Disso India 2018

Recent Drug Regulation and the Pharmacop(o)eias

Roger L. Williams, M.D.

Society for Pharmaceutical Dissolution Science

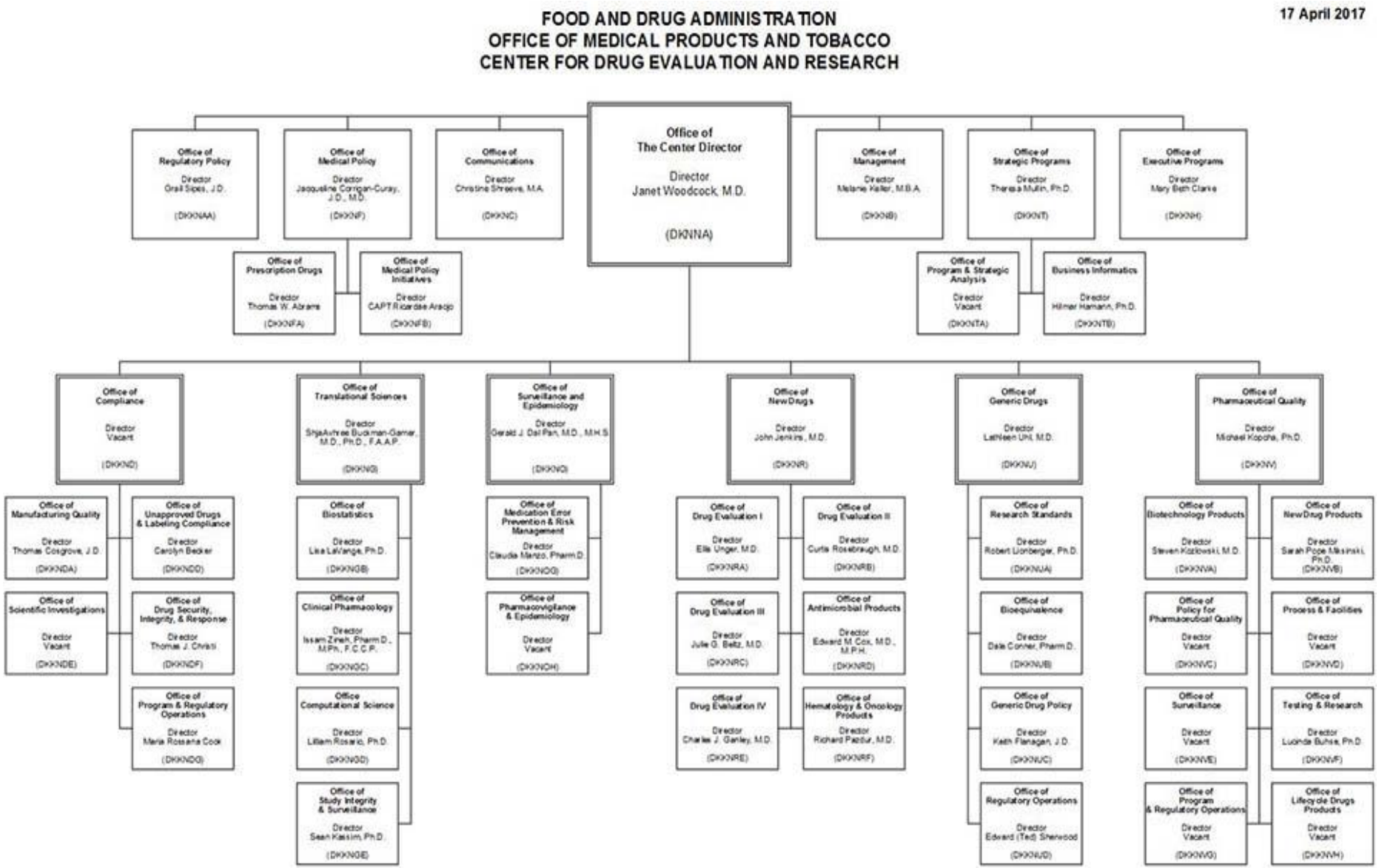
Hyderabad

June 28, 2018

Topics

- **Past to Present**
  1. **FDA**
  2. **ICH and IGBA**
  3. **USP**
  4. **BCS**
- **Discussion**

