Disso India 2017

Regulatory Science: the Paradigm of Dissolution

Roger L. Williams, M.D.

Society for Pharmaceutical Dissolution Science

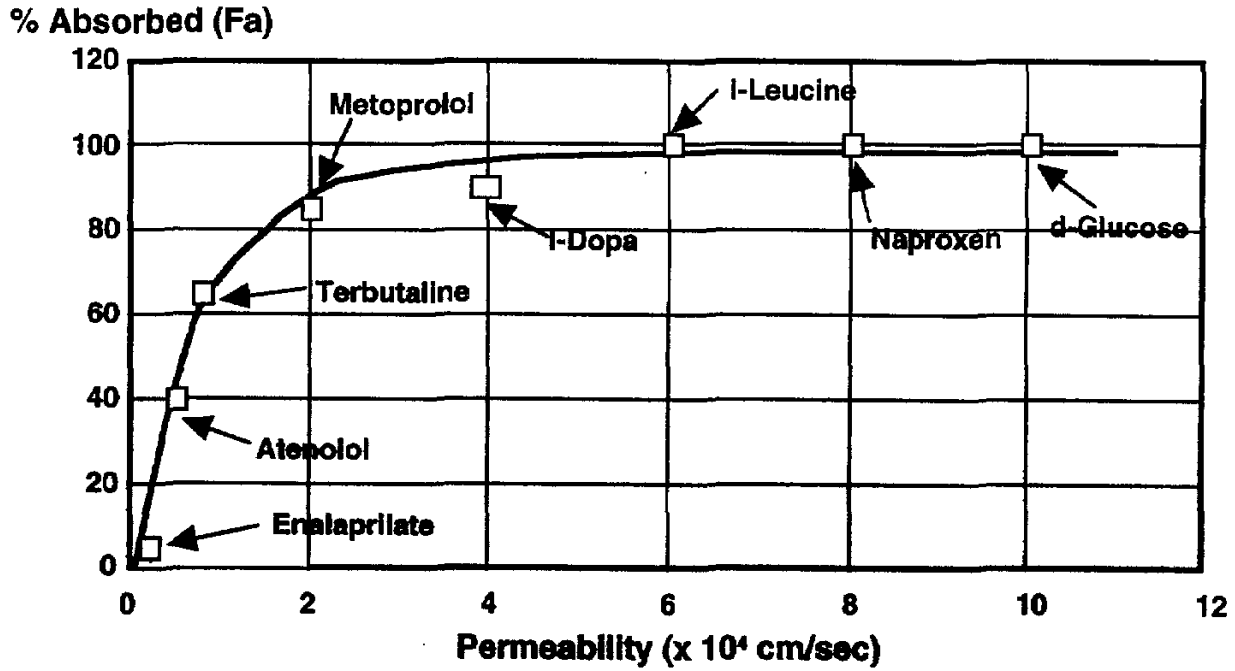
Mumbai

June 9, 2017

Topics

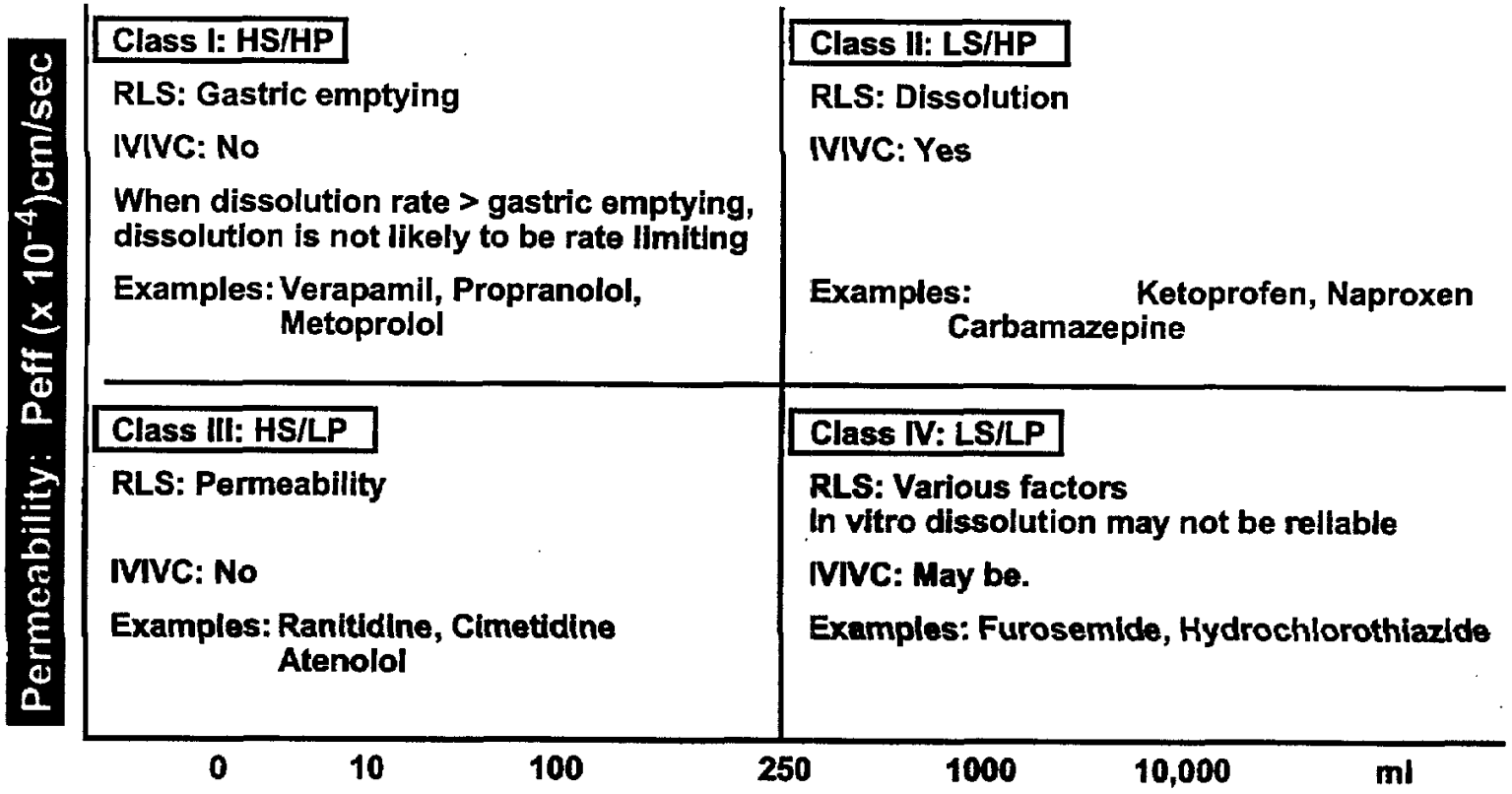
1. Dissolution
2. Science
3. Law, Regulation, Guidance
4. FDA
5. Future Directions

