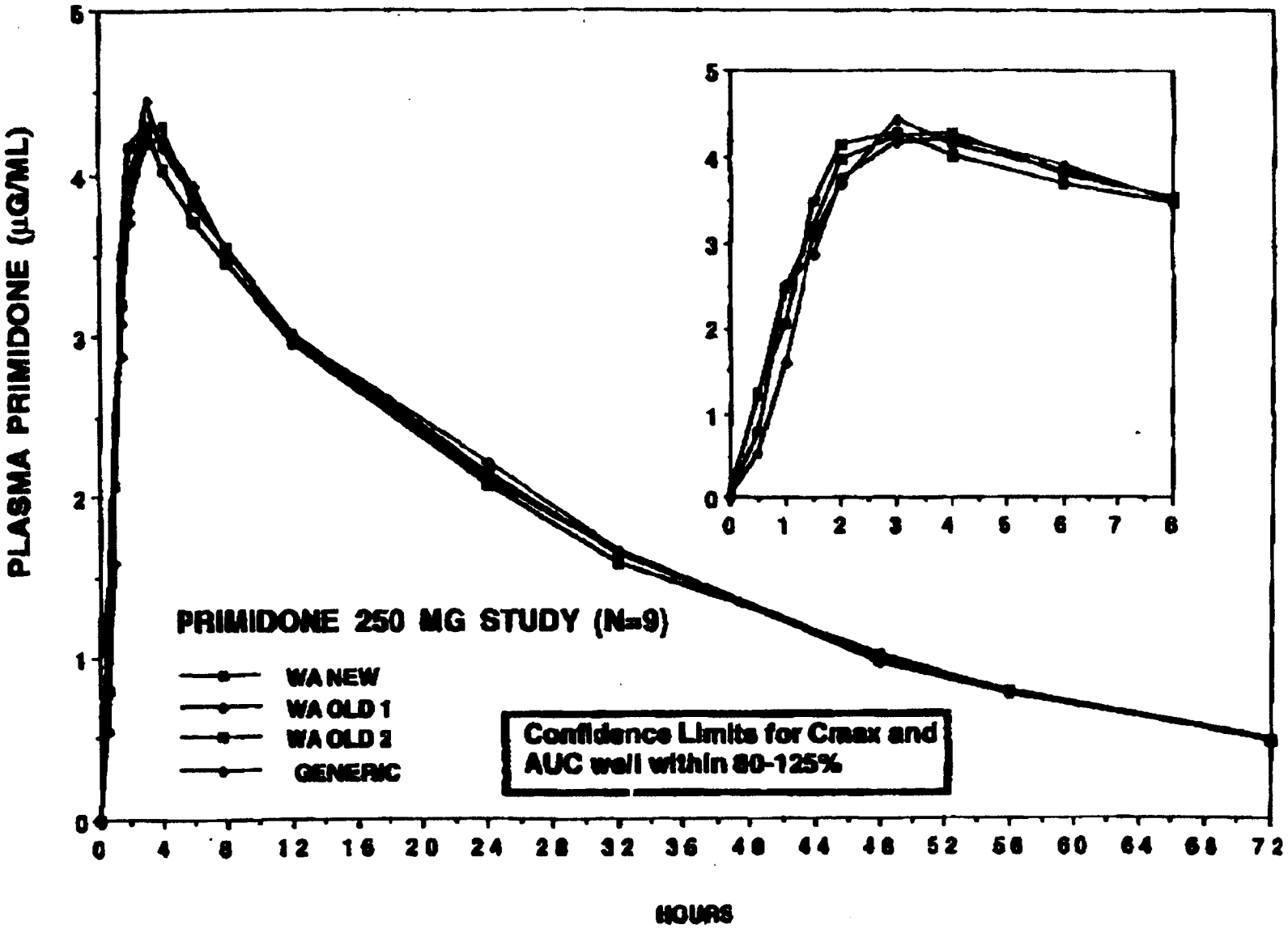
200 MG DYPHYLLINE TABLETS (n=12)