FDA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17 April 2017
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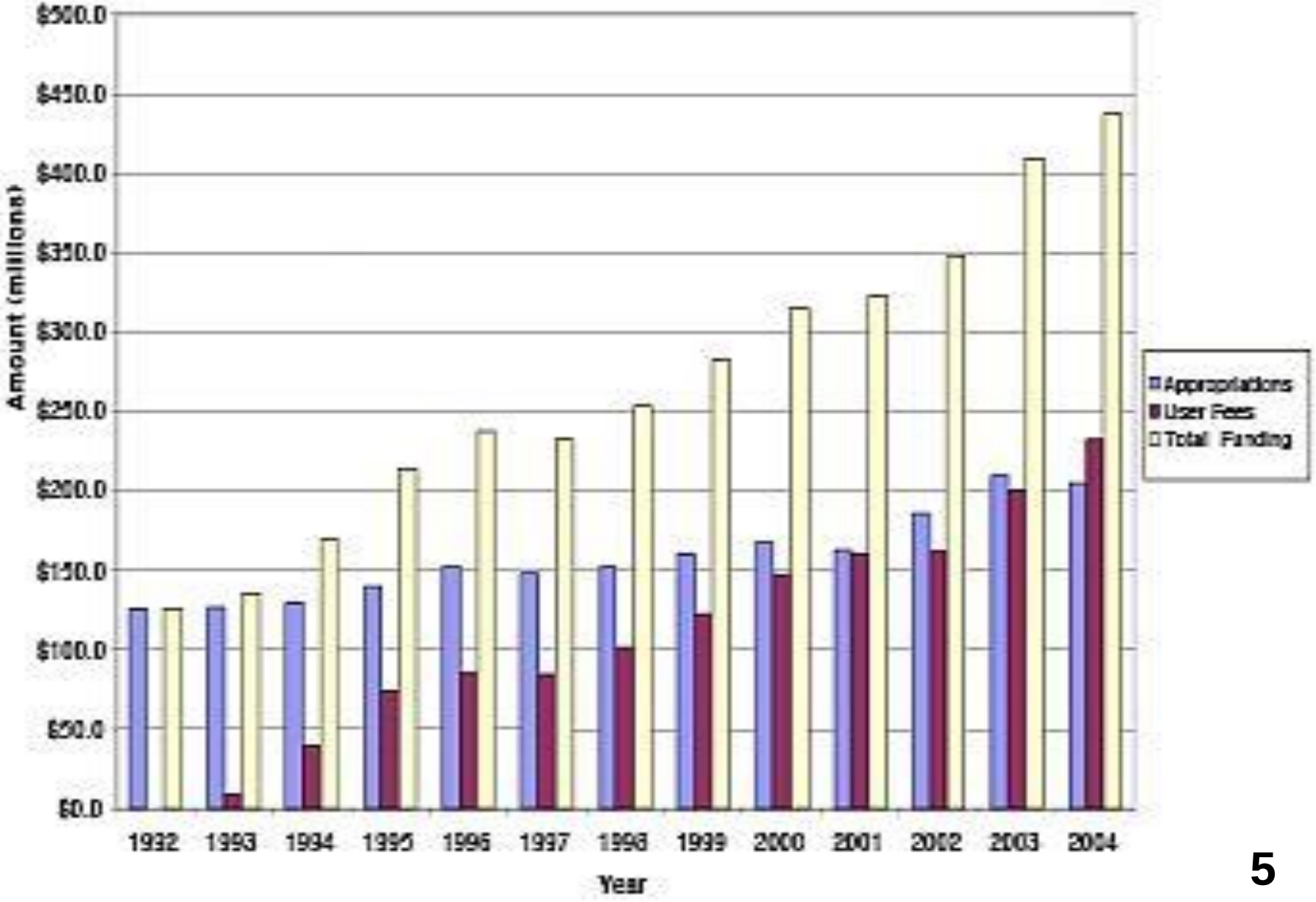
Figure 1.1 History of Funding for Review of Human Drugs



USER Fees

- **FDA** **$5.1 billion**
- **User Fees** **3.2 billion**
- **Discretionary** **1.9 billion**
- **CDER** **> 80% user fees**

AMENDING the FD&C Act

- 1938: FDC Act
- 1962: H-K Amendments
- 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 FDAMA
- 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 ACA/BPCI
- 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 FDARA (PDUFA VI, GDUFA II, BsUFA II)

Quality Changes Related to the UFAs

- FDA Reauthorization Act, signed into law 8/18/17, reauthorizes:
  - The Generic Drug User Fee Amendments (GDUFA) for the first time
  - The Prescription Drug User Fee Act (PDUFA) for the fifth time
  - The Biosimilar User Fee Act (BsUFA) for the first time
- User fees provide critical resources to conduct product assessments in a timely fashion and help ensure the quality, safety, and effectiveness of drug products


115TH CONGRESS 1st Session | HOUSE OF REPRESENTATIVES | REPORT 115–201

FDA REAUTHORIZATION ACT OF 2017

JULY 11, 2017.—Committed to the Committee of the Whole House on the State of the Union and ordered to be printed


Scott Gottlieb, M.D.
@SGottliebFDA
Follow

FDA Reauthorization Act enables @US_FDA to continue advancing patient care. We're grateful to those who made this #bipartisan law possible