Extent of Absorption vs. Human Jejunal Permeability



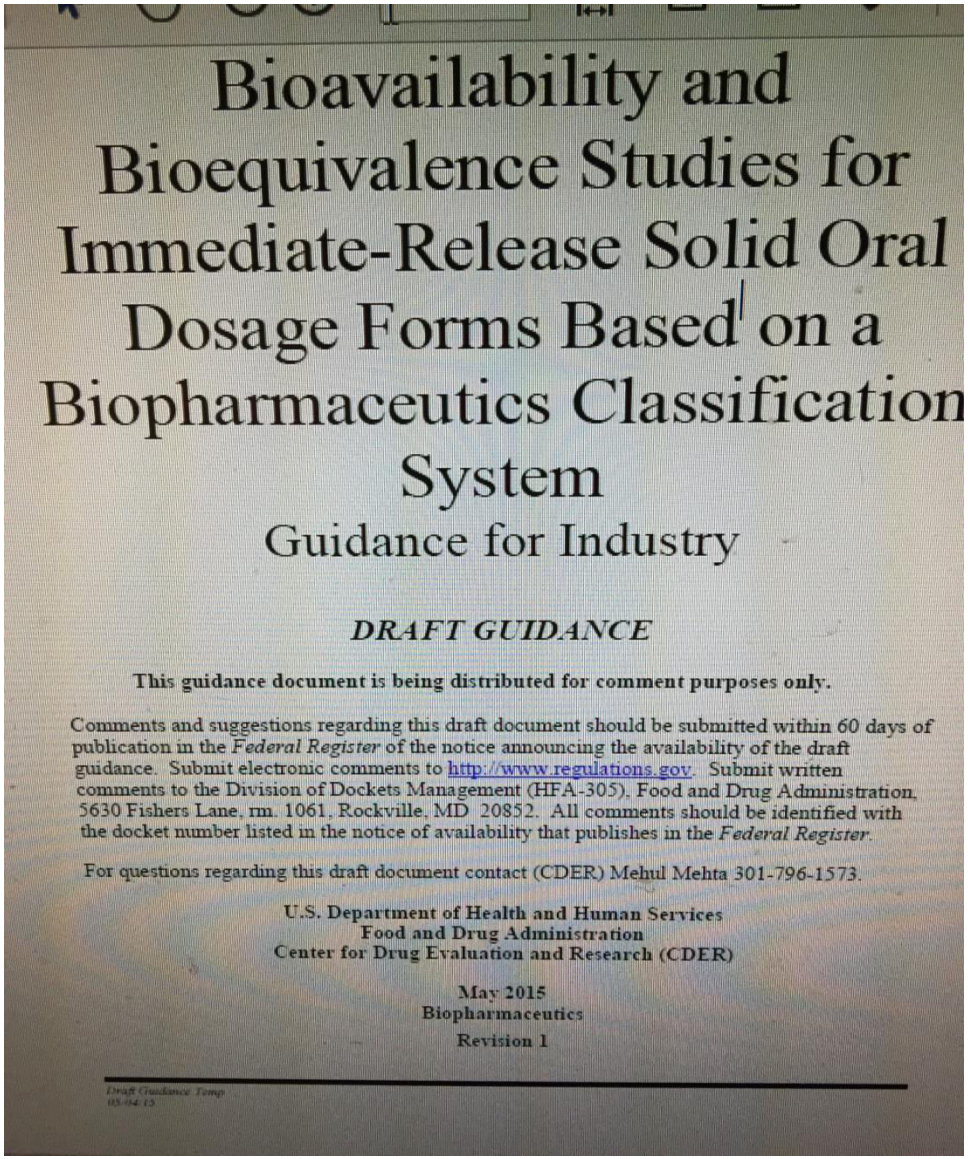
GL Amidon, H Lennernas, VP Shah, and JR Crison, *Pharm Res, 12, 413-420 (1995)*

Biopharmaceutics Classification System



Volume of aqueous buffer needed to dissolve the highest unit dose, pH 1-8 arrange.

RLS: Rate limiting Step.



Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Mehul Mehta 301-796-1573.

