

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: February 8, 2000
To: Dockets Management Branch (HFA-305)
From: Melissa Lamb
Office of Generic Drugs
Subject: Office of Pharmaceutical Science Update

This memorandum forwards overheads of a presentation to the Dockets Management Branch for inclusion in Docket 90S-0308. The following is information on the presentation for the Docket records:

Title of Presentation: Office of Pharmaceutical Science Update
Presented for: 1999 Fall Technical Workshop
Date Presented: 10/19/99
Presented by: Roger L. Williams, M.D.
Number of Pages: 50



Attachment

905-0308
3873 '00 FEB 11 A9:26

905-0308

M661

1999 Fall Technical Workshop
The Generic Pharmaceutical Industry:
Regulatory and Scientific Challenges
NAPM, GPIA, NPA, FDA
Hyatt Regency, Bethesda
October 19, 1999

Office of Pharmaceutical Science Update

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

Topics

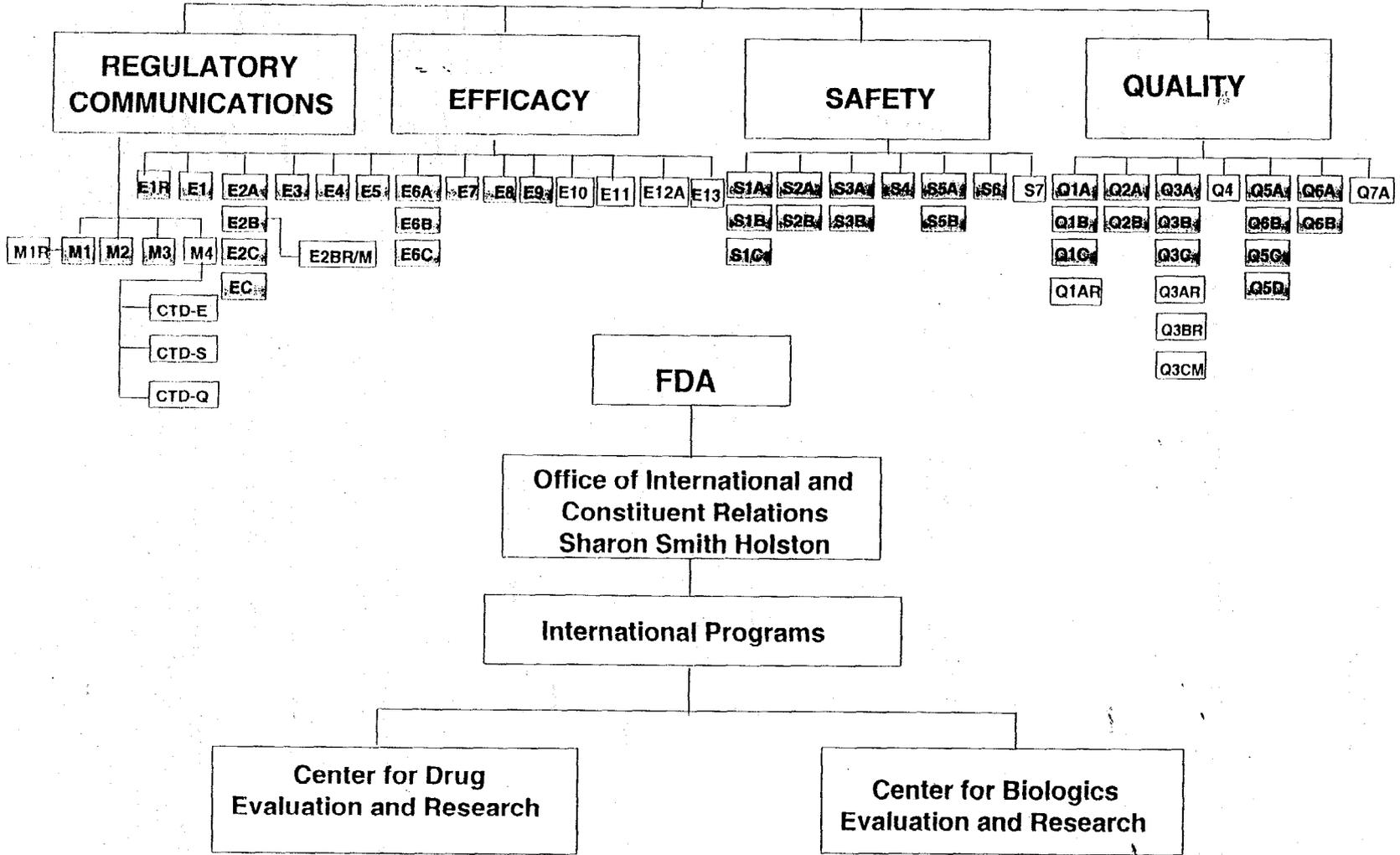
- • Guidances for Industry
 - 1 ICH
 - 2 WHO
 - 3 FDA
- Guidances for Reviewers
- The Future

INTERNATIONAL CONFERENCE ON HARMONIZATION

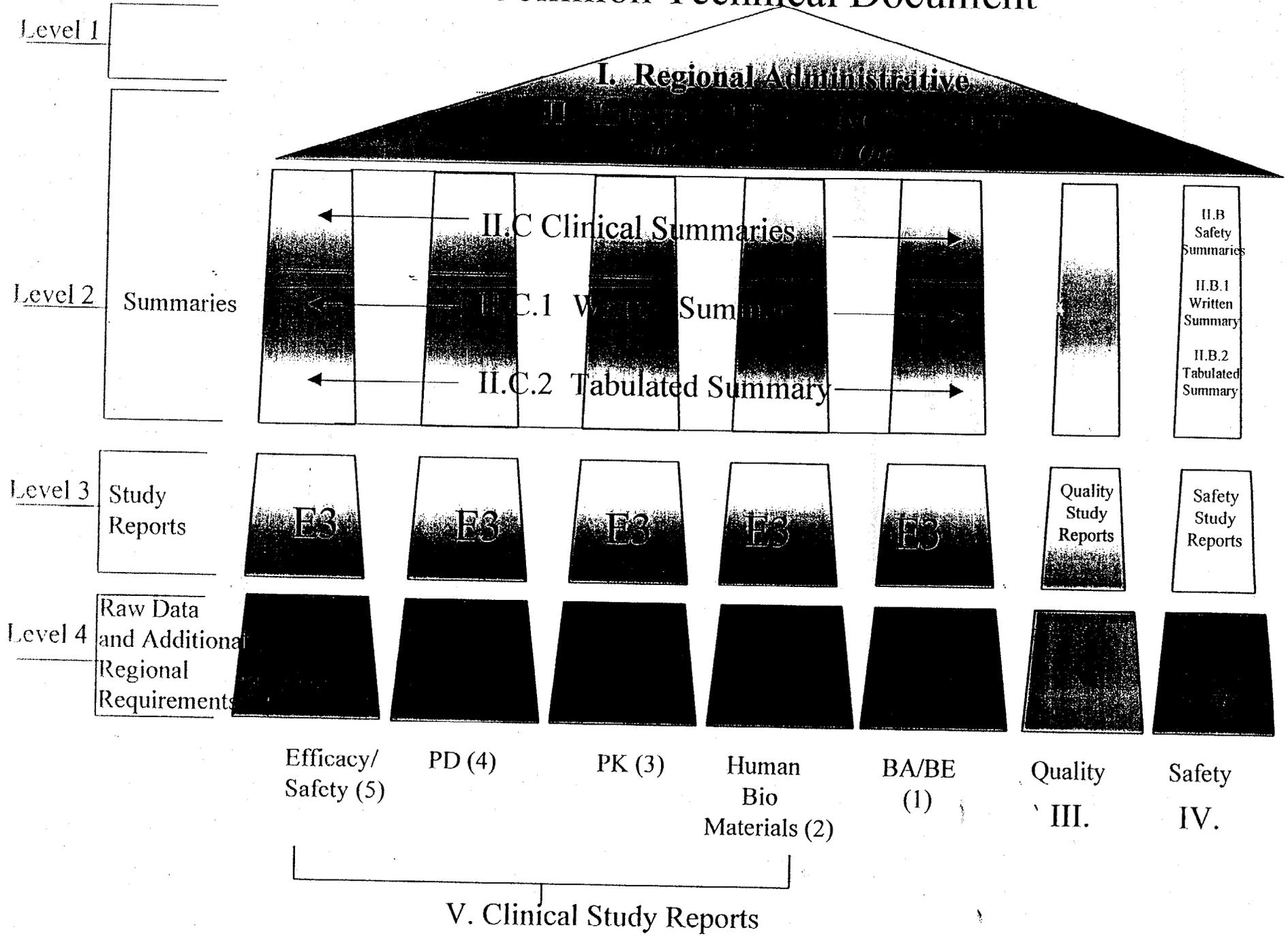


- Japan's MHW, FDA, EU/EC
- JPMA, PhRMA, EFPIA
- Observers: WHO, Canada, EFTA
- First Conference: Brussels 1991
- Second Conference: Orlando 1993
- Third Conference: Yokohama 1995
- Fourth Conference: Brussels 1997
- Fifth Conference: San Diego 2000