PRODUCT	CMAX (µg/ml)	TMAX (hr)	AUC(0-∞) (µg/ml)*hr
1	8.21	0.6	20.16
3	7.80	0.7	20.39
5	8.15	0.7	20.51
	(5%)		(2%)

PHENYTOIN Na EXTENDED CAPSULE BIOAVAILABILITY
(All are lots from the Innovator Firm - Product 1 and Product 4 are the same lot given on two occasions)

MEAN (N=24) and (CV%)

PARAMETER	PRODUCT 1	PRODUCT 2	PRODUCT 3	PRODUCT 4
C_{MAX} (µg/ml)	1.79 (22)	1.73 (19)	1.76 (22)	1.71 (21)
T_{MAX} (hr)	3.6 (64)	4.3 (105)	3.9 (43)	4.0 (56)
AUC(0-) (µg*hr/ml)	54.1 (59)	53.0 (73)	53.6 (57)	53.0 (66)


PLASMA PRIMIDONE (µG/ML)
HOURS
PRIMIDONE 250 MG STUDY (N=9)
WA NEW
WA OLD 1
WA OLD 2
GENERIC
Confidence Limits for Cmax and AUC well within 80-125%

THEOPHYLLINE IR CAPSULES 200 mg

Parameter	MEAN (CV%) n= 18 Winthrop	Forest	Fisons	Percent Difference
C_{max} (µg/ml)	5.4 (17)	5.5 (19)	5.3 (21)	4%
T_{max} (hr)	1.3 (71)	1.4 (55)	1.3 (69)	
AUC(0-)	59.0 (32)	60.5 (35)	58.1 (37)	4%

Barr's Warfarin Bioequivalence Studies

Strength	Test/ Reference % (Conf. Lim.) Cmax	AUC (0-inf)
2 x 2.0 mg	98 (89-108%)	98 (95-100%)
2.5 mg	103 (98-108%)	99 (96-102%)
5.0 mg	103 (98-109%)	101 (98-104%)
10.0 mg	102 (95-110%)	102 (99-105%)

CONCLUSIONS

1. It is important to remember the reason for the NTI List - it was not developed as a negative formulary.

2. There are numerous reasons to monitor patients and titrate the dosage regimen:

   A. Changes in patient response.
   B. Drug-drug interactions.
   C. Changes in clearance or Vd.
   D. Patient Compliance
   E. Bioinequivalent Products

Lots Of Examples of Reasons A, B, C and D

NO Well Documented Examples of Reason E for a FDA Approved, AA or AB rated product.

3. The available data does not support a need for FDA to modify the present standards for approval of drug products on the basis of bioequivalence studies.

Narrow Therapeutic Index
State Initiatives

ARIZONA

CALIFORNIA

COLORADO

GEORGIA

IDAHO

ILLINOIS

INDIANA

MASSACHUSETTS

MICHIGAN

MISSOURI

NEVADA

NEW JERSEY

NEW YORK

NORTH CAROLINA

OHIO

OREGON

PENNSYLVANIA

TENNESSEE

TEXAS

VIRGINIA

WASHINGTON

WISCONSIN

BIOEQIVALENCE STANDARDS FOR WARFARIN SODIUM

C.T. Rhodes
Professor of Applied Pharmaceutical Sciences
University of Rhode Island

FDA
11 December, 1997

STARTING POINTS

1. Existing FDA standards for bioequivalence have worked well in assuring the U.S. population of a reliable supply of safe, effective, and relatively inexpensive drugs. FDA standards have been used as a model for standards in other jurisdictions.

2. Any change to bioequivalence standards should only be made when there is a proven scientific case for such change. Unsubstantiated clinical anecdotes or crude fear tactics must not prevail.

3. Unless there are well-documented, reliable reports of substantial clinical problems with generic equivalents which are already on the market, changes in bioequivalency standards should not be applied retrospectively.

4. Changes to bioequivalency standards should be made at the national level by FDA, working in concert, when necessary, with USP (e.g., potency, content uniformity).