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

May 2015
Biopharmaceutics
Revision 1

Draft Guidance Temp
05-04-15

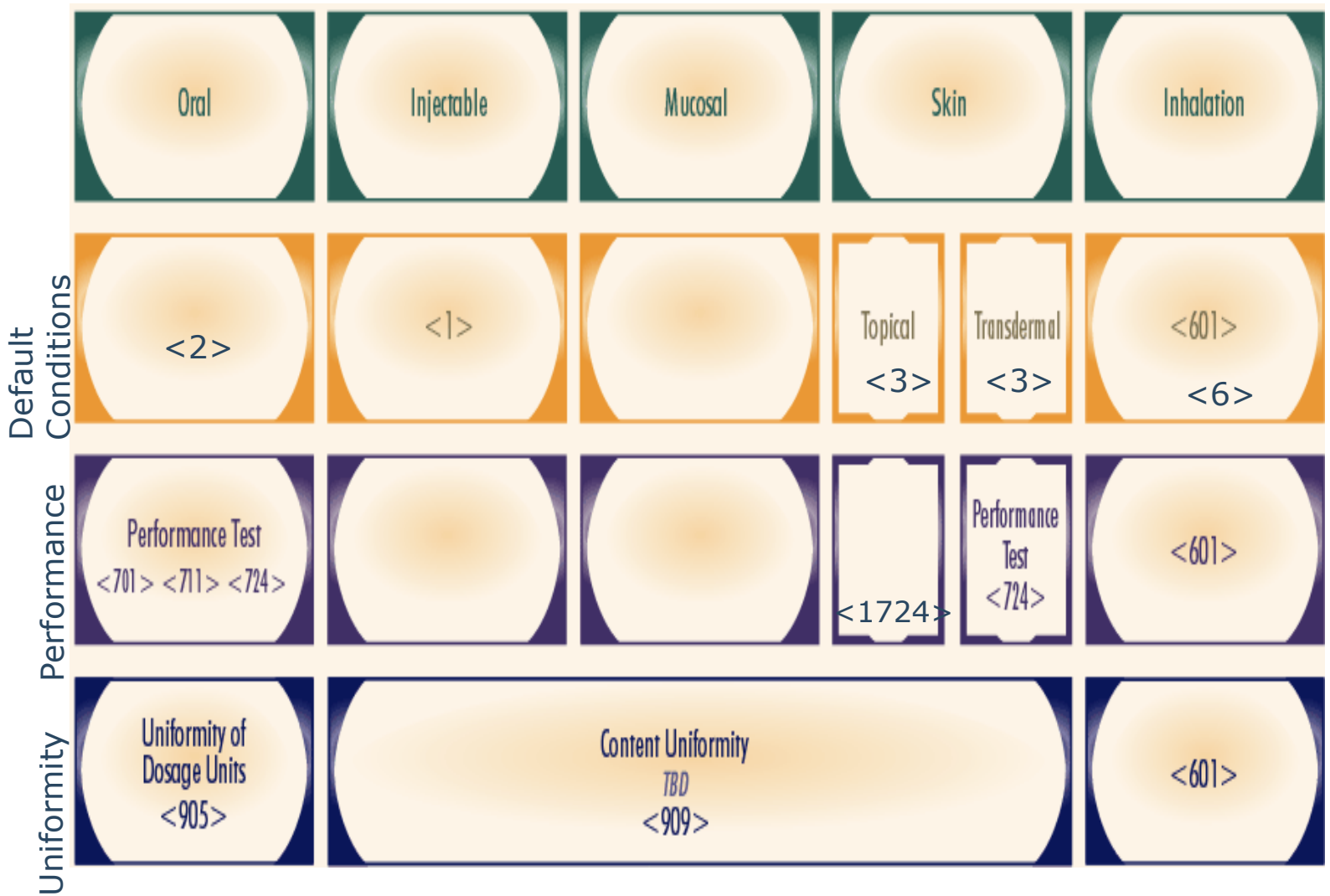
World Health Organization

Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability

WHO Technical Report Series, No. 937, 2006. Annex 7, p 347 - 390

Quality and Performance Tests

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients



Product Quality & Product Performance Tests

- **Product Quality Test**
  Intended to assess attributes such as identity, strength, purity, content uniformity, pH, minimum fill, microbial limits.

- **Product Performance Test**
  Designed to assess product performance and in many cases relates to drug release from the dosage form.

- **Quality tests assess the integrity of the dosage form, whereas performance tests assess drug release and other attributes that relate to *in vivo* drug performance.**
-
- **Taken together, quality and performance tests assure the identity, strength, quality, and purity of the pharmaceutical dosage form.**

Dosage Form Taxonomy (USP)

Route of Administration	Intended site of release	Dosage Form Examples	Dosage Form Quality Tests	Dosage Form Performance Tests*
Parenteral	Body tissues and fluids	Injectables, Liposomes, micro and nano particles, implants, stents	<1>	<1001>**
Oral	Gastro intestinal tract	Tablets and capsules, liquids	<2>	<701>, <711>
Topical / Transdermal	Skin	Semisolids, TDS	<3>	<724>, <1724>
Mucosal (Local or Systemic)	Mouth, eye, ear, rectum, vagina, intra-uterine	Films, tablets, liquids, suspensions, suppositories	<4>	<1004>**
Inhalation	Nasal cavity, lung	Liquids, aerosols, powders	<5>	<601>, <602>, <603>, <604>, <1601>

* CK Brown et. al., FIP/AAPS Workshop Report: Dissolution/*in vitro* release testing of novel/special dosage forms. AAPS PharmSci Tech. 12(2): 782-794, 2011

** Under Development

Topics

1. Dissolution
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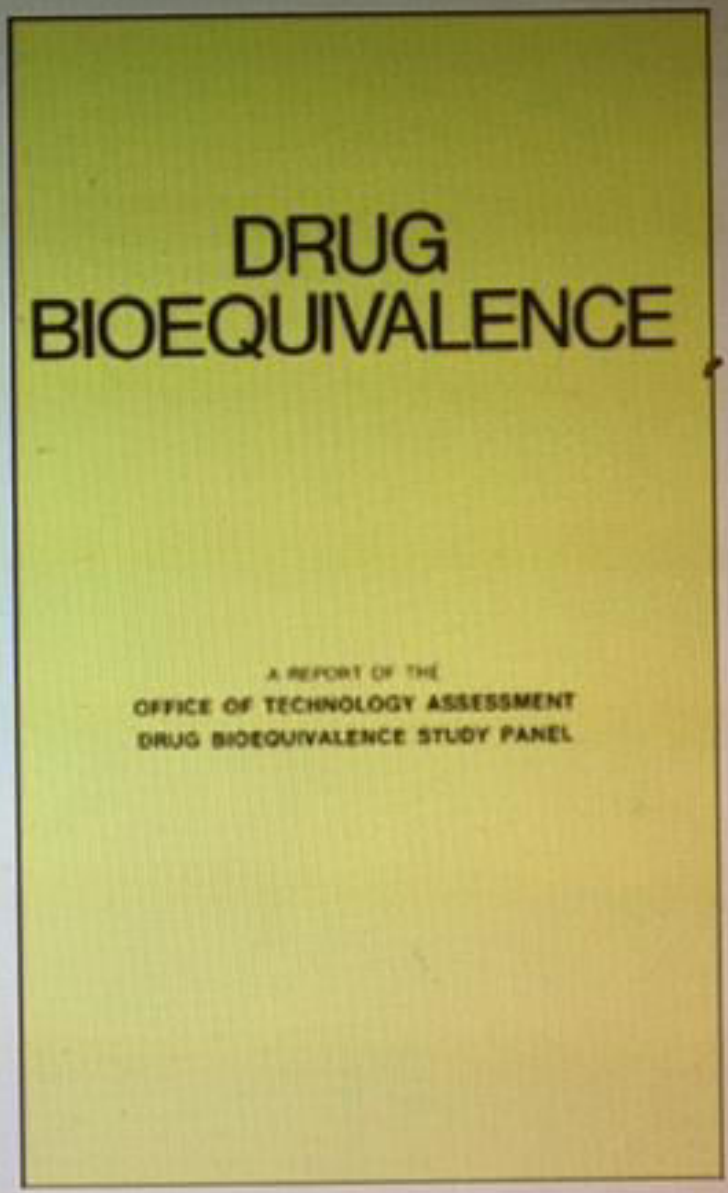
5. Future Directions

I

Drug Bioequivalence

July 1974

NTIS order #PB-244862



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University of Florida

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Marvin Zelen, Ph.D., Director
Statistical Laboratory
State University of New York at Buffalo

Frederick C. Robbins, M.D., Dean
Case Western Reserve Medical School
Case Western Reserve University
(Ex Officio Member)