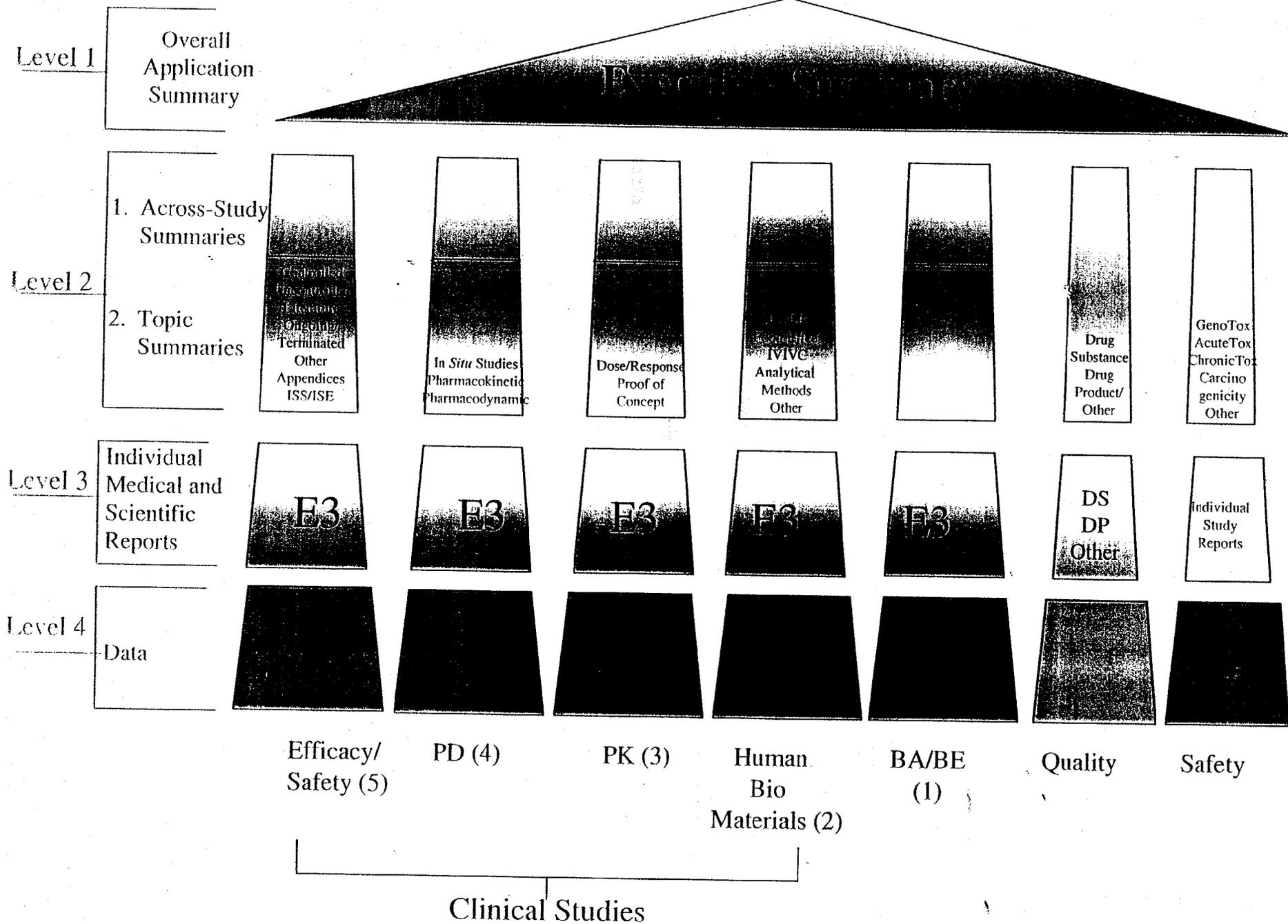
ICH Steering Committee



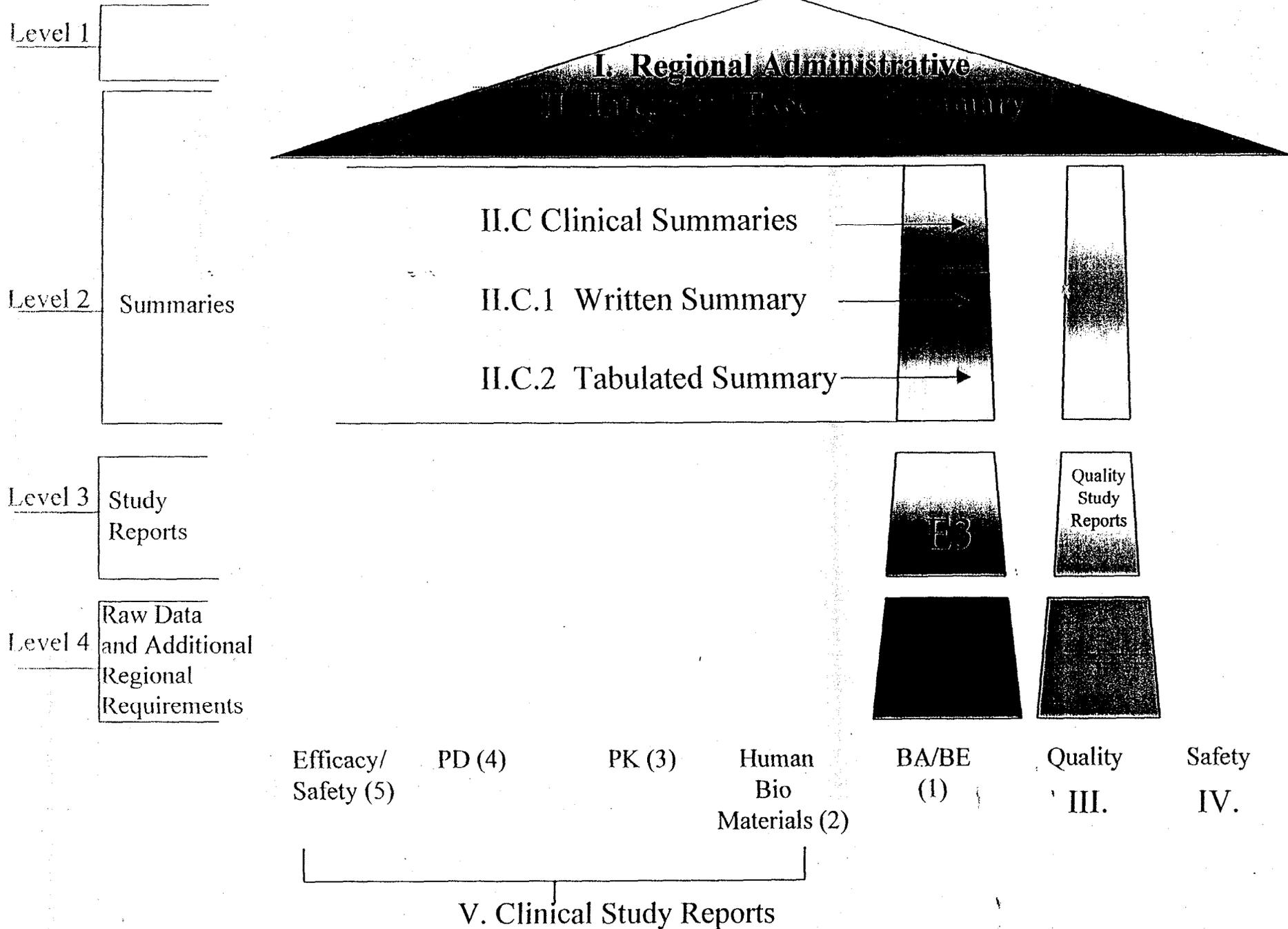
Common Technical Document



Common Technical Document



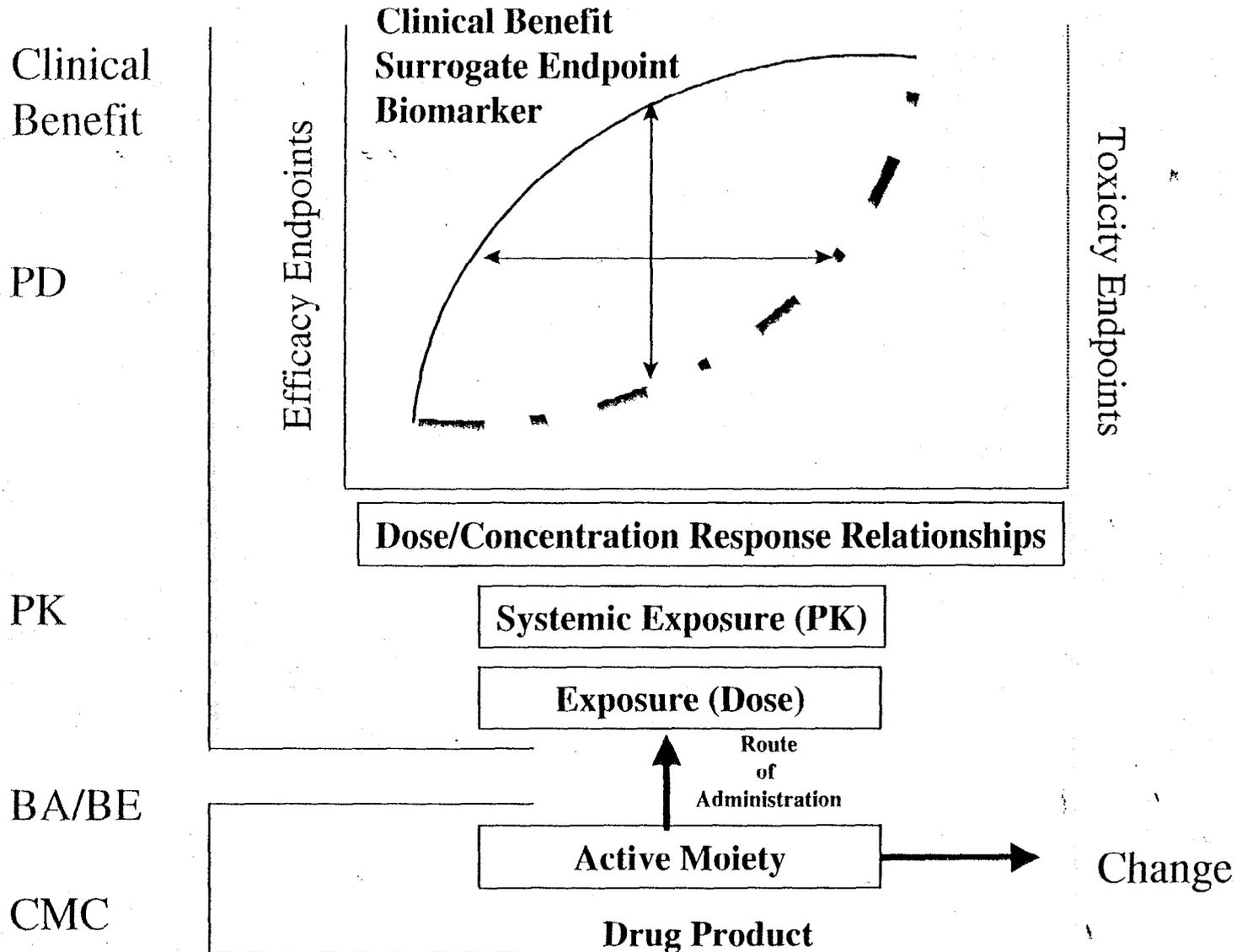
Common Technical Document

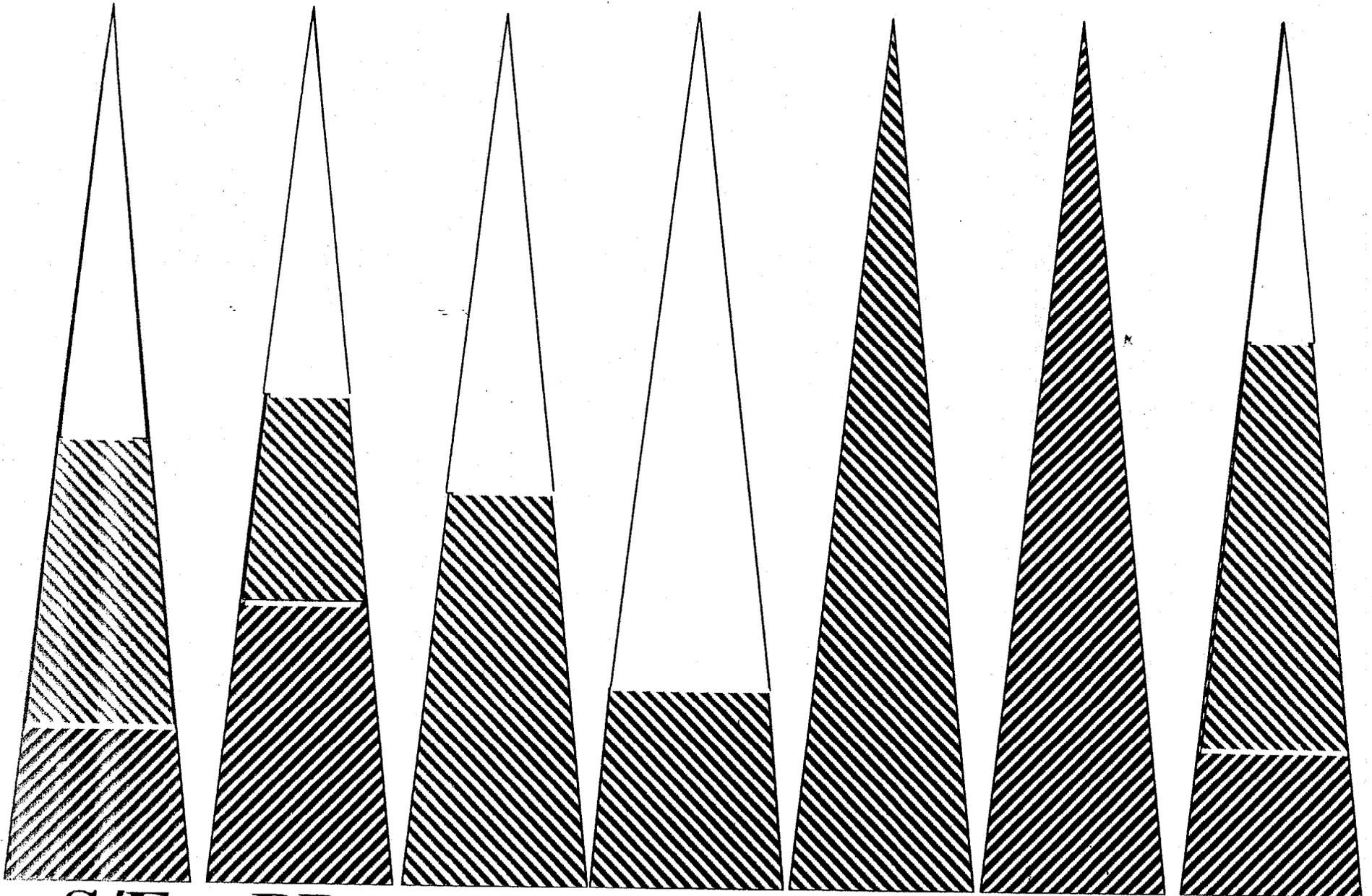


ICH CTD Modules

Optimal Dose \updownarrow Therapeutic Range \leftrightarrow

Safety/Efficacy





S/E

PD

PK

BM

B

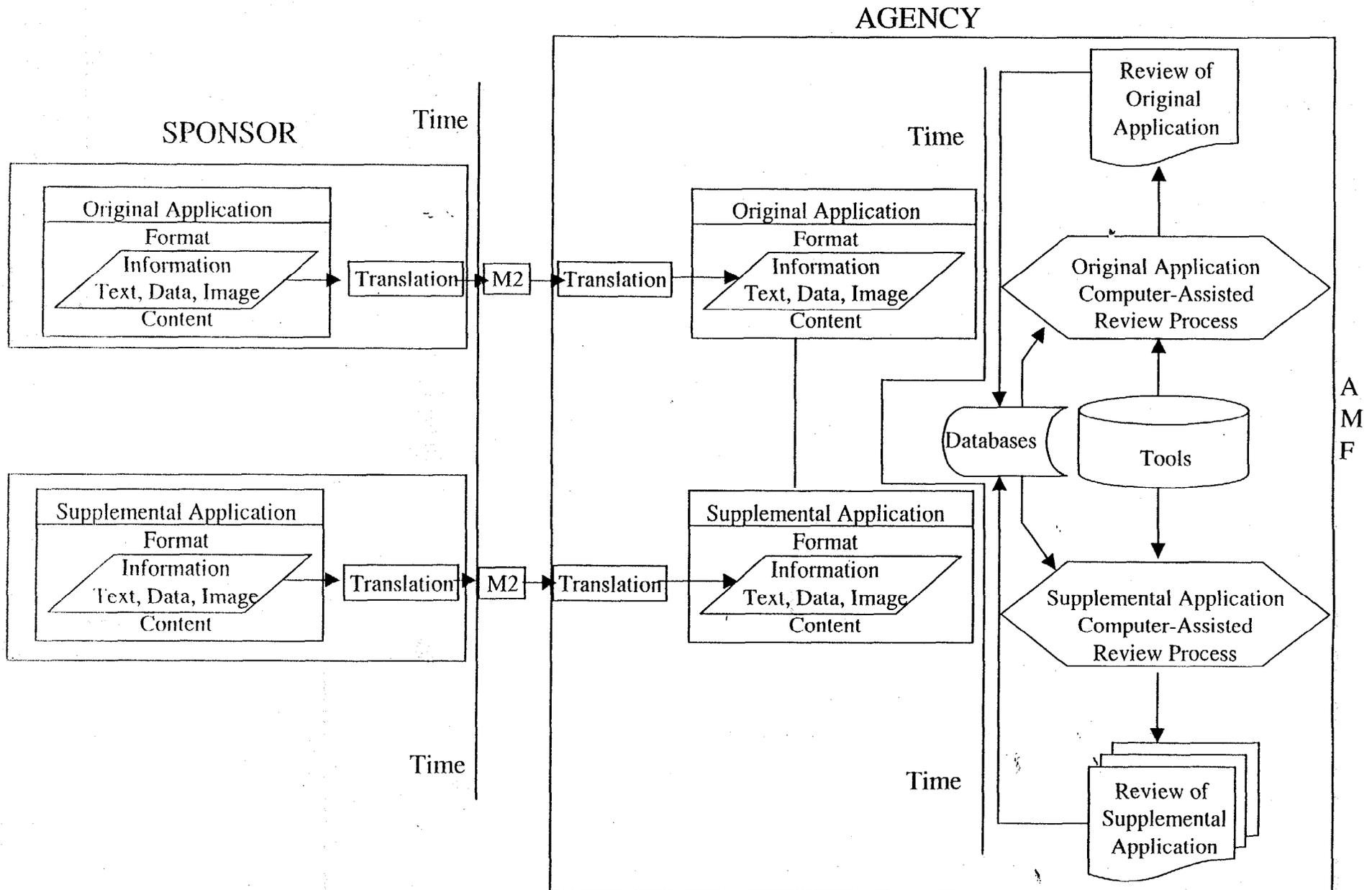
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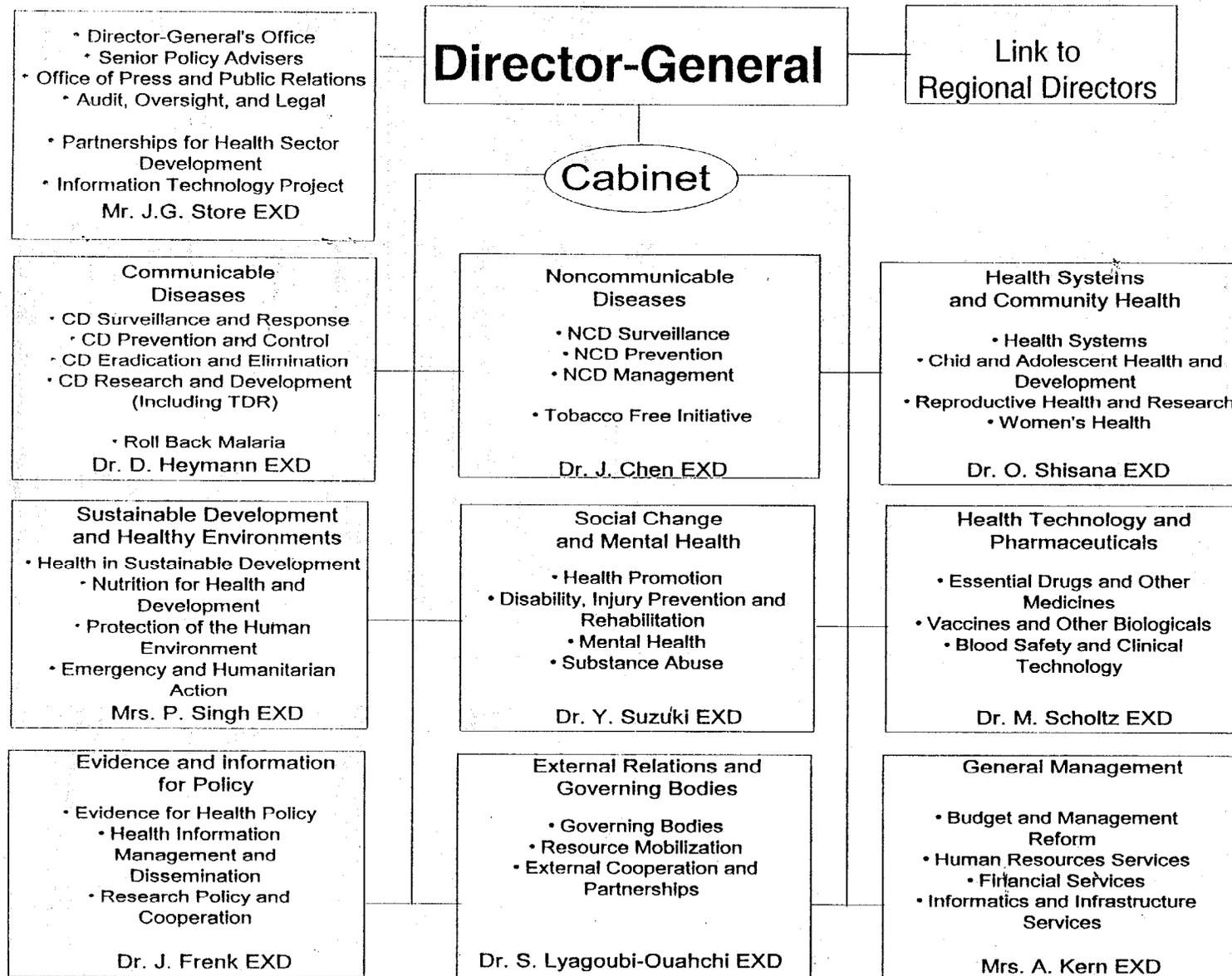
 = ICH

 = CDER/FDA

Electronic Regulatory Submission and Review OVER TIME and CENTER



WHO Structure at Headquarters



Health Technology and Pharmaceuticals HTP

Special Adviser on Health