5:04 PM - 18 Aug 2017

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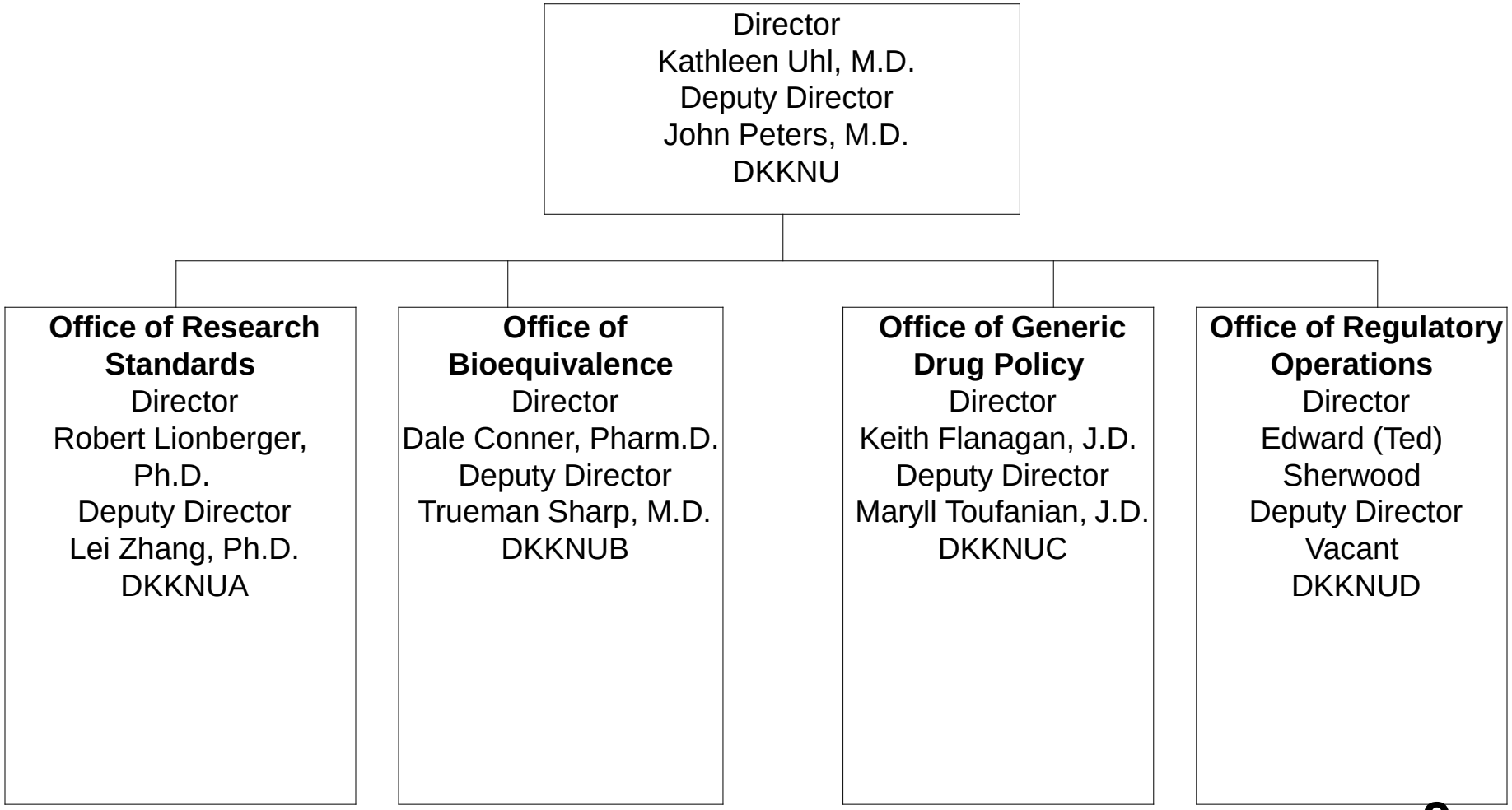
Food and Drug Administration
Office of Medical Products and Tobacco
Center for Drug Evaluation and Research
Office of Generic Drugs