Reference Scaling: Origins

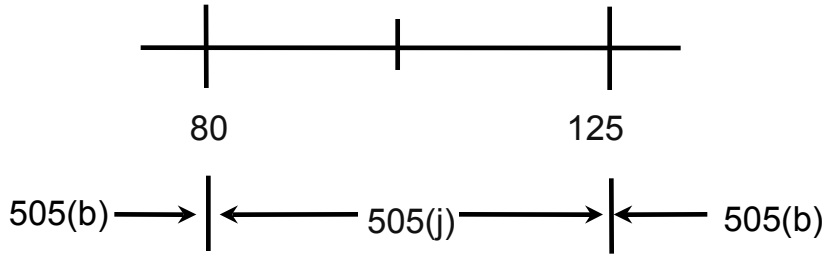
- **1999 Draft Guidance**
- **Equivalence Approaches, Williams et al, CPT, 72, 226-237, 2002**
- **Novel Bioequivalence Approach for Narrow Therapeutic Index Drugs, Yu et al, CPT 97, 286-291, 2015**
- **Implementation of a Reference-Scaled Average Bioequivalence Approach for Highly Variable Generic Drug Products by the US Food and Drug Administration, AAPS J, 14, 915-24, 2012**
- **Sheiner's 3 Questions: 1) what is the question; 2) what are we willing to rely on; 3) how confident do we need to be in the answer**

How Confident Do We Need to Be in the Answer?

CURRENT

Average response
test within 80-125% reference

$$\ln.8 \le (\mu_T - \mu_R) \le \ln 1.25$$



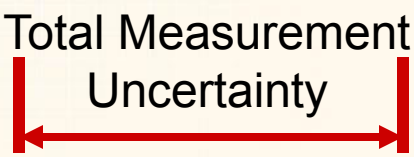
CONSIDERED

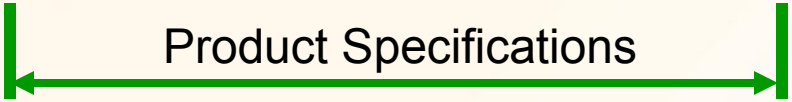
$$\frac{T - R}{R - R'} \le \sim 1 \rightarrow \frac{(\mu_T - \mu_R)^2 + \text{☞}_D^2 + (\text{☞}_{WT}^2 - \text{☞}_{WR}^2)}{\text{☞}_{WR}^2} \le 1.25$$

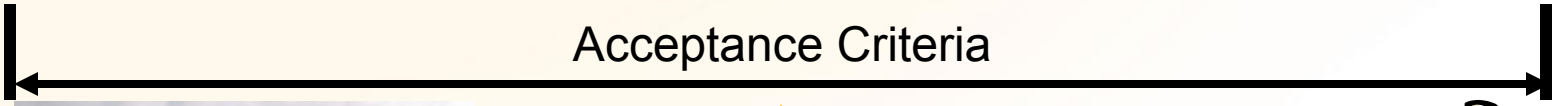
BIPM

- Paris-based international weights and measures organisation
- Task to ensure the world-wide uniformity of measurement
- The committee covering chemical measurement is the CCQM

Score!!!!

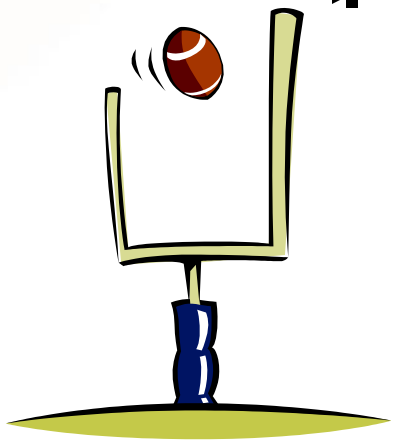






"Trueness"

Or Right Down the Middle



Primary and Secondary Reference Materials for Procedures to Test the Quality of Medicines and Foods

USP Council of Experts • USP Reference Standards Committee • Walter W. Hauck

Received: 11 August 2011 / Accepted: 17 January 2012 / Published online: 8 February 2012

ABSTRACT At present a complex global patchwork of private and public monographs and reference materials is variously available to help ensure the quality of medicines and foods. The relationship of these monographs and reference materials, one to another, frequently is inconsistently understood and documented. This article considers the complexity of monographs and reference materials with a focus on qualifying one reference material relative to another.

KEY WORDS comparability · metrology · quality assurance · reference materials · standards

information (e.g., definitions and labeling and storage statements) followed by the specification for the article—its tests, procedures, and acceptance criteria that should be met throughout its life cycle. Monographs and their allied reference materials may be used by first parties (manufacturers and compounding professionals), second parties (purchasers), and/or third parties (governmental bodies and others independent of the supplier and purchaser) as a product standard to allow testing. The availability of these product testing standards allies with staff education and training (people standards), process standards such as good manufacturing practices (CGMP), and good supply chain management and good storage and distribution practices.