Informatics and Telematics

Management Support Unit
HTP-MSU

Special Adviser on Quality
Assurance and Safety

Essential Drugs
and other Medicines
EDM

Quality Assurance
& Safety: Medicines
QSM

Policy, Access & Rational Use
PAR

Country Drug Action Programme
DAP

Traditional Medicine
TRM

Vaccines and
other Biologicals
V&B

Quality Assurance
& Safety: Biologicals
QSB

Vaccine Development
VAD

Vaccine Assessment
& Monitoring
VAM

Access to Technologies
ATT

Expanded Programme
on Immunization
EPI

Blood Safety and
Clinical Technology
BCT

Quality Assurance
& Safety: Blood Derivatives
QSD

Blood Transfusion Safety
BTS

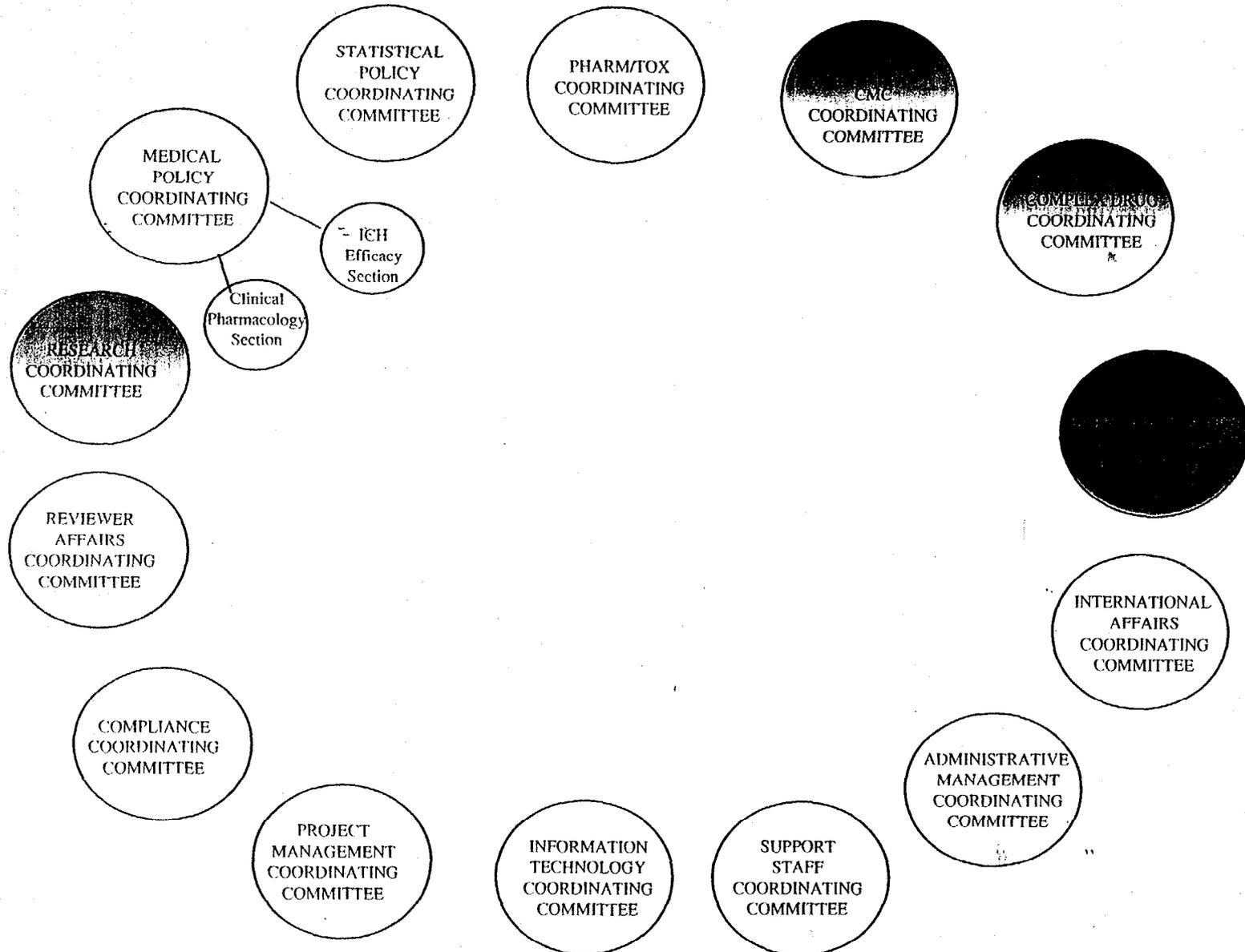
Diagnostic Imaging and
Laboratory Technology
DIL