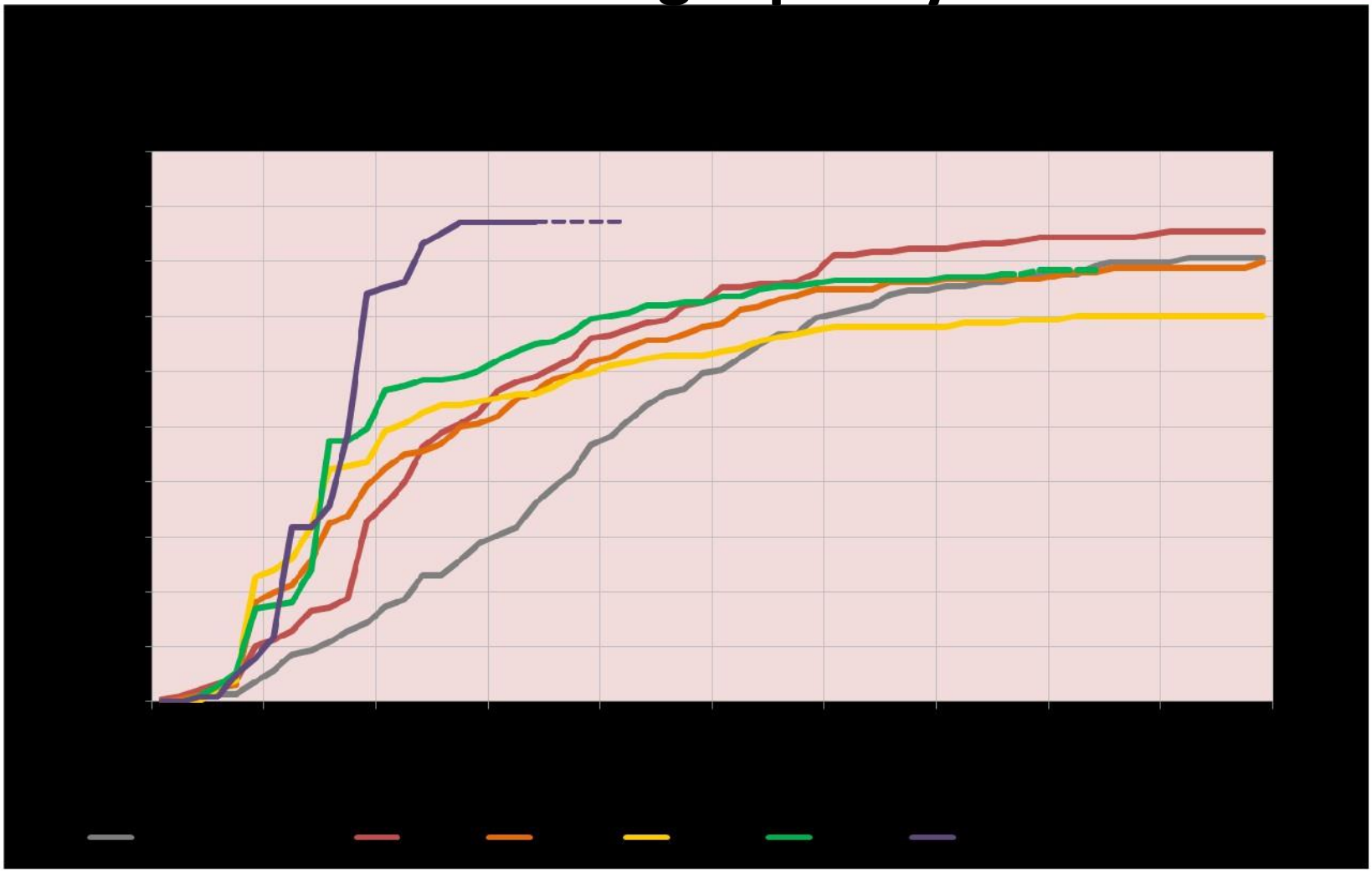
FIRST CYCLE APPROVALS*

FY2015	**10.7%**
FY2016**	**14.3%**
FY2017**	**12.8%**

- Low %
- Lots of rework
- Inefficient use of resources
- Large number of ANDAs "pending" with industry, issued CR letters
- Critical to improve the ANDA Quality UP FRONT

*Updated 10/1/2017. Numbers are based on preliminary data that will be reviewed and validated for official reporting purposes.
Cohort Year 3 (FY2016) - Some are still under review and within goal; all mature by December 31, 2017.
Cohort Year 4 (FY2017) - Many are still under review and within goal; all mature by July 31, 2018.
**Percent represents the current percentage of regulatory actions FDA completed within the review-time goal. Final performance will depend on the outcome of pending submissions.
DEFINITION: The percentage of AP and TA original and original-response to RTR ANDAs that were received for extensive review and were given a regulatory action (excluding ANDAs under review).

PDUFA Experience: Higher first cycle approval rate achievable with high quality submissions



* PDUFA V estimates based on 77 NMEs submitted in FY 2013 - mid FY 2015 (it is too early to estimate performance for later submissions)
Projection estimates account for actions to date and elapsed time to date for non-approvals
Data as of 9/30/16

GDUFA I Regulatory Research "Game Changers"

($Billion Impact)

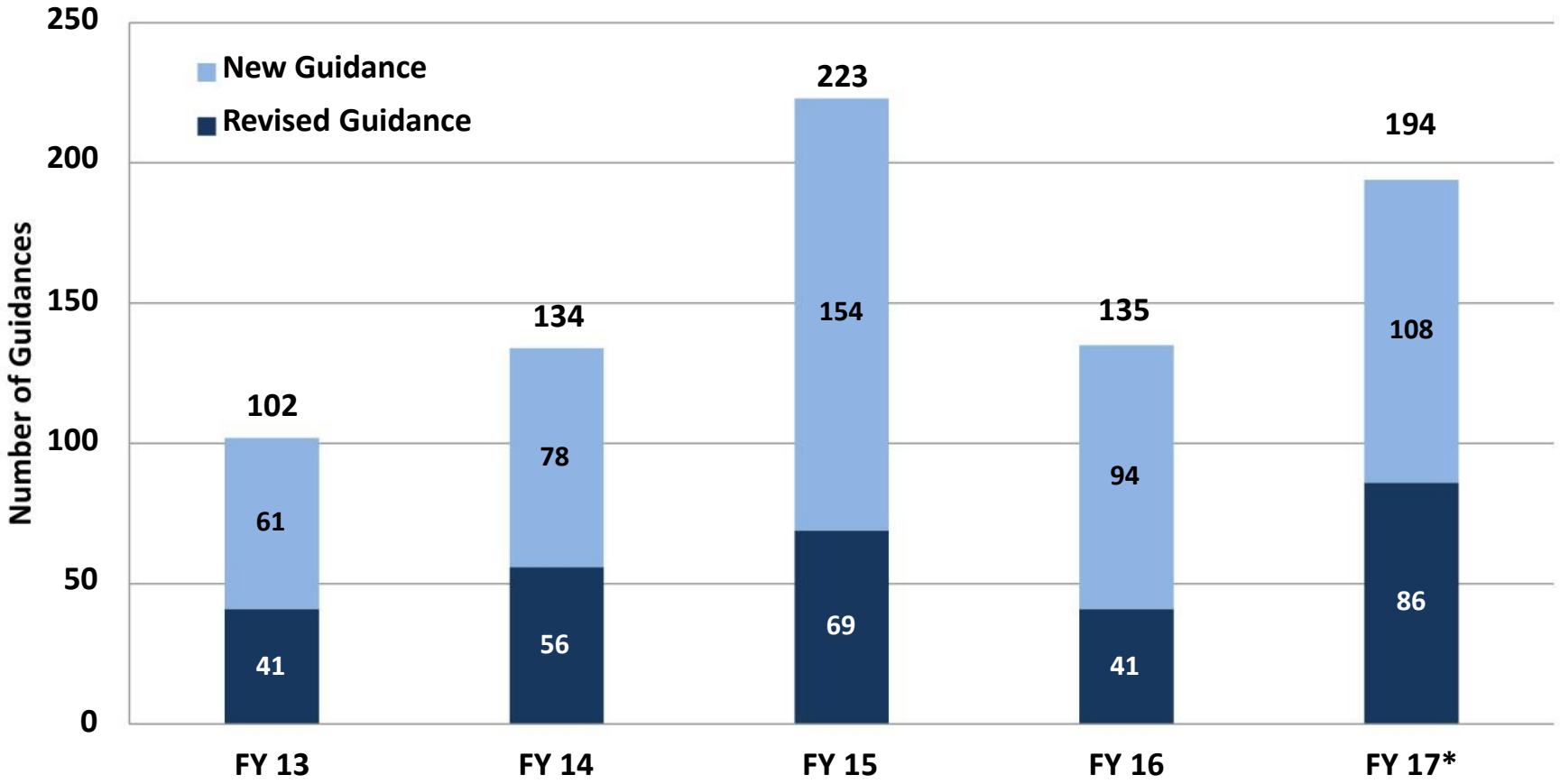
- PSGs for:
  - -17 inhalation products
  - – Conjugated estrogens
  - - In vitro equivalence for topical ointments, topical creams, GI binding agents, ophthalmic emulsions
- Stand alone guidance for:
  - - Generic abuse deterrent opioid formulations
  - - BCS class III biowaivers
  - - Synthetic peptides referencing rDNA RLDs
  - – Adhesion for transdermals
- ANDA Approvals for:
  - - Generic glatiramer acetate
  - - Nasal spray suspension based on novel particle size methods
  - - Topical ointments (in vitro approach)
  - - GI binding agents (in vitro approach)
- Scientific Advances
  - - Polymer characterization for long-acting injectables
  - - First open flow microdialysis BE study for a topical cream