Reducing Burden: Public Standards/

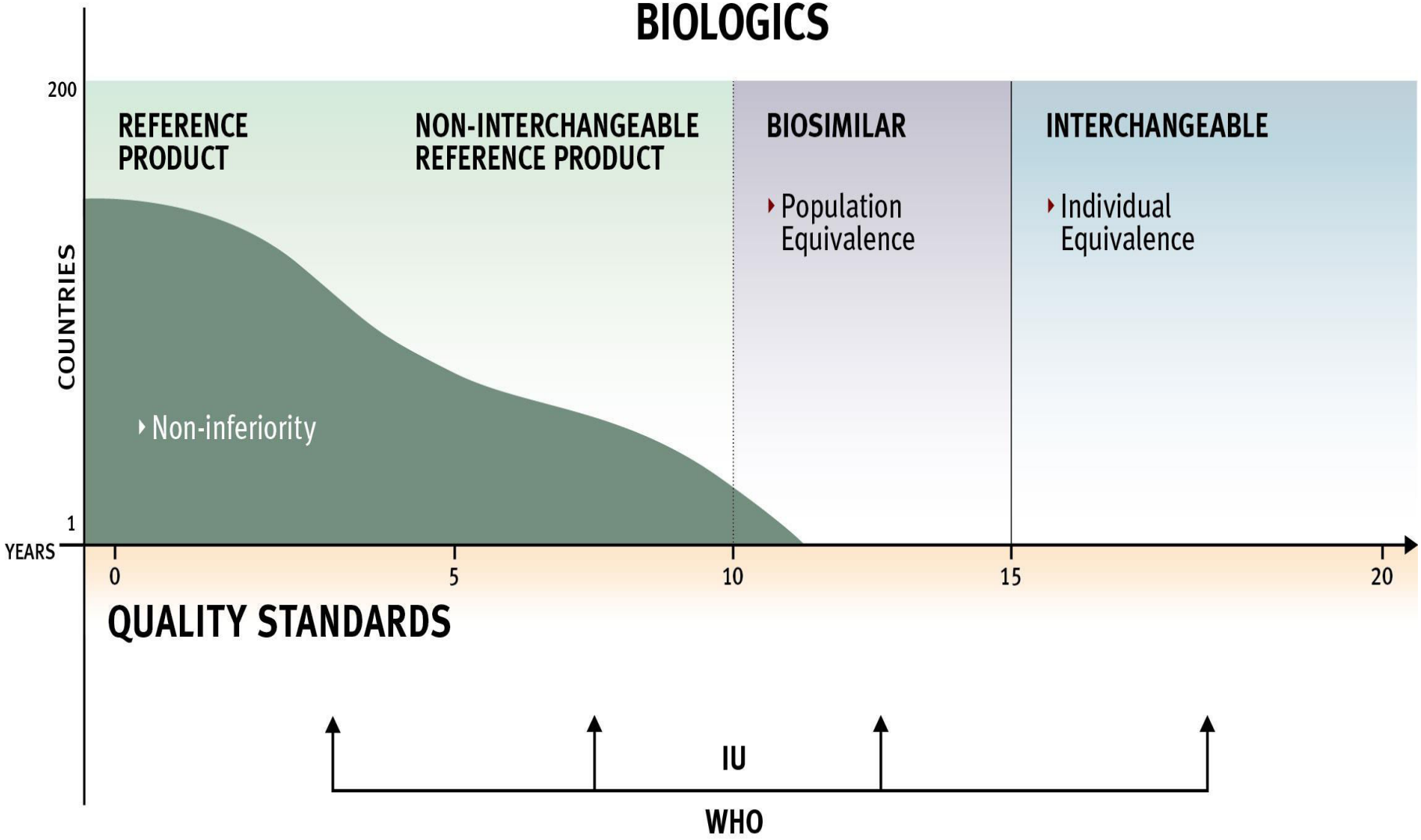
Certification MARKS

Role of Public Standards in the Safety and Efficacy of Biologic Medicines. AAPS Journal

Roger L. Williams, Adrian F. Bristow, Walter W. Hauck, V. Srini Srinivasan, Tina Morris, Fouad Atouf, Michael Ambrose, Koduru V. Surendranath, Ranjan Chakrabarty, and Krishna Menon

Abstract

In this report, we emphasize the importance of public monographs with reference materials, coupled with careful process and change control and attention to GMPs, as a means of advancing access to good quality, safe, and effective medicines, with emphasis on available and incoming biologic medicines. With adequate control of articles covered by a monograph, these public standards can form the basis for a global public quality platform that covers reference products, non-interchangeable reference products, biosimilars, and interchangeable biosimilars. Working collaboratively with all stakeholders, new approaches allow these public standards to emerge nationally and globally in a timely way. Yet, there are increasing limitations in the availability of public standards for biologic medicines, which may reverse many decades of progress. Solutions are considered in this report.


BIOLOGICS
200
REFERENCE PRODUCT
NON-INTERCHANGEABLE REFERENCE PRODUCT
BIOSIMILAR
Population Equivalence
INTERCHANGEABLE
Individual Equivalence
COUNTRIES
Non-inferiority
1
YEARS
0
5
10
15
20
QUALITY STANDARDS
IU
WHO

Birds Eye View of the New Buildings

The Medicines Compendium

- Pharmacopoeias working independently can create a harmonized comprehensive monograph
- Drug Substance Monograph
  - Suitable for all sources of API (drug substance)
  - Includes studies for degradant impurities
- Drug Product Monograph
  - Suitable for all sources of drug product except for: Performance test—needs further information
  - Controls degradant impurities
- Includes validation data
- Supports verification studies by applicants/manufacturers

Continuing equivalence: Is there an end to the story?

Received (in revised form): 16th June, 2008

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Vinod P. Shah
is a consultant at USP. Previously he served at FDA, and he is past president of the American Association of Pharmaceutical Scientists.

Abstract For many active pharmaceutical ingredients and their corresponding drug products, the possibility of a single global system of harmonised bioequivalence and pharmaceutical equivalence requirements for first-entry and interchangeable multi-source drug products may be considered. The topic should be of interest to all manufacturers, to practitioners and patients as well, and to government policy-makers. In an era when substandard, counterfeit, and adulterated medicines are increasingly available, the topic requires careful consideration.
Journal of Generic Medicines (2008) **5**, 297–304. doi:10.1057/jgm.2008.19; published online 15 July 2008

Keywords: *bioequivalence, bioavailability, generic drug, comparator pharmaceutical product, reference listed drug, biopharmaceutics classification system*

INTRODUCTION

Drug development and registration processes focus on safety and efficacy relative to an adequately characterised drug product, which usually contains one or more drug substances (active pharmaceutical ingredients, APIs) and excipients, which should also be adequately characterised and controlled. From characterisation data come specifications that allow control and help ensure continuing equivalence — both pharmaceutical equivalence and bioequivalence — over many years. The general precepts are intrinsic to current thinking about quality by design (QbD) and lifecycle management.[1–3]

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Substantial progress has been made in the science and technical topics that underpin approaches to ensure continuing equivalence. In view of such progress, this paper reviews the status of harmonisation for the various issues involved in bioequivalence and, where not globally harmonised, suggests an approach for APIs and their corresponding drug products. The end result would be better patient care, reduced utilisation of scarce industry and regulatory resources, and reduction in unnecessary clinical trials.