Devices and Clinical Technology
DCT

WHO/Guidelines

- Multisource Guideline
- International Comparator
Pharmaceutical Product
- Model Application
- Assessment Practices Document
- GMPs
- Pharmacopoeia/Other

SCIENCE/TECHNICAL REGULATORY POLICY CDER COORDINATING COMMITTEES



Biopharmaceutics Coordinating Committee

General Approaches/Orally Administered Drug Products

**Bioavailability and Bioequivalence Studies for NDAs and ANDAs:
Orally Administered Drug Products (Draft/August 1999)**

Food Effect Bioavailability and Bioequivalence Studies (Draft/December 1997)

**Waiver of In Vivo Bioequivalence Studies for Immediate Release Solid
Oral Dosage Forms Based on a Biopharmaceutics Classification
System (Final/October 1999)**

**Bioanalytical Methods Validation for Human Studies Based On Drug
or Metabolite Assay in a Biological Matrix (Draft/January 1999)**

Locally Acting Drug Products

Nasal Inhalation Drug Products: In Vivo BA/BE (Draft/May 1999)

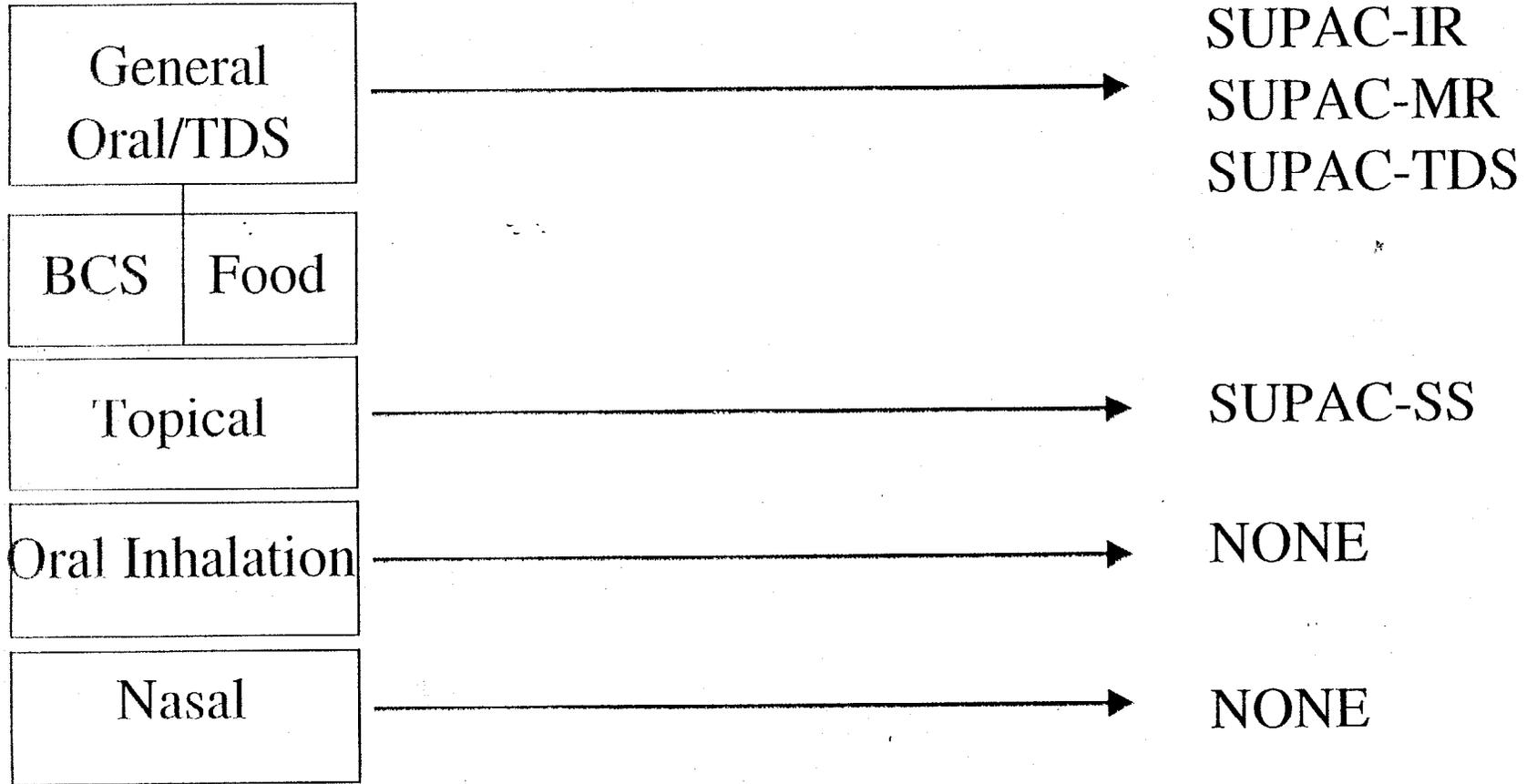
Oral Inhalation Drug Products: In Vivo BA/BE (Draft in preparation)

**Topical Dermatological Drug Product NDAs and ANDAs - In Vivo BA,
BE, In Vitro Release and Associated Statistics (Final/Fall 1999)**

Criteria For Comparisons

**Average, Population and Individual Approaches to Establishing
Bioequivalence (Draft/August 1999)**

Biopharmaceutics Coordinating Committee Guidances



Methodologic

1. Criteria
2. Analytical Methods

Pre-Approval

Drug Substance

General
 Impurities: Q3A, D-ANDA/NDA
 Residual Solvents: Q3C
 Tests and Specifications: Q6A
Chiral Information (May 1992 Update)

Drug Product

General
 Tests and Specifications (Q6A)
 Degradants: Q3B, D-ANDA/NDA
 Residual Solvents: Q3C
 Container Closure Systems
 Sterilization Process Validation
 Oral Inhalation/Nasal (MDI/DPI, Other)
 Ophthalmic/Otic
 Topical/SS

General

Methods Validation: Q2A, Q2B, D
 DMFs
 Environmental Assessments
 Stability Q1A, Q1B, Q1C, D
 CMC IND Phase 2/3
 CMC IND Formal Meetings
 Proprietary Drug Names

CMC CC

314.70

Post-Approval

General
 Guidance

BACPAC I and II

SUPAC: IR/MEA, MR/MEA

PAC-SAS

PAC-OI/N

PAC-OO

PAC-SS/MEA

PAC-Analytical Testing Labs

CDS CC

314.70
 (g)

Changes
 Guidances

1) Biologicals
 2) Specified
 Biotech/Other

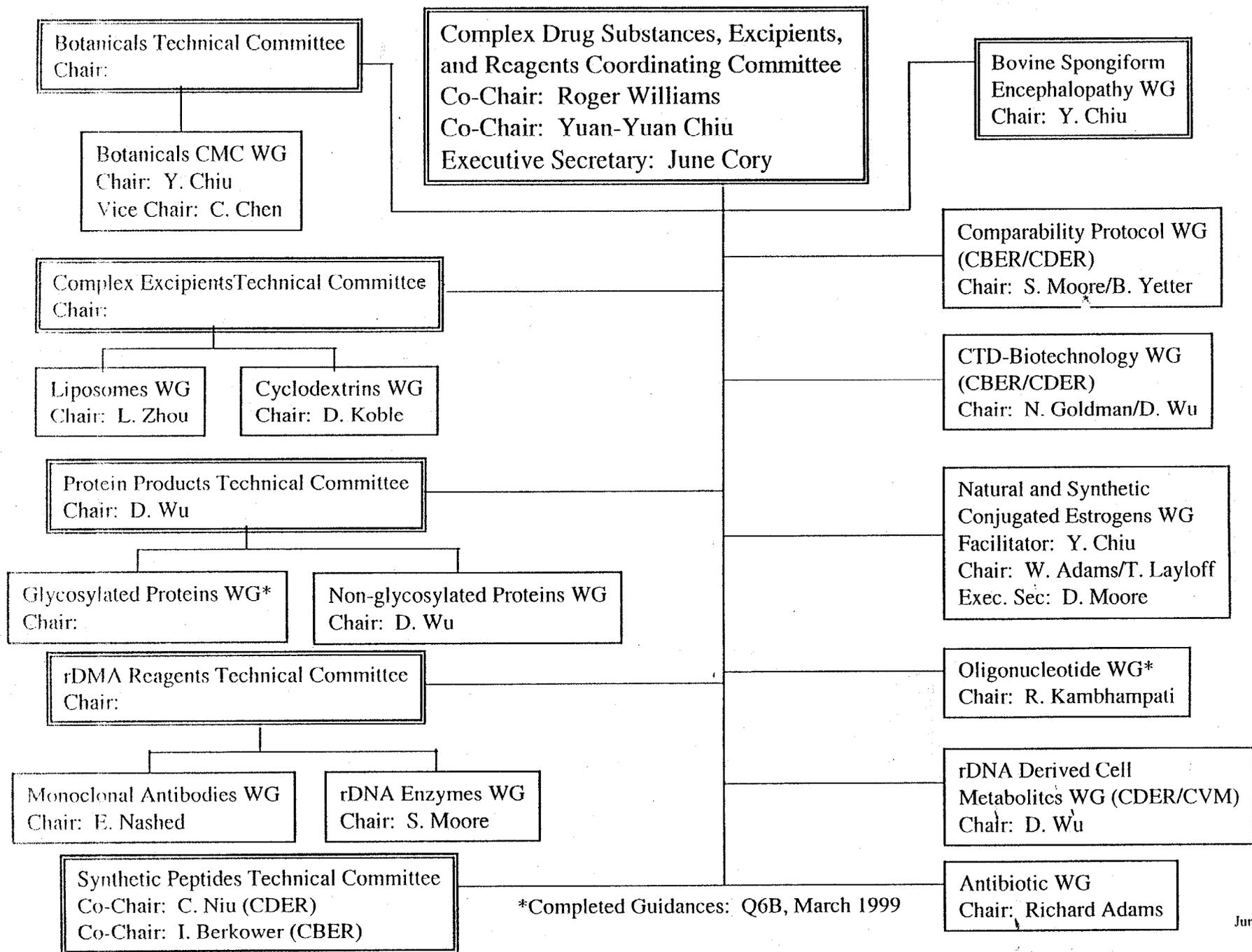
PAC by CDS*

Comparability Protocol
 (April 96)

Complex Drug Substance

rDNA Derived Cell Metabolites
 Synthetic Peptides
 rDNA Proteins (g/ng)
 Natural Proteins (g/ng)
 Conjugated Estrogens
 Botanicals
 rDNA Reagents
 Complex Excipients

*May be part of the guidance on individual topics or drugs.