5. Decisions about changes to bioequivalency standards must be made on an individual basis. Thus, it is not appropriate to move all drugs on the Low Therapeutic Range list en masse into a new bioequivalency class.

6. Any new bioequivalency standard must apply to variability of the innovator's product (potency, stability, content uniformity, batch-to-batch variability), as well as to generic products.

7. Physiochemical Classification System developed by Dr. Amidon, and accepted by FDA, is an excellent starting point for consideration of any rational approach to possible changes in bioequivalency standards.

THE GOLDEN RULE

If variation in the clinical response of patients to different versions of the same drug product is due to the inherent nature of the drug molecule, per se, rather than differences in formulation and/or processing factors, then it is counter-productive to attempt to reduce intra- and inter-patient variability by tightening bioequivalence standards.

WARFARIN SODIUM

1. Water soluble, rapid dissolution

   DISSOLUTION NOT A PROBLEM

2. Good membrane flux rate

   ABSORPTION NOT A PROBLEM

3. Basically a stable molecule

   STABILITY NOT A PROBLEM

4. Dry mixing of ingredients followed by direct compression

   FORMULATION AND PROCESSING VERY SIMPLE AND ROBUST, YIELDING PRODUCTS WITH EXCELLENT QUALITY ATTRIBUTES

CLINICAL RESPONSE TO WARFARIN SODIUM

As stated in USP DI (Information for Health Professionals):

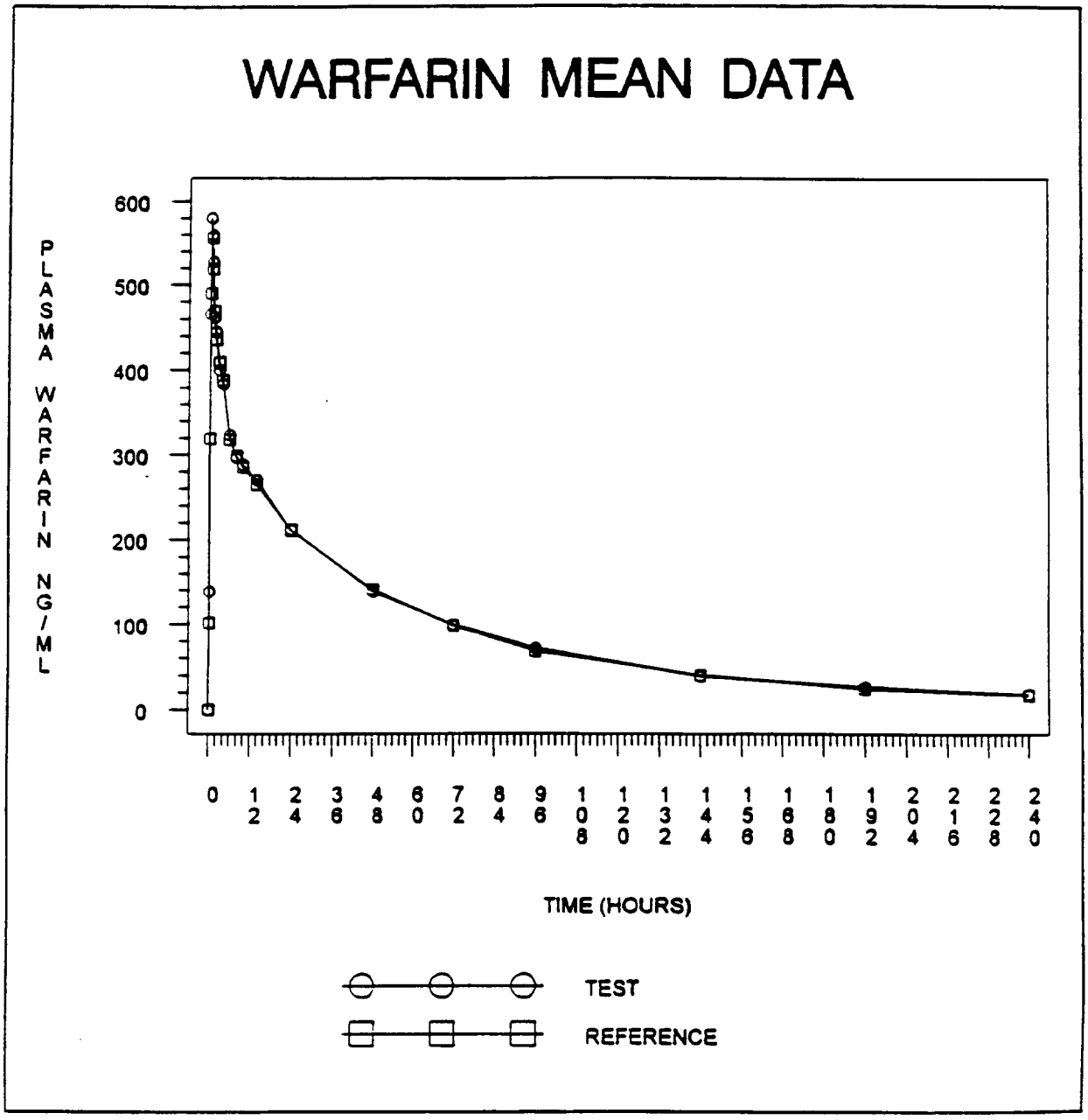
1. Half life is about two days. Thus, at steady state the patient who takes one fixed dose a day has about 2 to 2-1/2 doses already in his or her body each time he or she takes their daily dose. Content Uniformity, therefore, is not unusually critical for control of the clinical response of this drug.
2. Warfarin is an "indirect acting coagulant (which) prevents the formation of active procoagulation factors II, VII, IX, and X in the liver inhibiting the vitamin K mediated gamma carboxylation of precursor proteins." (emphasis added).
3. USP DI specifically warns that increase or decrease in anticoagulation effect can occur in previously stabilized patients if the diet is changed.