*Updated 10/1/2017. Numbers are based on preliminary data that will be reviewed and validated for official reporting purposes.

General Considerations

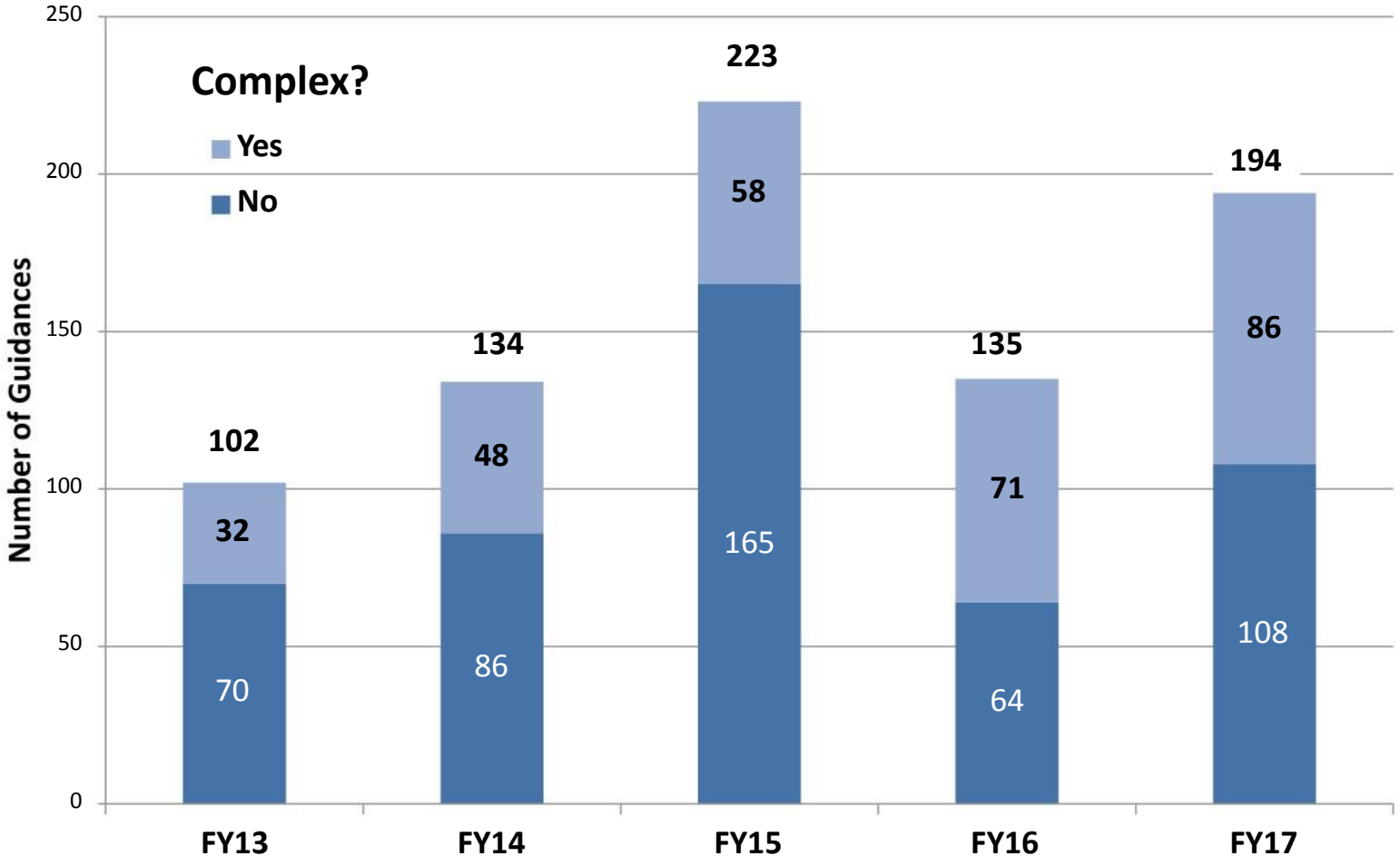
- **2003 Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations Withdrawn**
- 2014 **Guidance for Industry** Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs — General Considerations

Product-Specific Guidances (PSGs)



*Updated 10/1/2017. Numbers are based on preliminary data that will be reviewed and validated for official reporting purposes.