*Completed Guidances: Q6B, March 1999

Topics

- Guidances for Industry

 - 1 ICH

 - 2 WHO

 - 3 FDA

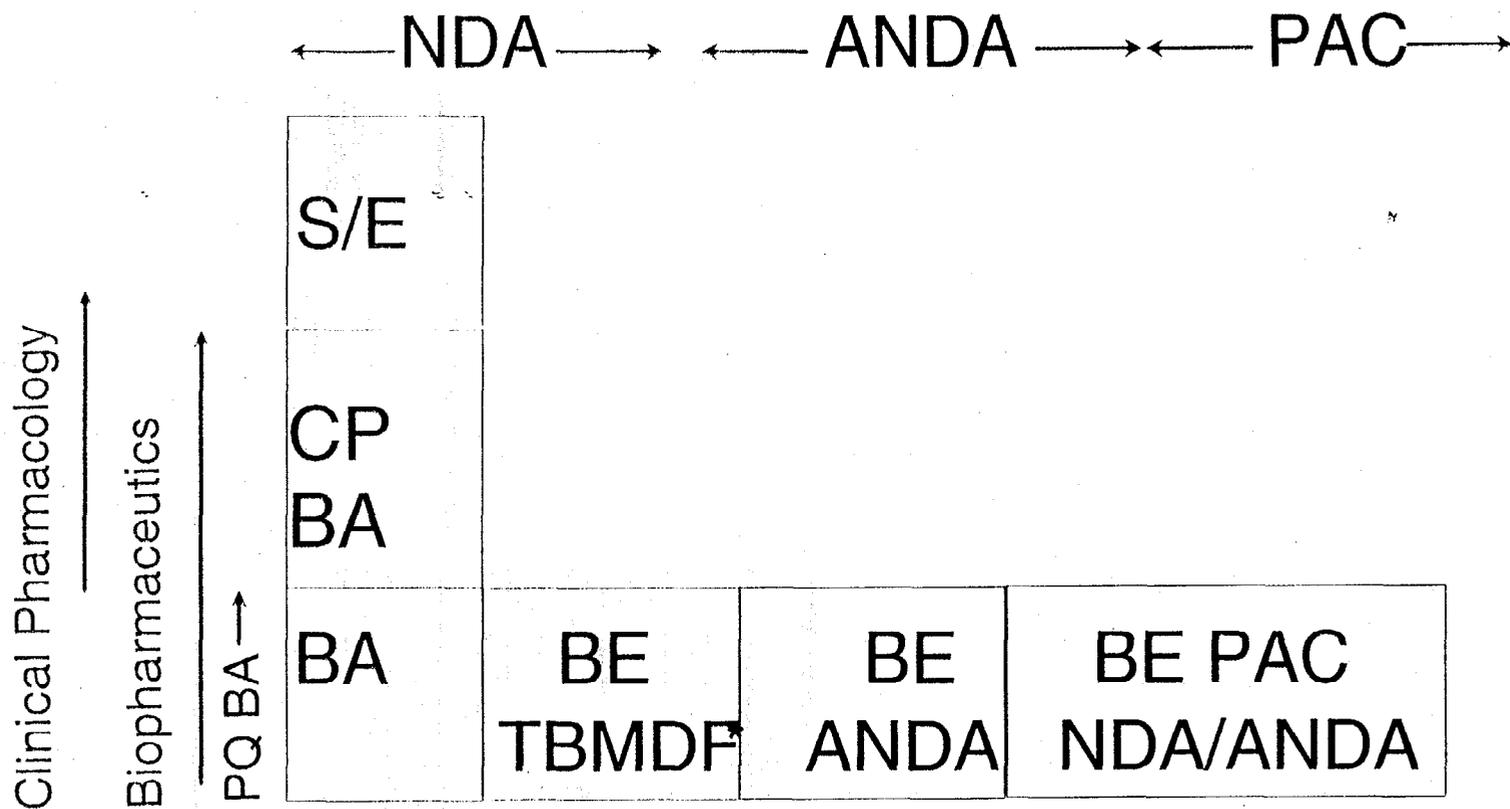
- • Guidances for Reviewers

- The Future

Questions: BE and PE

- • What do we want to know?
- What are we willing to assume/rely on?
- How sure do we want to be?
- When do we ask the question?

Differences Between Clinical Pharmacology, Biopharmaceutics and Product Quality BA/BE



*To be marketed dose form

Product Quality BA/BE

RELEASE OF DRUG SUBSTANCE FROM DRUG PRODUCT

BIO-International '94 Conference

Munich, Germany

Bioequivalence:

“Two pharmaceutical products are considered to be equivalent when their concentration versus time profiles from the same molar dose are so similar that they are unlikely to produce clinically relevant differences in therapeutic and/or adverse effects.”

CPMP Definitions

Bioavailability/Bioequivalence: Bioavailability means the rate and extent to which the active substance or therapeutic moiety is absorbed from a pharmaceutical form and becomes available at the site of action.

Bioequivalence: Two medicinal products are bioequivalents if they are pharmaceutical equivalents or alternatives and if their bioavailabilites (rate and extent) after administration in the same molar dose are similar to such degree that their effects, with respect to both efficacy and safety, will be essentially the same.

Therapeutic Equivalence: A medicinal product is therapeutically equivalent with an other product if it contains the same active substance or therapeutic moiety and, clinically shows the same efficacy and safety as that product, whose efficacy and safety has been established.

FOOD, DRUG, AND COSMETIC ACT

SECTION 505(j)(7)

BIOEQUIVALENCE

- (A) The term "bioavailability" means the rate and extent to which the active ingredient or therapeutic ingredient is absorbed from a drug and becomes available at the site of drug action.
- (B) A drug shall be considered to be bioequivalent to a listed drug if-
- (i) the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses.

Questions: BE and PE

- What do we want to know?
- • What are we willing to assume/rely on?
- How sure do we want to be?
- When do we ask the question?

Exposure Metrics

- Early exposure: Partial AUC
- Peak exposure: C_{max}
- Total exposure: AUC

Questions: BE and PE

- What do we want to know?
- What are we willing to assume/rely on?
- • How sure do we want to be?
- When do we ask the question?

Criteria, Confidence Intervals, Goalposts

[CRITERION] < GOALPOST (BE LIMIT)



Confidence
Interval

Aggregate Criteria

Individual BE

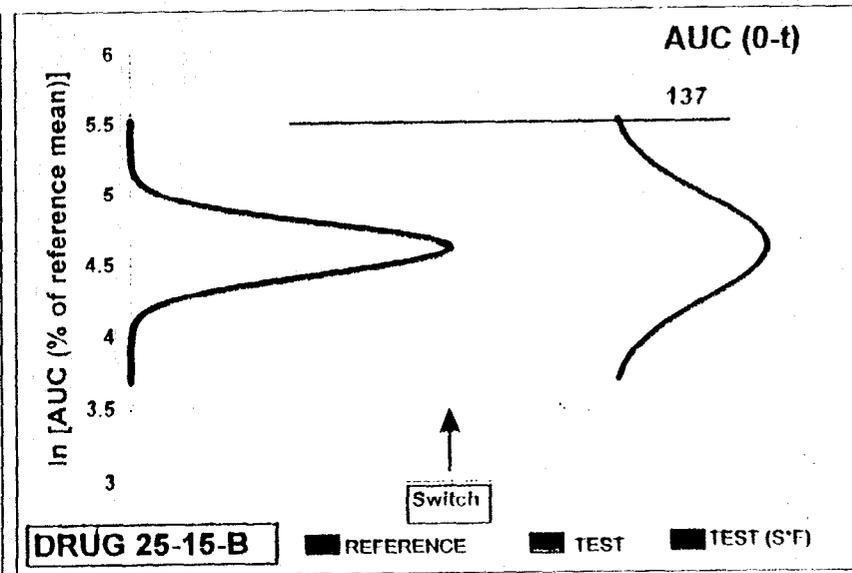
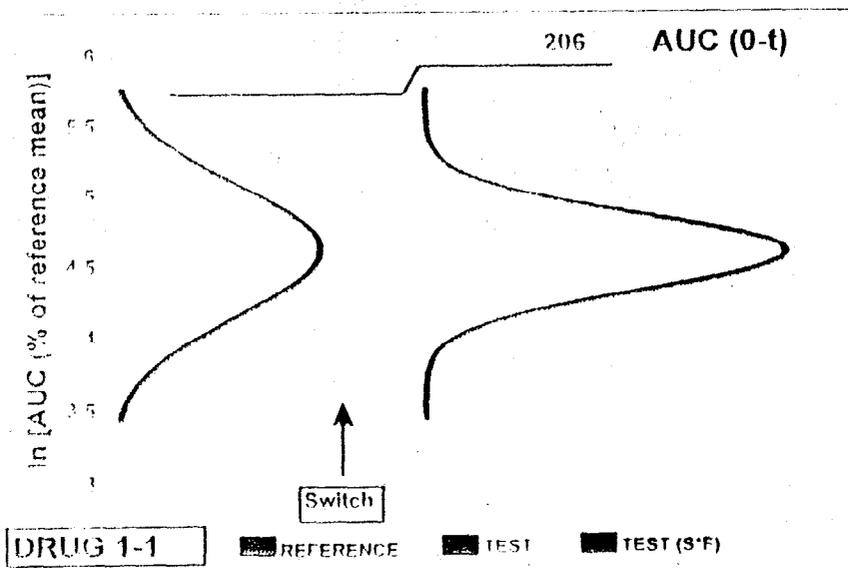
$$\frac{(\mu_T - \mu_R)^2 + \sigma_D^2 + (\sigma_{WT}^2 - \sigma_{WR}^2)}{\sigma_{WR}^2} \leq \theta_I$$

Population BE

$$\frac{(\mu_T - \mu_R)^2 + (\sigma_{TT}^2 - \sigma_{TR}^2)}{\sigma_{TR}^2} \leq \theta_P$$

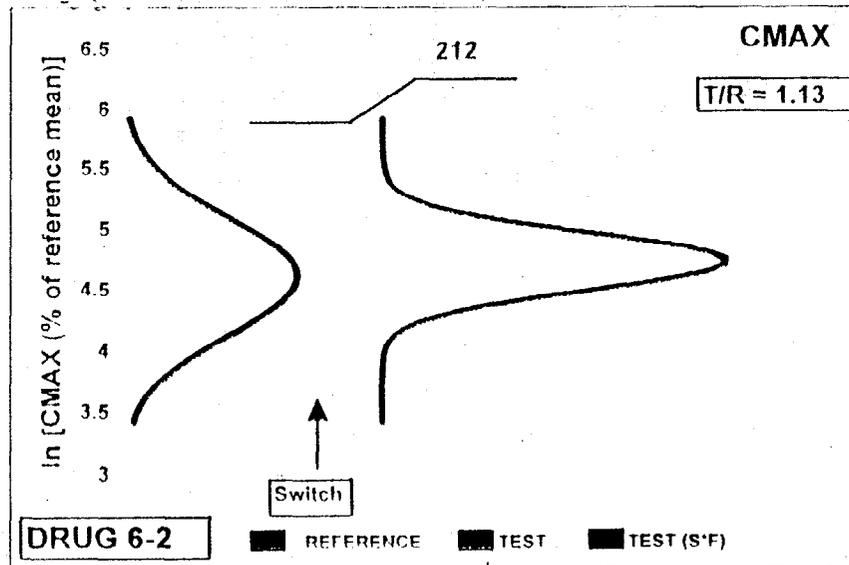
EFFECT OF WITHIN-SUBJECT VARIANCE - SIMPLE CASE - AUC (0-t)