GLOSSARY

The definitions in this section generally follow those used by the World Health Organization (WHO) in its 2006 guidance (see below).[4]

- *Bioavailability*: This term means the rate and extent to which the active ingredient or active moiety is absorbed from a drug

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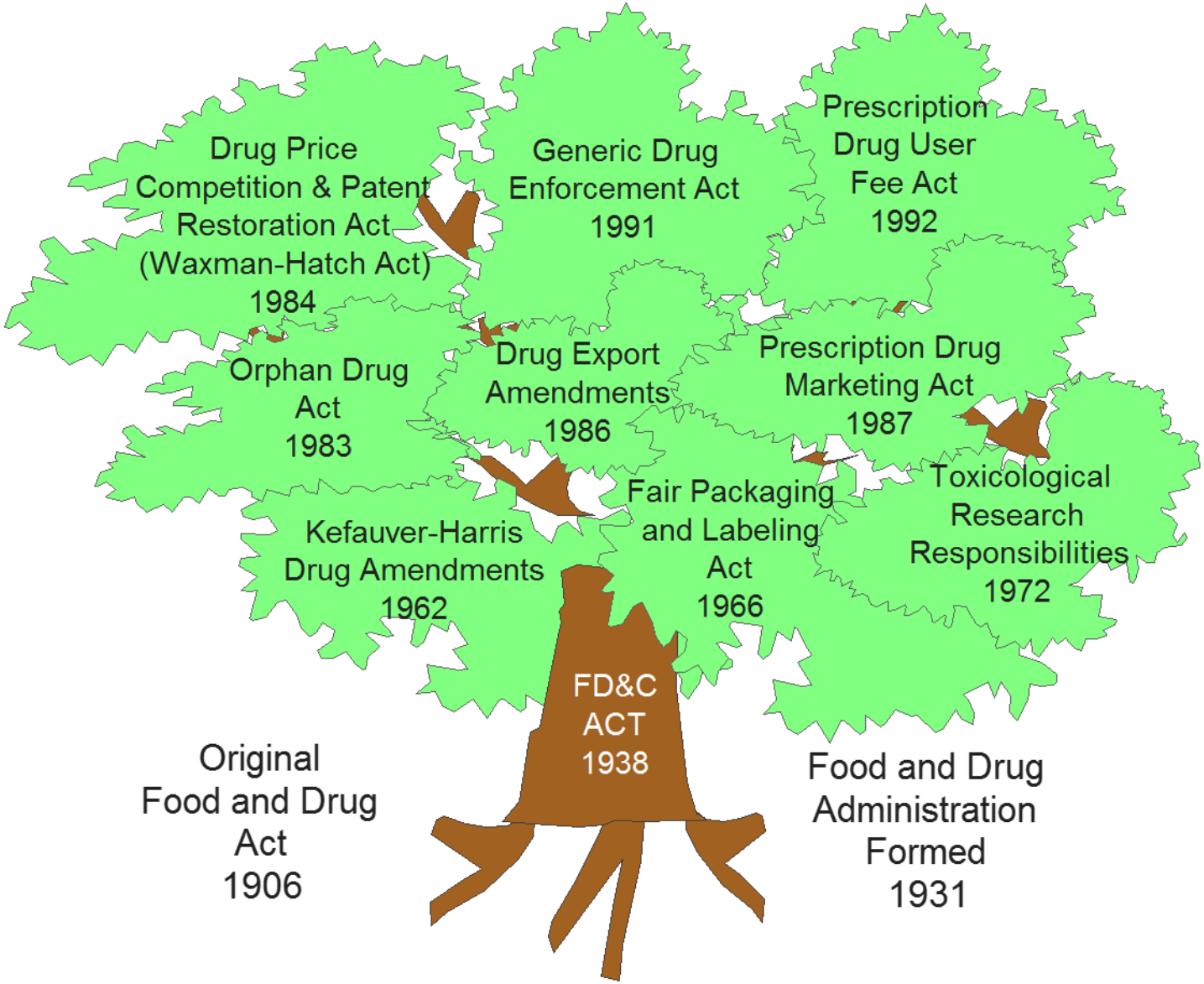

AN AGENCY WITH GROWING CONSUMER PROTECTION RESPONSIBILITIES

SIGNIFICANT Acts AMENDING the FD&C Act

- 1980 Infant Formula
- 1983 Orphan Drug
- 1984 Generic Drug Act (H-W)
- 1987 Prescription Drug Marketing
- 1988 Generic Animal Drug
- 1990 Nutrition Labeling and Education
- 1990 Safe Medical Devices
- 1992 Medical Devices
- 1991 Generic Drug Enforcement Act
- 1992 Prescription Drug User Fee
- 1994 Animal Medicinal Drug Use Clarification
- 1994 Dietary Supplement Health and Education Act
- 1996 FDA Export Reform and Enhancement
- 1996 Food Quality Protection
- 1996 Animal Drug Availability
- 1997 FDA Modernization Act
- 2002 Best Pharmaceuticals for Children
- 2002 Medical Device User Fee and Modernization
- MMA/ Title XI
- 2003 Animal Drug User Fee
- 2003 Pediatric Research Equity Act
- Obamacare/BPCI (Biosimilars)
- 2004 Minor Use and Minor Species Animal Health
- 2006 Dietary Supplement and Nonprescription Drug Consumer Protection
- 2007 FDA Amendments (FDAAA)
- 2009 Family Smoking Prevention and Tobacco Control
- 2011 FDA Food Safety Modernization
- 2012 FDASIA /Generic Drug User Fee
- 2013 Drug Quality/Security Act (Compounding)
- 21 Century Cures
- 2017 PDUFA VI

CDER Guidances [October 27, 2014]

- Advertising/Draft 13
- Biopharmaceutics/Draft 12
- Biosimilarity Draft 5
- CMC (Quality)/Draft 49
- Clinical Antimicrobial/Draft 42
- Clinical Medical /Draft 93
- Clinical Pharmacology/Draft 10
- CMC Microbiology Draft 2
- Combination Products (Drug/Device/Biologics) 3
- cGMP/Compliance/Draft 39
- Drug Safety/Draft 16
- Electronic Submissions 18
- Generic Drug/Draft 34
- Good Review Practices 1
- INDs 1
- Industry Letters 10
- Labeling/Draft 19
- Modernization Act /Draft 18
- OTC/Draft 19
- Pharmacol/Toxicology/Draft 21
- Procedural 81
- Small Entity 9
- User Fees 8
- Also Manual of Policies and Procedures (MaPPs)

- **TOTAL 523**

ICH Guidelines/PDG

- Efficacy/Draft 28
- Multidisciplinary/Draft 12
- Quality/Draft 28
- Safety 17

- TOTAL 85
- Pharmacopoeias (Q4B) 18

[Harmonized Compendial Text]

- Pharmacopoeial Discussion Group (PDG)
- ~60 Excipient Monographs
- ~30 General Chapters