CLINICAL RESPONSE TO WARFARIN SODIUM (Continued):

4. It is recommended that Prothrombin Times be monitored "at 1-4 week intervals for the duration of the treatment."

5. It is noteworthy that patients who are only being treated with the brand product often require re-titration. Thus, in one New England clinic, approximately 50% of patients receiving only the brand-name product had unacceptable INR values.

Linear Plot of Mean Plasma Warfarin
Concentrations *vs* Time (0-240 Hours)



CONCLUSION

The variability in clinical response is a function of the inherent nature of the drug molecule, its mode of action, and its peculiar sensitivity to factors such as diet.

It is thus inappropriate, unhelpful, and unjustifiable to impose unusually rigorous bioequivalency standards for Warfarin Sodium.

CLIN. RESEARCH & REG. AFFAIRS, 14(2), 127-137 (1997)

ACCEPTANCE LIMITS FOR BIOEQUIVALENCE STUDIES

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The University of Rhode Island
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ABSTRACT

At present, bioequivalence acceptance standards are the same for all drugs. The test article must exhibit pharmacokinetic parameters which are within the range of 80% to 120% of those which characterize the reference product (80-125% for log transformed data). However, there are arguments in favor of individual-izing the acceptance standards so as to allow for recognition of the unique pharmacokinetic and pharmacodynamic properties of any given drug. The present paper explores some of the factors which need to be taken into account if such changes in bio-equivalence acceptance standards are to be implemented in a rational manner.

During the past thirty years or so, developments in biopharmaceutics, pharmacokinetics, and related disciplines have focused the attention of those responsible for pharmaceutical standards, such as FDA and USP, on bioavailability. In particular, the topic of bioequivalence and generic substitution has elicited much lively debate with respect to both scientific and political aspects. The Waxman-Hatch Act which, inter alia, provides the present regulatory structure for the approval of generic products is generally credited, both nationally and

internationally, with providing a reasonable balance between the commercial interests of research-based pharmaceutical companies which introduce new drug substances onto the market and generic companies desirous of selling their versions of the product once patent protection has expired.