DRUG #	n	MEAN (TEST/REF) RATIO (%)	SUBJ*FORM	90% CI	WITHIN-SUBJECT STANDARD DEVIATION				INDIVIDUAL BE RESULTS	IMPLIED UPPER BE LIMIT	AVERAGE BE - 90% CI
					TEST	REF.	T/R RATIO	90% CI			
1-1	40	97.79	0	0 - 0.244	0.265	0.459	0.578	0.436 - 0.766	PASS	206	88.92 - 107.55
25-15-B	40	99.08	0	0 - 0.271	0.364	0.177	2.056	1.382 - 3.065	FAIL	137	90.33 - 108.68



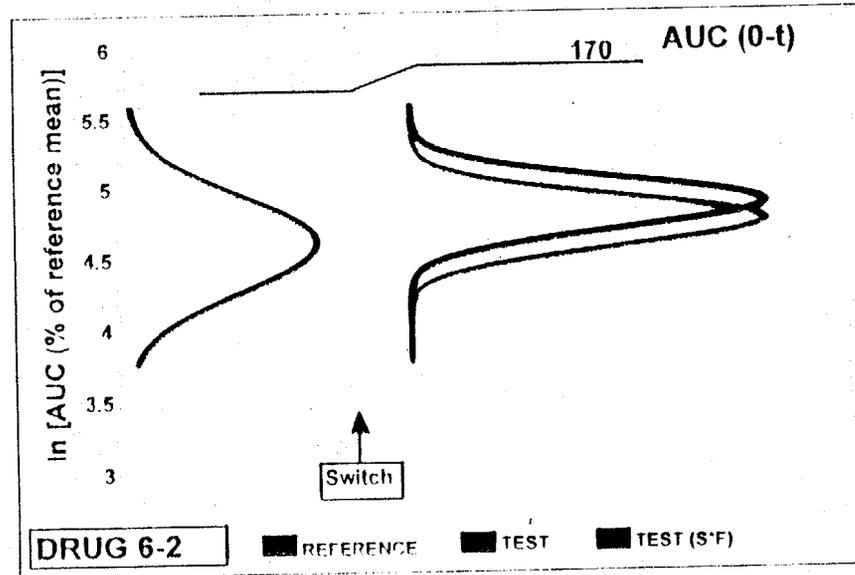
COMBINED EFFECTS OF WITHIN-SUBJECT VARIANCE AND MEAN - CMAX

DRUG #	n	MEAN (TEST/REF) RATIO (%)	SUBJ*FORM	90% CI	WITHIN-SUBJECT STANDARD DEVIATION				INDIVIDUAL BE RESULTS	IMPLIED UPPER BE LIMIT	AVERAGE BE - 90% CI
					TEST	REF.	T/R RATIO	90% CI			
6-2	22	112.78	0	0 - 0.352	0.235	0.478	0.491	0.330 - 0.731	PASS	212	98.28 - 129.43



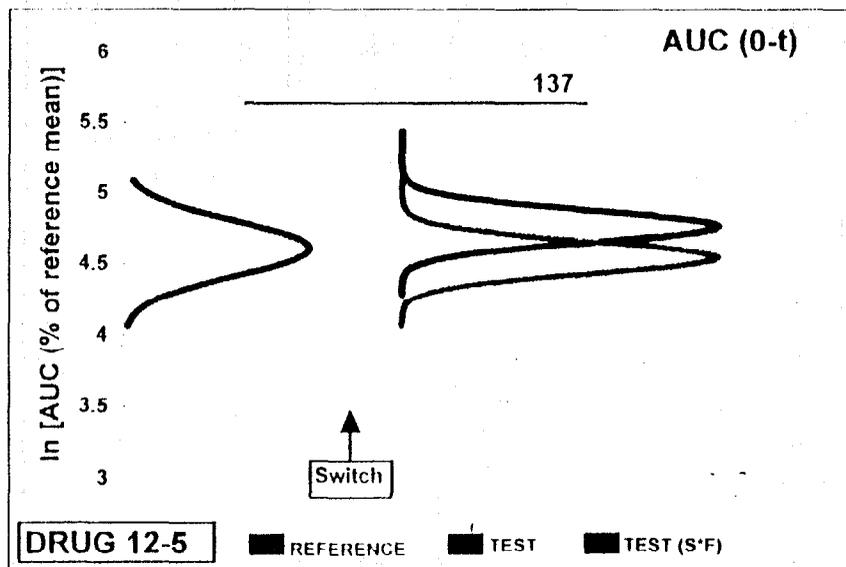
I. EFFECT OF WITHIN-SUBJECT VARIANCE - AUC (0-t) (Mean - Variance Trade Off)

DRUG #	n	MEAN (TEST/REF) RATIO (%)	SUBJ*FORM	90% CI	WITHIN-SUBJECT STANDARD DEVIATION				INDIVIDUAL BE RESULTS	IMPLIED UPPER BE LIMIT	AVERAGE BE - 90% CI
					TEST	REF.	T/R RATIO	90% CI			
6-2	22	114.35	0.078	0 - 0.285	0.176	0.336	0.522	0.351 - 0.778	PASS	170	102.96 - 127.00



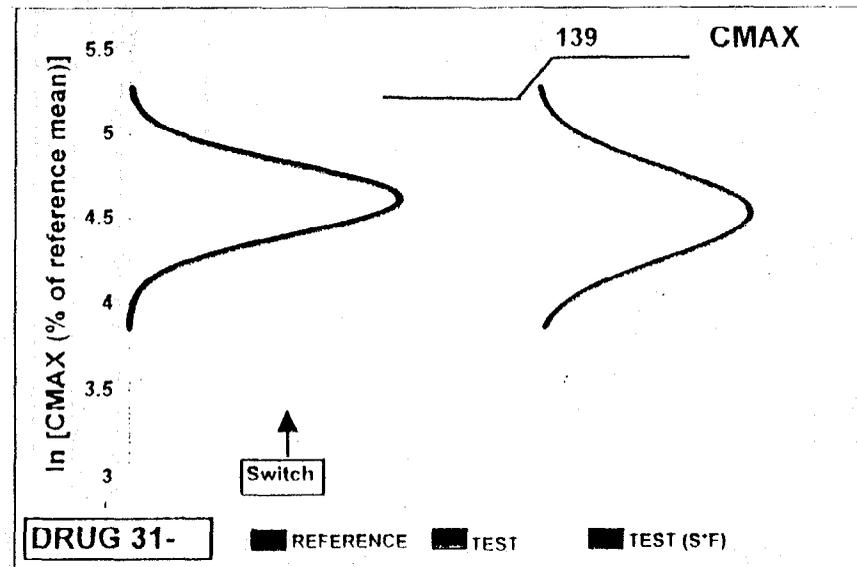
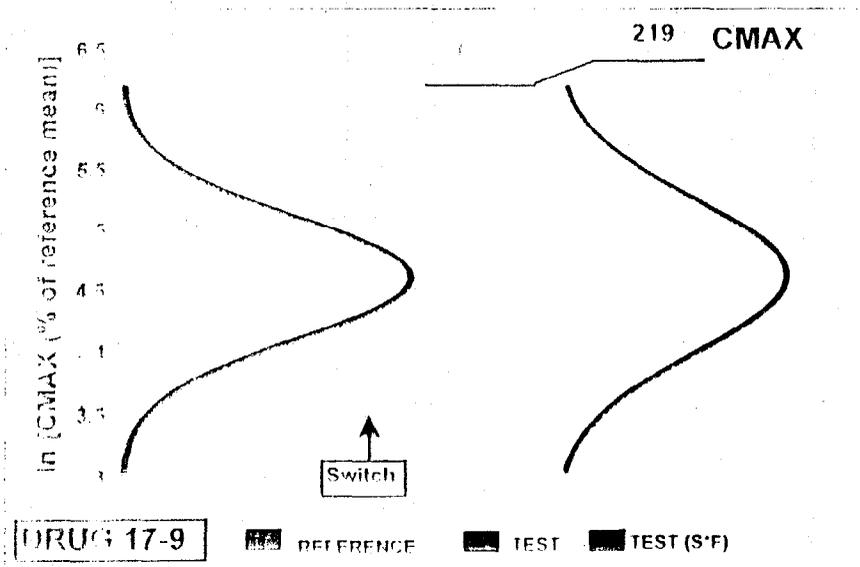
I. EFFECT OF WITHIN-SUBJECT VARIANCE - AUC (0-t) (Variance and Subj*Form. Interaction)

DRUG #	n	MEAN (TEST/REF) RATIO (%)	SUBJ*FORM	90% CI	WITHIN-SUBJECT STANDARD DEVIATION				INDIVIDUAL BE RESULTS	IMPLIED UPPER BE LIMIT	AVERAGE BE - 90% CI
					TEST	REF.	T/R RATIO	90% CI			
12-5	23	94.09	0.133	0 - 0.243	0.112	0.192	0.586	0.389 - 0.883	PASS	137	87.22 - 101.50



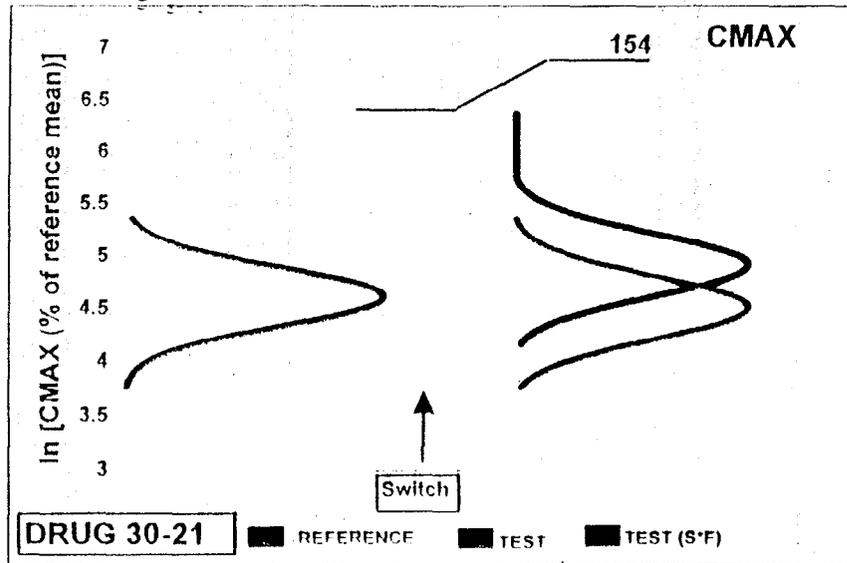
II. EFFECT OF SCALING - CMAX (Scaling and Variance)

DRUG #	n	MEAN (TEST/REF) RATIO (%)	SUBJ*FORM	90% CI	WITHIN-SUBJECT STANDARD DEVIATION				INDIVIDUAL BE RESULTS	IMPLIED UPPER BE LIMIT	AVERAGE BE - 90% CI
					TEST	REF.	T/R RATIO	90% CI			
17-9	30	101.91	0	0 - 0.321	0.622	0.498	1.250	0.906 - 1.725	PASS	219	87.23 - 119.06
31-22	17	91.63	0	0 - 0.193	0.264	0.209	1.261	0.810 - 1.979	FAIL	139	83.65 - 100.39