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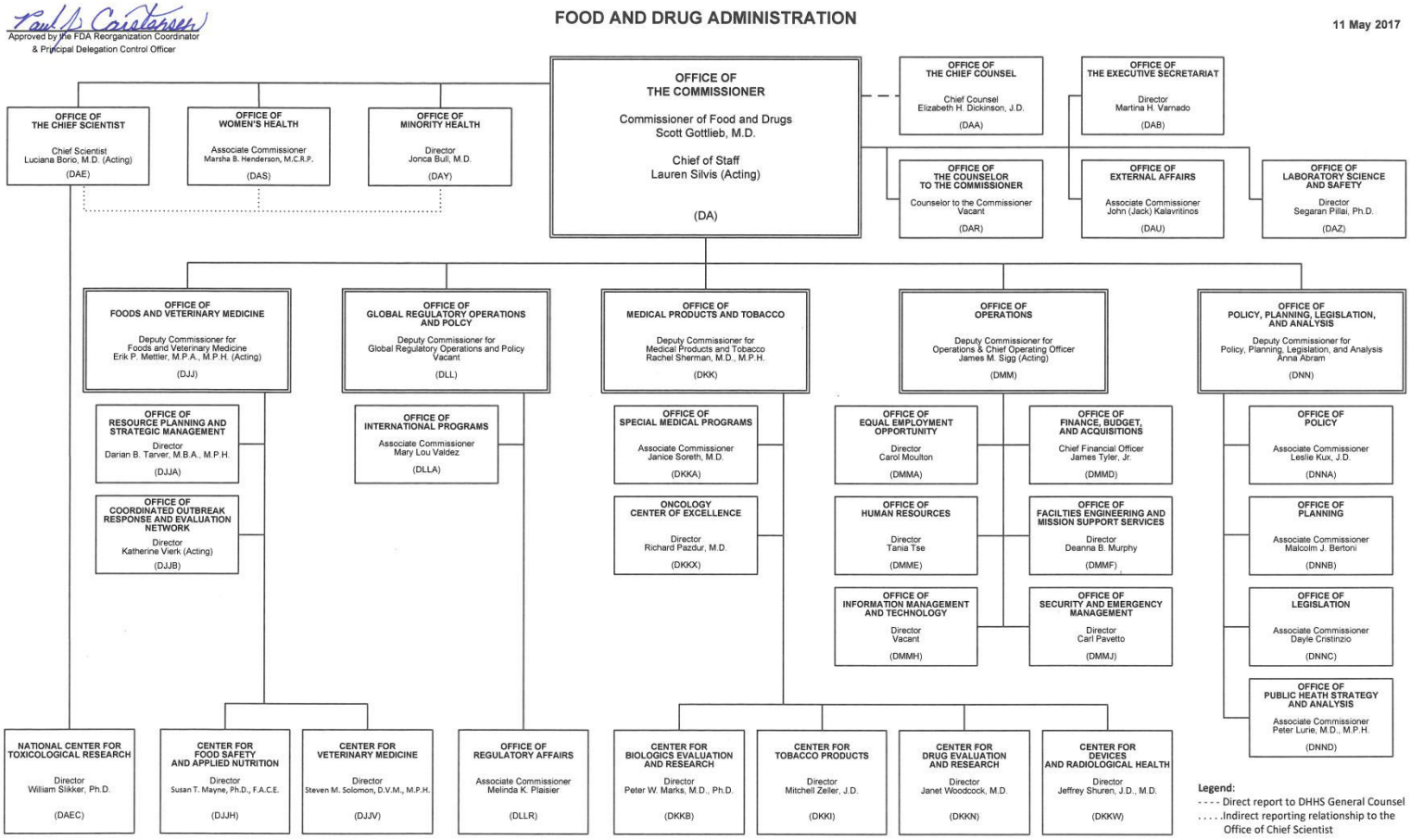
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11 May 2017
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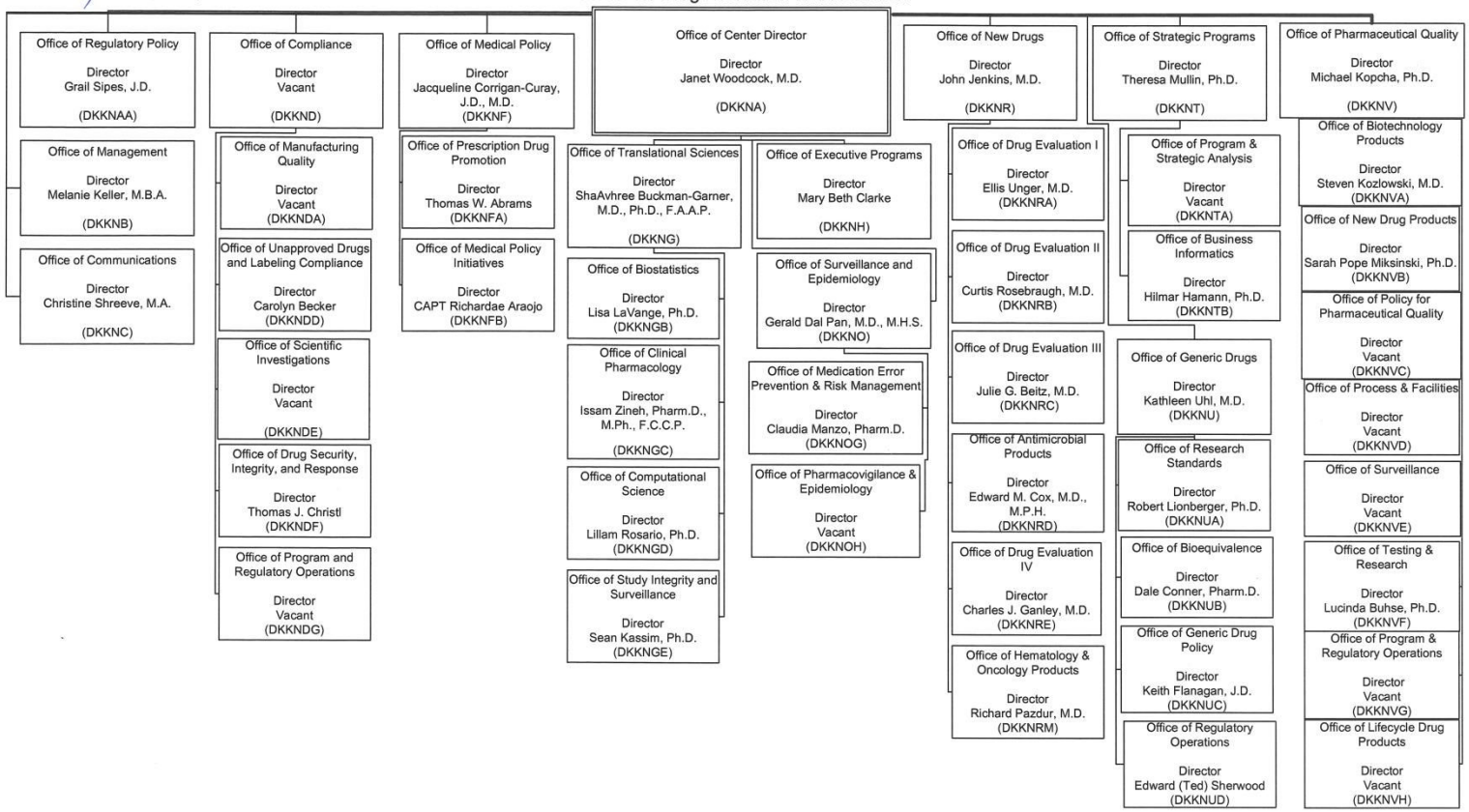
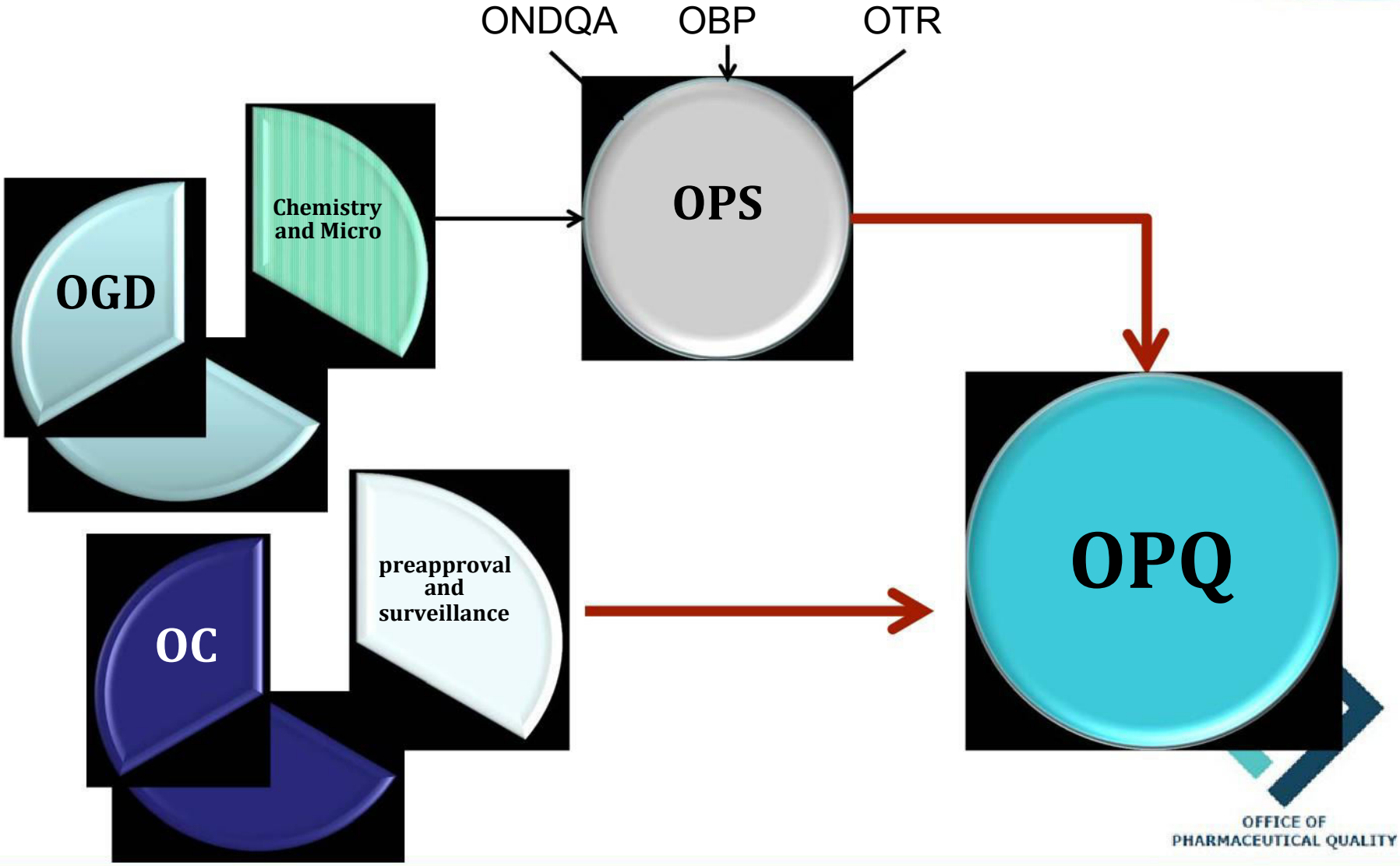
---- Direct report to DHHS General Counsel
. . . . .Indirect reporting relationship to the Office of Chief Scientist