Obviously, there is a dichotomy of interest between the two types of pharmaceutical companies. It is not surprising that the research-based company which introduced the innovative drug onto the market does not greet the approval of generic products with joy. There is abundance of evidence to show that the introduction of generic products often results in substantial reduction in prices which, together with loss of market share, can cause the innovator company to experience a dramatic loss of profits. During the period when the innovator's product was covered by a valid patent, the research-based company was provided with an opportunity to recoup the very substantial sums which were expended in the research and development of the new product. Once the patent has expired, the innovator may well feel distinctly chagrined at the loss of monopoly status and, in some instances at least, they will be severely tempted to take extreme and unjustifiable measures in their attempts to defend their market status.

It is also apparent that generic companies, in their desire to enter the market as soon as possible, may sometimes have difficulty in appreciating the need for all the necessary regulatory hurdles which they have to jump before their ANDA is approved.

Because of the very large financial implications for the pharmaceutical industry, it is particularly important that pharmaceutical scientists and regulators concerned with generic equivalence standards be especially vigilant against specious arguments that, although articulately projected by company spokespersons, are essentially "smoke and mirrors" devices. The interests of the community in

general should be of paramount importance when decisions are made on bioequivalence and generic substitution. The very substantial savings to consumers/patients (and, more particularly, taxpayers) when good-quality generic products are available require that we must be on our guard against the introduction of irrational standards for generic products which are not well based on reliable scientific or clinical data.

The present standard for bioequivalence with respect to the log transformed pharmacokinetic parameters AUC, T_{MAX} and C_{MAX} is that the average and confidence bounds for the test article be within 80% to 125% with respect to the innovator's product which is designated as the reference product. The literature contains previous reports which have indicated possible improvements to present procedures with respect to bioequivalence (1-4). However, there is probably a broad consensus that FDA policies on bioequivalence have generally worked well, and indeed there is good reason to believe that these policies have had significant influence on the development of comparable policies in other jurisdictions.

In essence, the argument in favor of considering modification of the present uniform bioequivalence standards for all drugs is that the uniform standard is difficult to justify, since we know that different drugs exhibit variation in certain properties that have the potential to impact on therapeutic interchangeability. For example, if drug A has a much steeper slope of the dose response curve than drug B, one will feel that, a priori, the bioequivalence acceptance stands for B could be broader than that required for A.

Given that the "one size fits all" approach is probably indefensible on theoretical grounds, the question which has to be addressed is: "What data is required so that an intelligent, practicable decision can be made about tightening or loosening bioequivalence standards for any given drug?" This is not a decision which should

be taken lightly. If our standards are too lax, there may be an increase in the occurrence in either or both sub-therapeutic blood levels or adverse side effects. If our standards are too rigorous, we may unjustifiably exclude perfectly good generic products which could provide satisfactory results. The exclusion of such generic products from the market has the potential to have vast adverse effects on health care costs, and the availability of necessary drug treatment for the poor.

There is one possible misconception about the FDA list of Low Therapeutic Range Drugs which was developed by the Agency some years ago. This list was developed in order to specify those drugs for which a bioequivalence waiver would not be allowed. The list was not issued as an indication that unusually rigorous bioequivalence standards would be imposed by the Agency for such drugs (5, 6). This list is also referred to in the 1994 FDA Pre-approval Inspection (7) document which makes it clear that for these drugs, pre-approval inspections are mandatory. It is also noteworthy that the November, 1995 FDA Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation (8) often referred to as SUPAC Guidelines, gave specific attention to bioequivalence requirements for drugs which appear on the list.

In considering the possibility of loosening or tightening the bioequivalence standards for individual drugs, it may be useful to categorize drugs into the following categories:

I. New drugs or drugs which have only been available on the market for a limited period and for which generic versions have not yet been approved, or

II. Drugs which have been on the market as both innovator's and generic products for a number of years.

For class II drugs, we have the advantage of clinical experience of using both innovator's and generic products, and thus it is possible that there may be reliable scientific data which could assist us in reaching an informed decision on whether to loosen or tighten the bioequivalence standards for any given drug.