Product-Specific Guidances (PSGs) Complex Drug Products



*Updated 10/1/2017. Numbers are based on preliminary data that will be reviewed and validated for official reporting purposes.

GDUFA II: Topics for pre-ANDA Meetings

- 127 pre-ANDA meeting packages reviewed in GDUFA I
  - No commitment in GDUFA I, mostly written responses
- Top categories
  - 35 on nasal/inhalation products
  - 31 on complex formulations
  - 25 on complex active ingredients
  - 10 on topical/transdermal
  - 8 on GI acting drugs
  - 8 on drug-device combinations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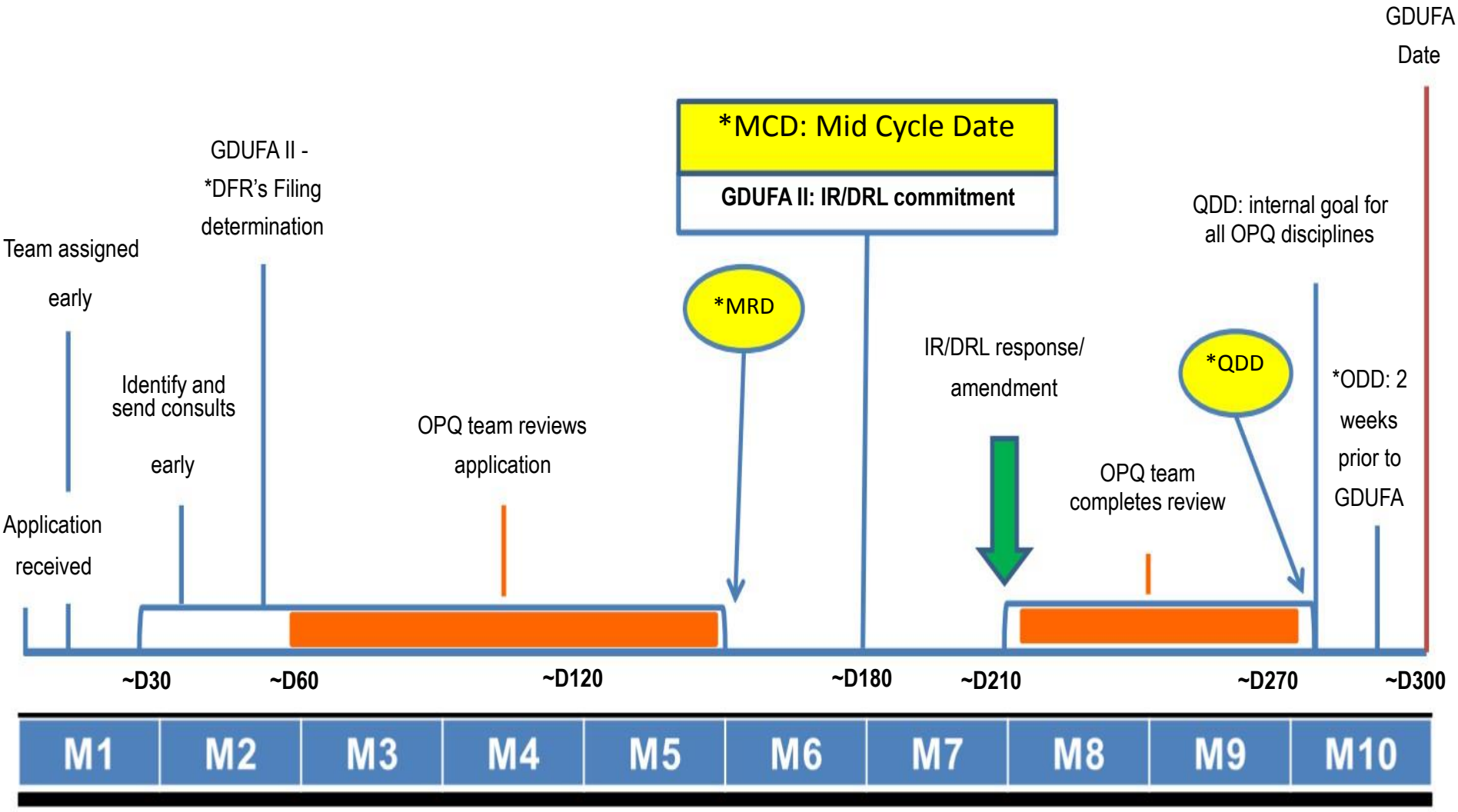
GDUFA II snapshot of OPQ process timeline - 10 month example for Original ANDAs



*DFR = OGD's Division of Filing Review; MRD = Mid Review Date;
MCD = Mid Cycle Date; QDD = quality Due date; ODD = owner due date