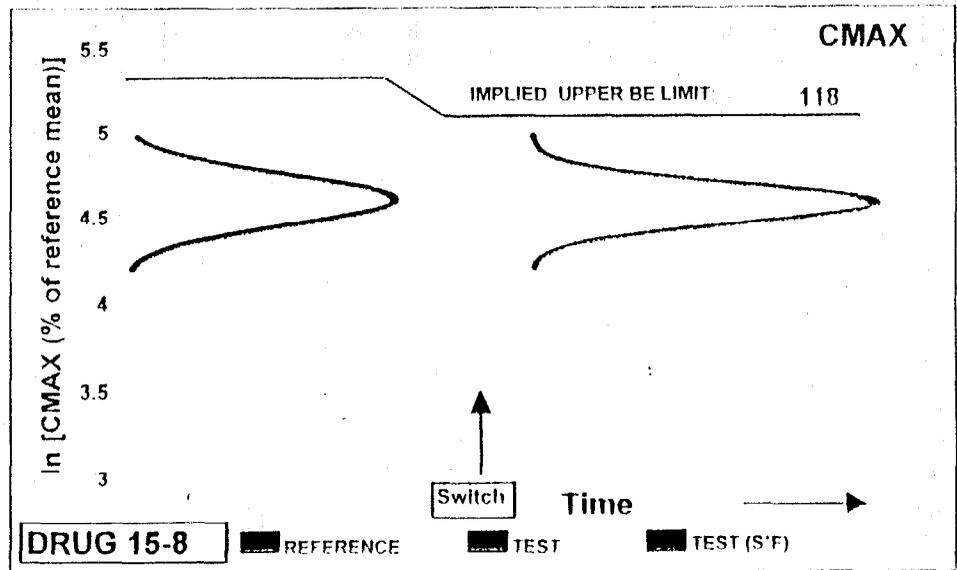
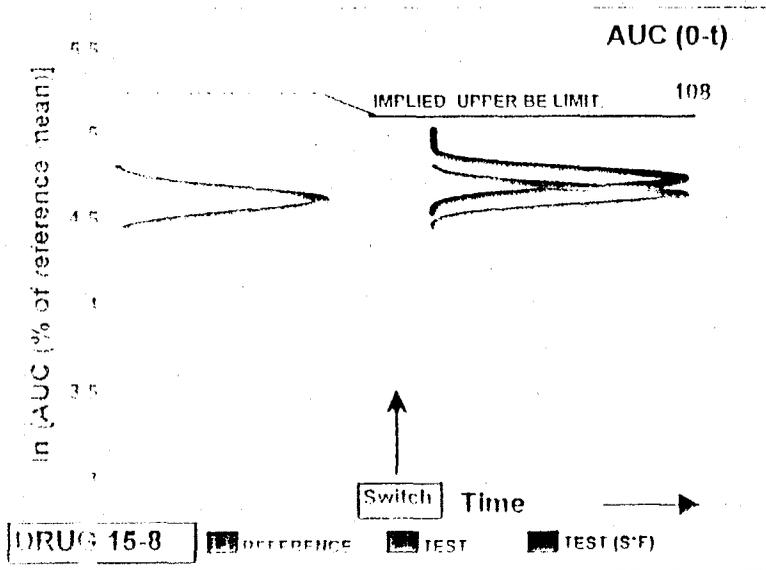
COMBINED EFFECTS OF WITHIN-SUBJECT VARIANCE AND SUBJECT*FORMULATION - CMAX

DRUG #	n	MEAN (TEST/REF) RATIO (%)	SUBJ*FORM	90% CI	WITHIN-SUBJECT STANDARD DEVIATION				INDIVIDUAL BE RESULTS	IMPLIED UPPER BE LIMIT	AVERAGE BE - 90% CI
					TEST	REF.	T/R RATIO	90% CI			
30-21	32	90.47	0.247	0.036 - 0.398	0.297	0.278	1.078	0.786 - 1.479	FAIL	164	80.74 - 101.37



IBE RESULTS FOR NTI DRUGS (WITHOUT EPSILON)

DATA SET #	MEASURE	n	MEAN T/R RATIO %	S*F	90% CI	WITHIN-SUBJECT STANDARD DEVIATION (SD)				IBE RESULTS (MIXED SCALE) WITH EPSILON	IBE RESULTS (REF.SCALE) WITHOUT EPSILON	IBE - IMPLIED UPPER BE LIMIT WITHOUT EPSILON	AVERAGE BE - 90% CI [†]
						TEST	REF.	T/R	90% CI.				
15-8	AUC(0-t)	23	102.82	0.059	0.006 - 0.097	0.055	0.067	0.818	0.566 - 1.181	PASS	FAIL	108	99.72 - 106.00
15-8	C _{MAX}	23	96.95	0	0 - 0.069	0.116	0.148	0.782	0.542 - 1.129	PASS	PASS	118	93.24 - 100.80

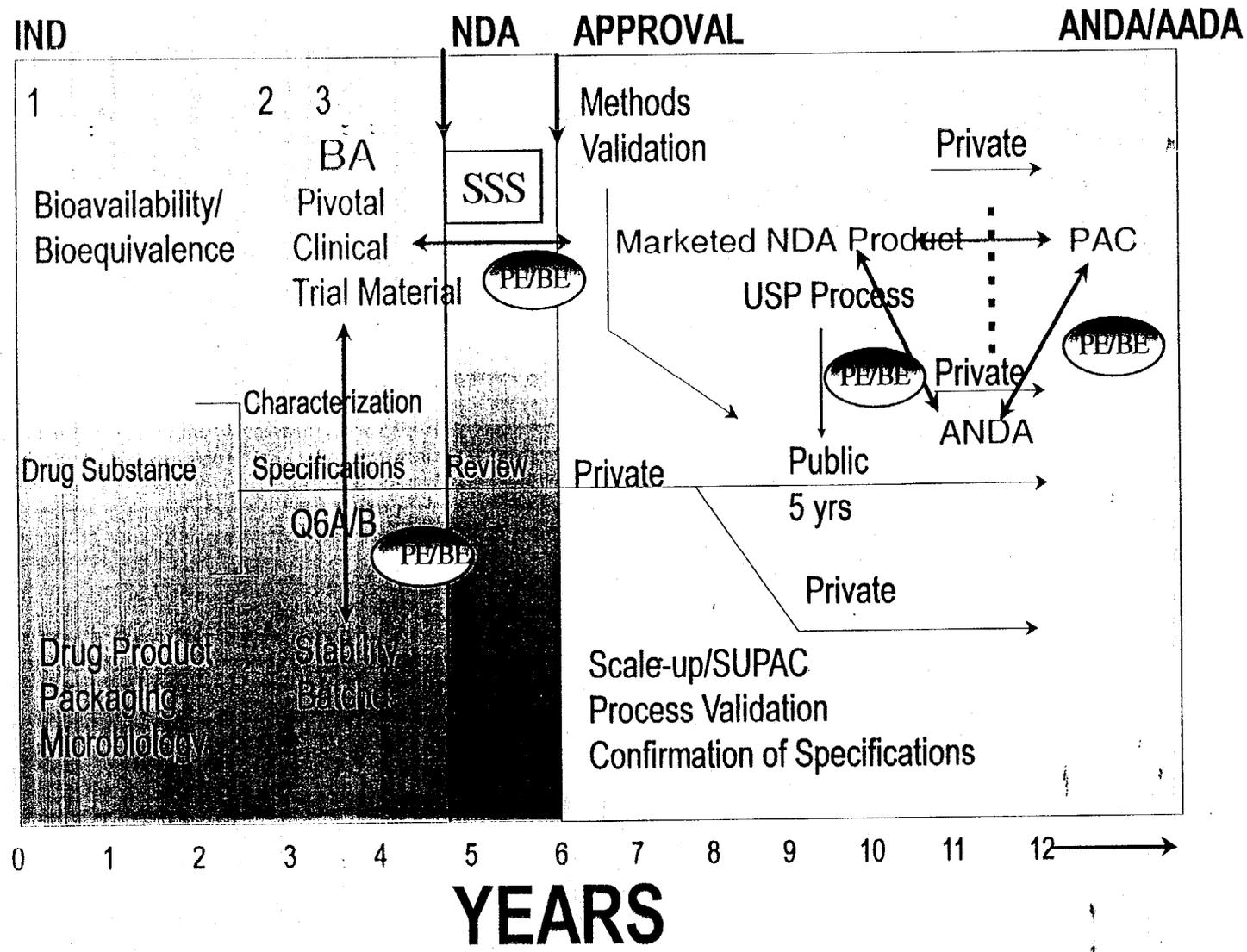


Questions: BE and PE

- What do we want to know?
- What are we willing to assume/rely on?
- How sure do we want to be?
- • When do we ask the question?

Quality: Specifications → Standards

↔ BE



Generic Versus Reference Product

PHARMACEUTICAL AND THERAPEUTIC EQUIVALENCE

- **Pharmaceutical Equivalence**

- Same active ingredient

- Same strength

- Same dosage form and route of administration

- Comparable labeling

- Meet compendial or other standards of identity, strength, quality, purity and potency

- Inactive ingredients may be different

- **Bioequivalence**

- In vivo measurement of active moiety (moieties) in biologic fluid (blood/urine)

- In vivo pharmacodynamic comparison

- In vivo clinical comparison

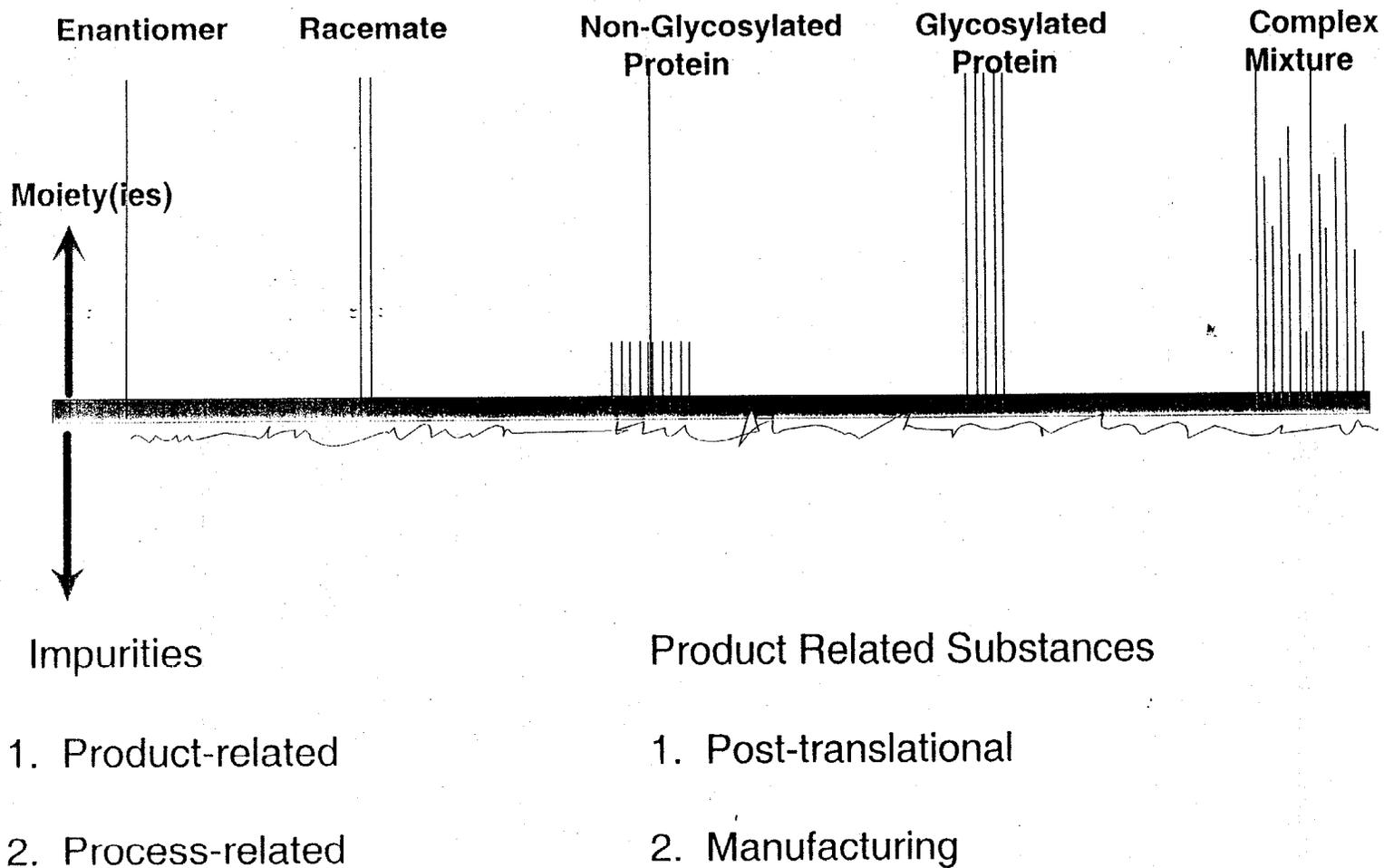
- In vitro comparison

- Other

→ THEN: THERAPEUTIC EQUIVALENCE

European Court of Justice (ECJ)

ECJ defined essential similarity as follows: a medicinal product is essentially similar to an original medicinal product where it satisfies the criteria of having the same qualitative and quantitative composition in terms of active principles, of having the same pharmaceutical form and of being bioequivalent, unless it is apparent in the light of scientific knowledge that it differs significantly from the original product as regards safety or efficacy.