What are some of the possible sources of data for class I drugs? It is suggested that the following list contains at least some of the factors which may be relevant:

1. Recall history or lack thereof for innovator or generic products where such recalls relate to sub- or supra-therapeutic blood levels of the drug.

If there have been significant numbers of recalls of products due to sub- or supra-therapeutic response, this factor might tend to point to the possibility of tightening bioequivalence standards for the drug substance in question. However, we must exercise caution; if one generic product has experienced problems and others have not, this would not indicate a deficiency in the bioequivalence standards per se but, rather, some specific company-related control problem.

2. Has USP established unusually rigorous potency or content uniformity standards for this particular drug?

If the USP potency or content uniformity standards are unusually rigorous, this might well suggest that there is already special concern as to the variability of blood concentrations, and thus such drugs may be possible for candidates for more rigorous bio-equivalence standards. Absence of such unusual USP standards points away from the possibility of tightening bioequivalence standards. Unusually lax USP requirements for potency or content might indicate the possibility of wider bioequivalence standards.

3. For high permeability, high solubility drugs, do all commercial articles exhibit $T_{85\%}$ in 0.1N HCl of 15 minutes or less?

If all versions of the drug product, generic and innovator's, for high permeability and solubility drugs have $T_{85\%}$ values of 15 minutes or less, there may be reason to consider having wider bioequivalence standards for that drug. (This test is that described in the SUPAC guideline.)

4. Low Permeability, High Solubility Drugs

Again, the SUPAC guideline test data may provide a possible indication for the introduction of more relaxed bioequivalence test standards.

5. High Permeability, Low Solubility Drugs

Again, the SUPAC guideline test data may provide a possible indication for the introduction of more relaxed bioequivalence test standards.

For drugs in class I, the situation is more difficult since the only data normally available will derive from the innovator's product, when available information on the batch-to-batch variability of the innovator's product with respect to blood levels of drug or dissolution could be of value. Obviously, if there is substantial variance in the inter-batch variance of the innovator's product, it would be inequitable and pointless to restrict the generic product to limits which are tighter than those seen between different batches of the innovator's product.

It has recently been suggested (9) by the present author that during the development of a new drug when development bioequivalence[1] is being quantified, it would be

[1]Development bioequivalence is the term applied to bioequivalence with respect to different formulations used in clinical trials.

useful for the sponsor of the NDA to generate data, pharmacologic, pharmacokinetic and pharmacodynamic, which would assist in the determination of rational bioequivalence standards for the specified drug. The definition of low-therapeutic-range drugs as being characterized of rational bioequivalence standards for the specified drug. The definition of low-therapeutic-range drugs as being characterized by a ratio of LD50 to ED50 of less than two (5) is of little practical value, since LD50's are not determined in humans when drugs are developed.

Even if we modify the definition of narrow-therapeutic-range drugs to those for which there is a less than a two-fold ratio between minimum toxic and minimum effective concentration of drug in the bloodstream, and when clinical pharmacokinetic titration of individual patients is generally regarded as essential, we are still faced with problems.

Firstly, if the variability in blood levels observed with the drug is an inherent property of the drug molecule, rather than the formulation and processing variables selected by individual companies, then a tightening of the standards for generic bioequivalence will not reduce variability of blood levels in patients. It will simply result in the exclusion of less-expensive, comparable products from the market.

Secondly, if we apply a tightened bioequivalence test to drugs which might be candidates for inclusion in the second definition of low-therapeutic range without taking into account the batch-to-batch variability possible stability changes of both

generic and innovator's product, we will not have achieved any result of practical value to individual patients if batch-to-batch variability in either the generic or innovator's product is so large as to have a significant affect on blood levels (1).

Thirdly, for those drugs where there is not a simple relationship between pharmacokinetic parameters and pharmacodynamic results, the policy would be misguided.