ONDP: Biopharmaceutics: Clinical Relevance

- QC in vitro release testing (e.g. dissolution) should ensure release of product that maintains clinical performance (i.e. bioequivalence)
- Attempts should be made to adhere to recommendations as outlined in the 2015 draft guidance "*Dissolution Testing and Specification Criteria for Immediate-Release Solid Oral Dosage Forms Containing Biopharmaceutics Classification System Class 1 and 3 Drugs*"
- Justifications can be provided (e.g. in silico modeling, literature) to ensure that quality specifications are able to detect changes that affect BE

https://www.fda.gov/downloads/Drugs/Guidances/UCM456594.pdf

FDA U.S. FOOD & DRUG ADMINISTRATION
OFFICE OF REGULATORY AFFAIRS

ORA: FY16 Scope of Work Snapshot

- >37,000 domestic inspections (~16,000 FDA/~21,000 states)
- >3,500 foreign inspections
- Collected and analyzed >35,000 samples
- Managed >36M import lines with >21,000 import refusals
- Managed ~$97M portfolio of state contracts, grants and cooperative agreements
- 257 arrests and 274 convictions
- Collected >$333M in fines and restitutions
- >$41M assets forfeited/seized
- Issued >14,000 WL
- 4 seizure, 17 injunctions
- >8,000 recalled products/2,847 events; 484 Class 1 recall events

Topics

- **Past to Present**
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- **Discussion**

Current ICH Association Members

- **Regulatory Members**
  - FDA, US
  - EC, Europe
  - PDMA/MHLW (Japan)
  - ANVISA, Brazil
  - Health Canada
  - Swissmedic, Switzerland
  - CFDA , China
  - MFDS, Korea
- **Industry Members**
  - PhRMA
  - EFPIA
  - JPMA
  - IGBA
  - WSMI
  - BIO
- **In addition there are currently 23 Observer organizations in ICH**

- **Full information on ICH may be found at the website: www.ich.org**

IGBA
INTERNATIONAL GENERIC AND BIOSIMILAR MEDICINES ASSOCIATION

ABOUT IGBA

- Founded in March 1997 as the International Generic Pharmaceutical Alliance
- Renamed **International Generic and Biosimilar Medicines Association (IGBA)** in September 2015
- Legally incorporated in Geneva, Switzerland
- Maintains constant dialogue with the WHO, WTO, WIPO, ICH and other national, regional and international bodies

IGBA
INTERNATIONAL GENERIC AND BIOSIMILAR MEDICINES ASSOCIATION

MEMBERS

- IGBA is committed to promoting generic and biosimilar medicines worldwide, and consists of the following associations:

  - Canadian Generic Pharmaceutical Association (CGPA-Canada)
  - Association for Accessible Medications (AAM-United States)
  - Japan Generic Medicines Association (JGA-Japan)
  - Jordanian Association of Pharmaceutical Manufacturers (JAPM-Jordan)
  - Medicines for Europe (Europe)
  - Generic and Biosimilar Medicines of Southern Africa (GBM)
  - Taiwan Generic Pharmaceutical Association (TGPA-Taiwan)

  The generic and biosimilar medicines associations of Australia, Brazil, Malaysia and Mexico are Associate Members.

- In addition, IGBA includes:

  - Biosimilars Canada
  - Biosimilars Council (AAM Division)
  - Biosimilar Medicines Group (Medicines for Europe Sector Group)

IGBA
INTERNATIONAL GENERIC AND BIOSIMILAR MEDICINES ASSOCIATION

IGBA Experts on Current ICH Topics

- **Q3D(R1) EWG - Revised PDEs for the cutaneous and transdermal Route of Administration**
- **Q12 EWG- Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management**
- **M9 EWG -Biopharmaceutics Classification System-based Biowaivers**
- **M10 EWG -Bioanalytical Method Validation**
- **E8(R1) Informal WG -GENERAL CONSIDERATIONS FOR CLINICAL TRIALS**
- **E19 EWG -Optimisation of Safety Data Collection**
- **M4Q(R1) IWG - M4Q (CTD Q) Questions and Answers**
- **M2 EWG -Electronic Standards for the Transfer of Regulatory Information**

IGBA Experts are from diverse companies from around the world.