ICH: Draft guidance on Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products. (FR June 9, 1998)

Table of Contents

- I. Introduction
- II. Scope
- III. Characterization/Setting Specifications
- IV. Equivalence Between Products Manufactured by Different Applicants
 - A. Pharmaceutical Equivalence
 - 1. Physicochemical methods
 - 2. Bioassay
 - 3. Pharmacology/toxicology
 - 4. Human PK/PD
 - 5. Clinical Studies
 - a. Safety (e.g., antigenicity)
 - b. Clinical Trials with an Equivalence Endpoint
 - B. Bioequivalence
- V. Pre-and Post-Approval CMC Changes (Within a Company)
General: 314.70 (g) and Accompanying Two Guidances for 314.70(g)
 - A. Pharmaceutical Equivalence (Reference Comparability Document)
 - 1. Physicochemical methods
 - 2. Bioassay
 - 3. Pharmacology/toxicology
 - 4. Human PK/PD
 - 5. Clinical Studies
 - a. Safety (e.g., antigenicity)
 - b. Clinical Trials with an Equivalence Endpoint
 - B. Bioequivalence

Guidance for Industry

Conjugated Estrogens: Pharmaceutical Characterization, Documentation of Pharmaceutical Equivalence, Measurement of Bioavailability, and Establishment of Bioequivalence

DRAFT GUIDANCE

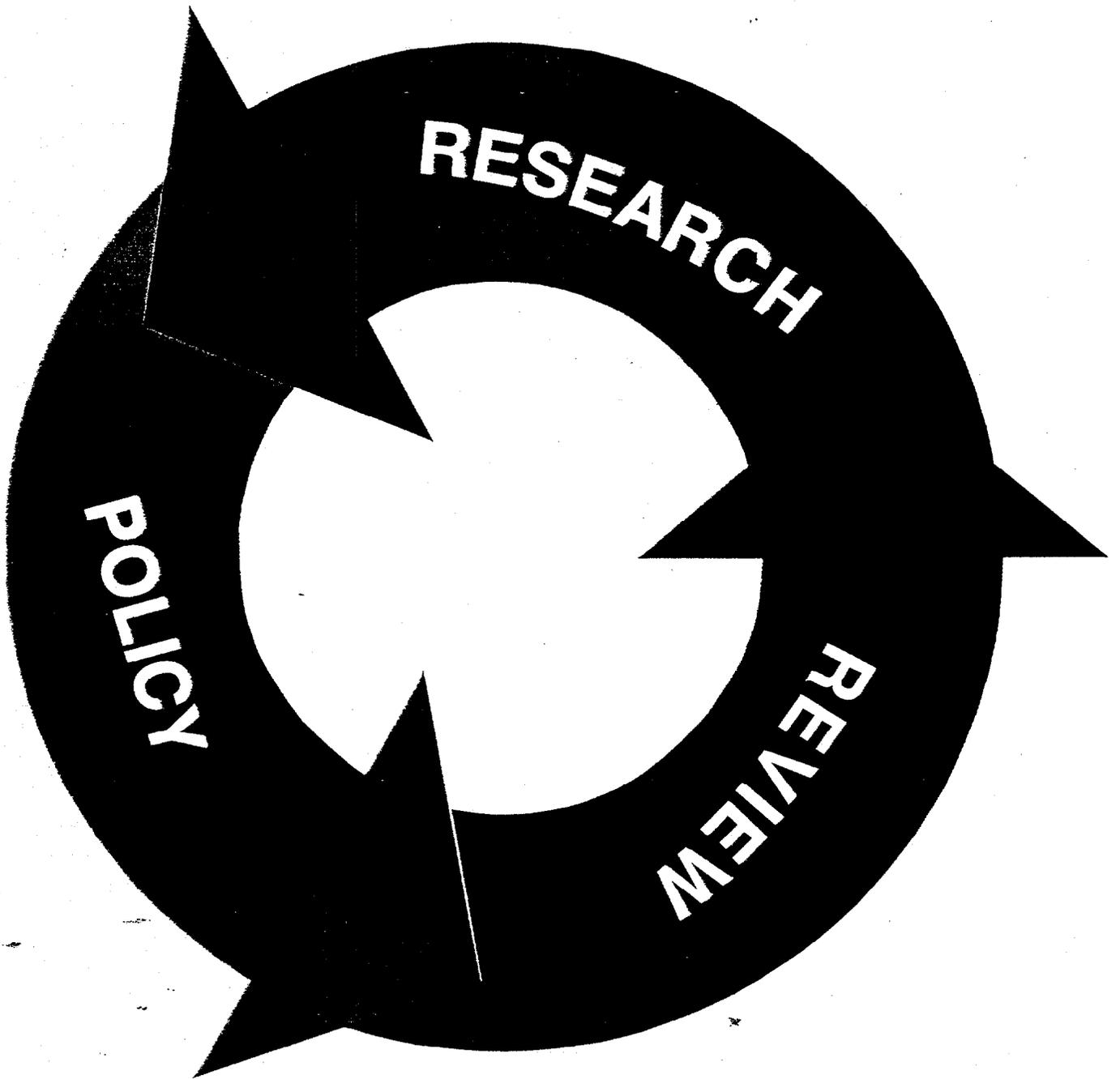
(if this is a final guidance, delete the following text)

This guidance document is being distributed for comment purposes only. Comments and suggestions regarding this draft document should be submitted within 90 days of publication of the Federal Register notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20857. All comments should be identified with the docket number listed in the notice of availability that publishes in the Federal Register.

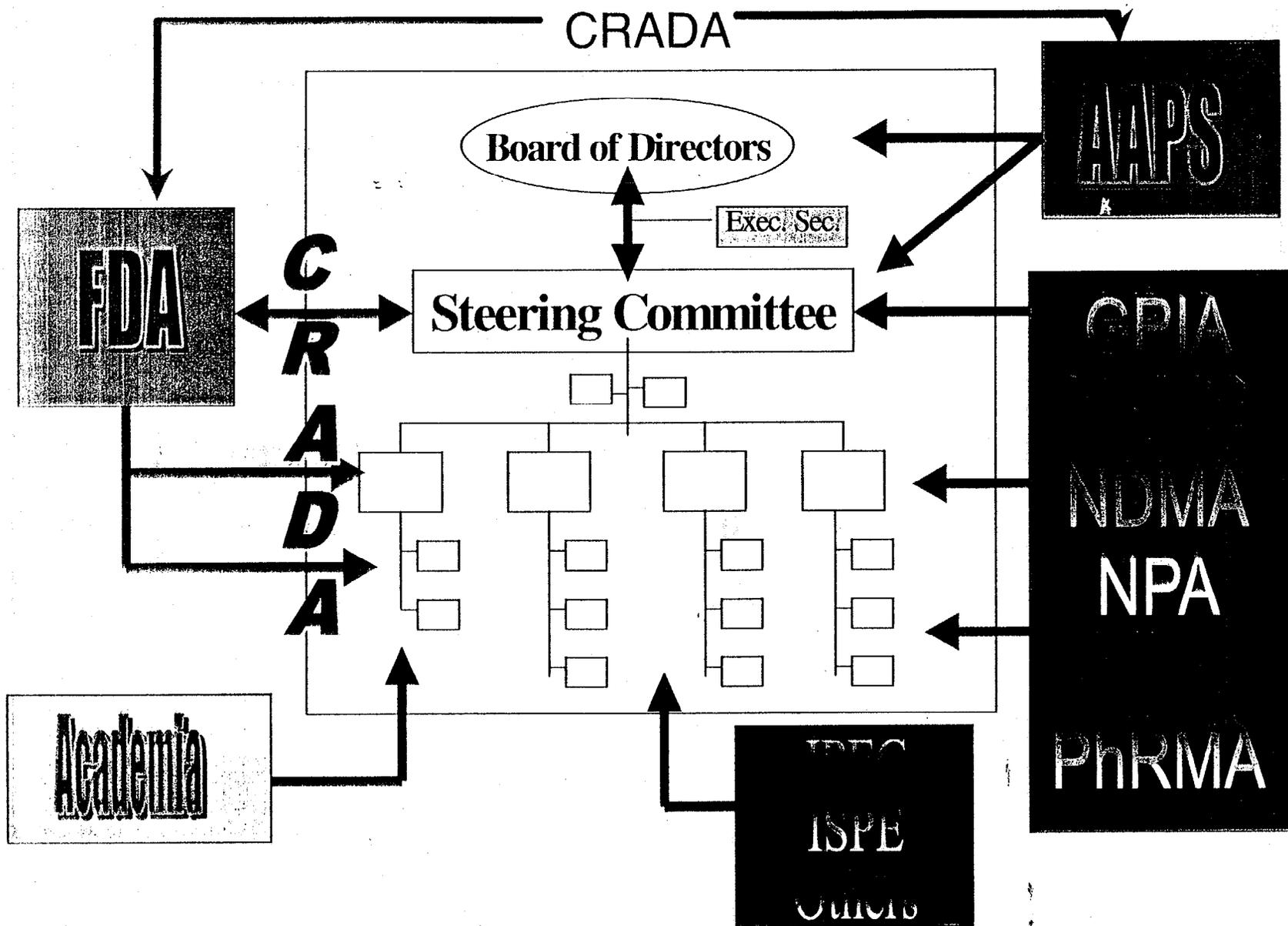
Additional copies of this draft guidance document are available from the Drug Information Branch, Division of Communications Management, HFD-210, 5600 Fishers Lane, Rockville, MD 20857, (Tel) 301-827-4573, or from the Internet at <http://www.fda.gov/cder/guidance/index.htm>.

For questions on the content of the draft document contact (301)____-____.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
June 1999



Product Quality Research Initiative, Inc.



Topics

- Guidances for Industry

- 1 ICH

- 2 WHO

- 3 FDA (MHW, EMEA)

- Guidances for Reviewers

- • The Future

PAHO
Drug Regulatory Conference
Washington, D.C.
November 18-20, 1997

Meeting of Americas
Regulators
Washington, D.C.
November 21, 1997

PAHO
Executive
Secretariat

- Participants
- Regulators
- Andean
- Caricom
- Mercosur
- NAFTA
- Sica
- Industry

Consultation for the
Establishment of the Steering Committee
for the Pan American Conferences
on Drug Regulatory Harmonization
Caracas, Venezuela
January 14-15, 1999

GMPs	BA/BE	GCPs	Counterfeit Products	Classification of Products (Drugs)
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Steering Committee and the
2nd Pan American Conference on
Drug Regulatory Harmonization
Washington, D.C.
November 2-5, 1999

International Comparator Pharmaceutical Product