Approved by the FDA Reorganization Coordinator and Principal Delegation Control Officer

Food and Drug Administration
Office of Medical Products and Tobacco
Center for Drug Evaluation and Research



How OPQ was formed?



OPQ

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OFFICE OF PHARMACEUTICAL QUALITY

Topics

1. Dissolution
2. Science
3. FDA: Law, Regulation, Guidance
4. Future Directions

21 Century Cures: Title III

- Subtitle A—Patient Focused Drug Development
- Subtitle B—Advancing New Drug Therapies
- Sec. 3011. Qualification of Drug Development Tools
  CDER has already issued guidance
- Subtitle C—Modern Trial Design And Evidence Development
- Sec. 3021. Novel clinical trial designs.
- Complex adaptive and other novel trial designs for the development and regulatory review of NDAs and BLAs.
- Sec. 3022. Real World Evidence
- New England Journal of Medicine article on the use of real world evidence.
- Subtitle D—Patient Access To Therapies And Information
- Subtitle E—Antimicrobial Innovation And tewardship
- Section F--blank
- Subtitle G—Improving Scientific Expertise And Outreach At FDA
- Subtitle H—Medical Countermeasures Innovation
- Subtitle I—Vaccine Access, Certainty, And Innovation

PDUFA VI: 2018-2022

- I. ENSURING THE EFFECTIVENESS OF THE HUMAN DRUG REVIEW PROGRAM
- II. ENHANCING MANAGEMENT OF USER FEE RESOURCES
- III. IMPROVING FDA HIRING AND RETENTION OF REVIEW STAFF
- IV. INFORMATION TECHNOLOGY GOALS
- V. IMPROVING FDA PERFORMANCE MANAGEMENT

505(b)(2) Opportunities

1. Grew out of Hatch-Waxman 1984
2. Parkman Letter
3. Replaced by 1999 Draft Guidance
   - NCE or Predicate Drug/Patent Certification
   - Applicant can rely on published literature and/or on Agency finding of safety and/or effectiveness for an approved drug product
4. Logical Next Step for India in US

Thank you!