One salient point which must always be kept in mind in any consideration of introducing more rigorous standards for the quantification of generic bioequivalence is that it would be scientifically unjustifiable to impose higher standards on the generic product than those that are applied to the innovator. Thus, if it were suggested that a generic product be required to conform to a 90-111% standard for both average data, and 90% confidence bounds for log-transformed data, such a test should only be applied to exclude generic products where the confidence bounds of the generic product were greater than those of the innovator. If the two products showed the same variance, or if the innovator's product showed greater variability, the exclusion of the generic product would obviously be counter productive.

If a USP drug product has an allowed potency range of 95% to 105% of label claim and a content uniformity limit characterized by a relative standard deviation of 6%, then individual tablets with a content of between 92% and 108% or more

of label claim might be observed in a product meeting USP standards. This is a range of 16%. Thus, if we were to impose confidence bounds of the bioequivalence test for this drug as being 90-111%, we restrict the range to 21% which, in effect, may only allow 5% (21-16) for inter- and intra-subject variability and analytical variance in the bioequivalency study.

Equally troubling is the effect of even a small amount of degradation, such as that permitted by USP and FDA, on the possible bioinequivalency between two batches of the innovator's product. Suppose a batch is released with an average potency of 102% of label claim and the 90% confidence bounds for the bioequivalence parameters were remarkably tight so that the difference between the two bounds was 92% to 111%. Now, suppose that another batch is on the market with a potency of only 97% (because of either a small amount of degradation or because the initial potency of the batch, although within USP limits, was a little under 100%). In this case, even tablets of average potency for the two batches would be bioinequivalent. When we allow for a content uniformity of RSD (relative standard deviation) of 6%, the possible level of bioequivalency discrepancy becomes even greater. Thus, to accommodate 90% to 111% confidence bounds, the USP potency and content uniformity limits must be tightened before any realistic consideration could be given to such a change.

The question of individualizing bioequivalence standards may indeed need to be addressed. The problem must be approached on a drug-by-drug basis. Decisions

can only be made when there is adequacy of reliable, well-quantified data. Anecdotal clinical accounts of possible therapeutic inequivalencies cannot be given weight unless they are supported by laboratory data on blood levels or other reliable, objective data. At present, our knowledge of the range of clinically effective blood levels for many drugs is somewhat defective. Perhaps additional studies in population pharmacokinetics may be of value in this area (10). Changes from the present 20% limit to either high or lower values should only be made by regulatory scientists who have the expertise and independence of judgment to make objective decisions based on well-substantiated scientific data. It is hoped that decisions concerning bioequivalence standards will be made by FDA and USP acting at the national level.

ACKNOWLEDGEMENT

I thank those individuals at USP, FDA, and various universities and pharmaceutical companies who have, over the years, discussed the topic of bioequivalence with me. However, the views presented in this paper do not purport to be those of any government or non-government organization with which I am or have been associated.

REFERENCES

1. C.T. Rhodes, *Clinical Research and Drug Regulatory Affairs* 11, 181-184 (1994).

2. L. Benet and J. Goyan, *Pharmacotherapy* 15, 433-440 (1995).

3. C.T. Rhodes, *Clinical Research and Drug Regulatory Affairs* 12, 267-272 (1995).

4. S.E. Rosenbaum and J. Lam, *Drug Development and Industrial Pharmacy* 23, 337-344 (1997).

5. CFR 320-33.

6. Letter from James S. Benson, Acting Commissioner of Food and Drugs, 1 October, 1990.

7. FDA Compliance Program Guide Manual, published 15 August, 1994.

8. SUPAC Guidelines, published November (1995).

9. C.T. Rhodes, Chapter on Bioequivalence in *Drugs for Clinical Trials*, edited by Monkhouse and Rhodes, Marcel Dekker (1997).

10. S.E. Rosenbaum, A.A. Carter and M.N. Dudley, *Drug Development and Industrial Pharmacy* 9, 1115-1139 (1995).