IGBA
INTERNATIONAL GENERIC AND BIOSIMILAR MEDICINES ASSOCIATION

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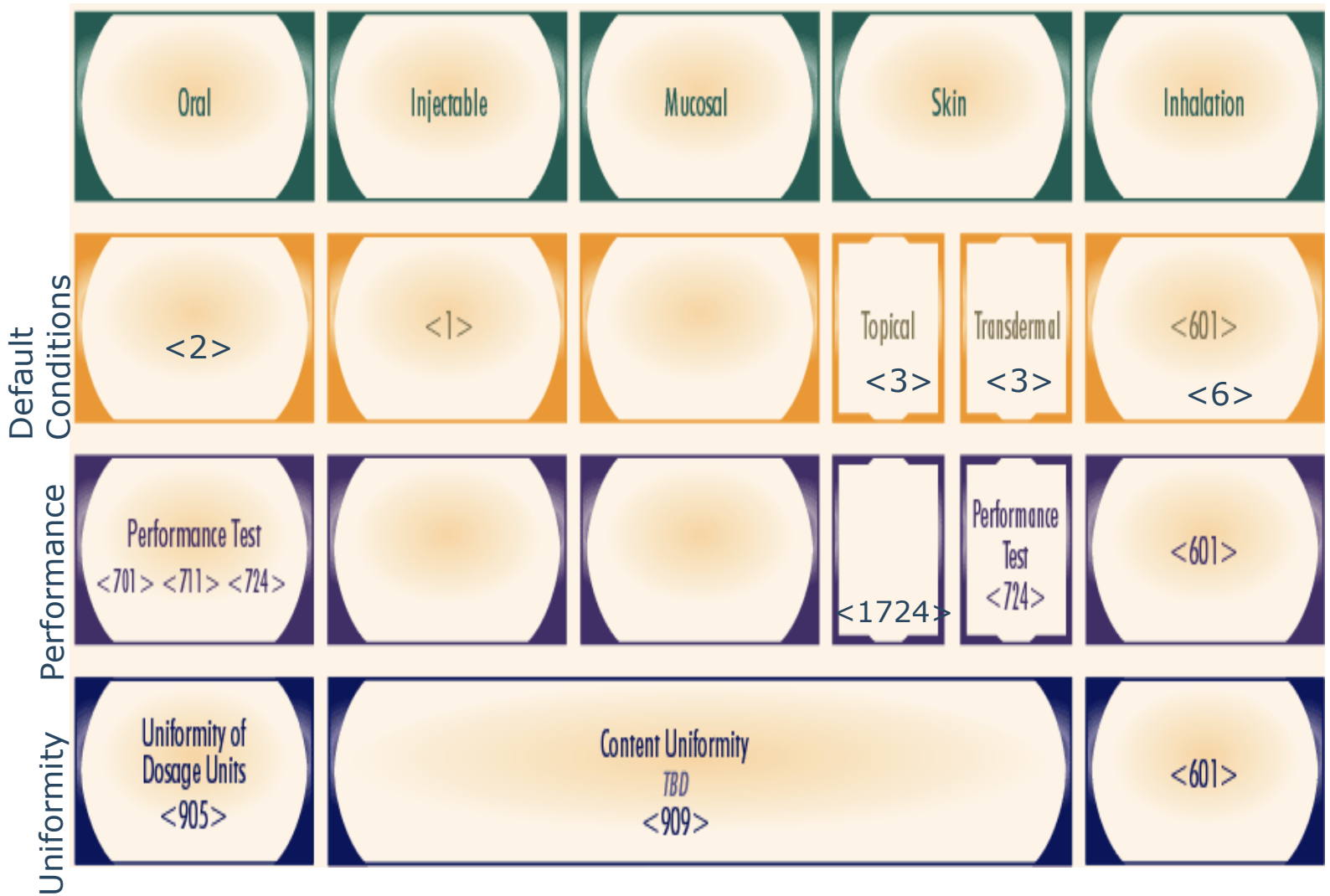
Quality and Performance Tests



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

USP General Chapters

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- <1> INJECTIONS AND IMPLANTED DRUG PRODUCTS (PARENTERALS)-PRODUCT QUALITY TESTS
- <2> ORAL DRUG PRODUCTS-PRODUCT QUALITY TESTS
- <3> TOPICAL AND TRANSDERMAL DRUG PRODUCTS-PRODUCT QUALITY TESTS
- <4> MUCOSAL DRUG PRODUCTS-PRODUCT QUALITY TESTS
- <5> INHALATION AND NASAL DRUG PRODUCTS-GENERAL INFORMATION AND PRODUCT QUALITY TESTS

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.

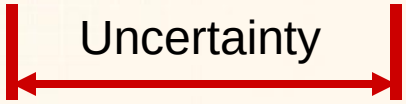
- **Quality tests assess the integrity of the dosage form, whereas performance tests assess drug release and other attributes that relate to *in vivo* drug performance.**

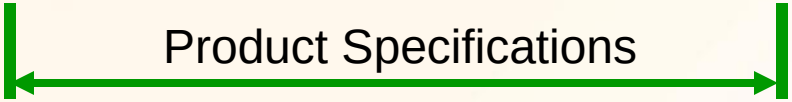
- **Taken together, quality and performance tests assure the identity, strength, quality, purity and potency/performance of the pharmaceutical dosage form.**

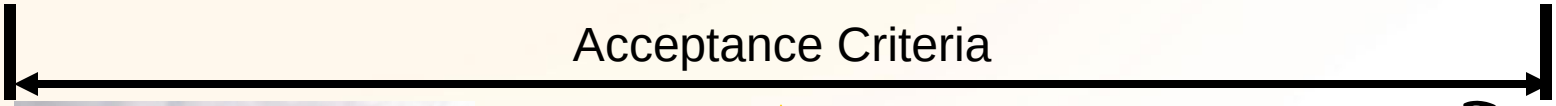
BIPM

- 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!!!!

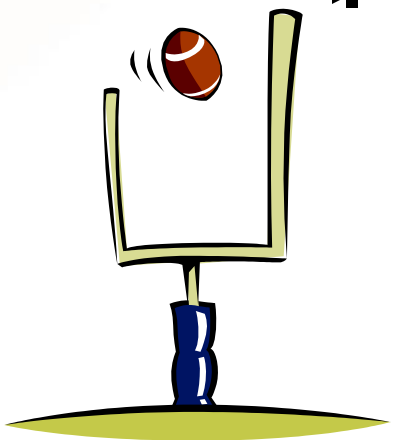






"Trueness"

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/

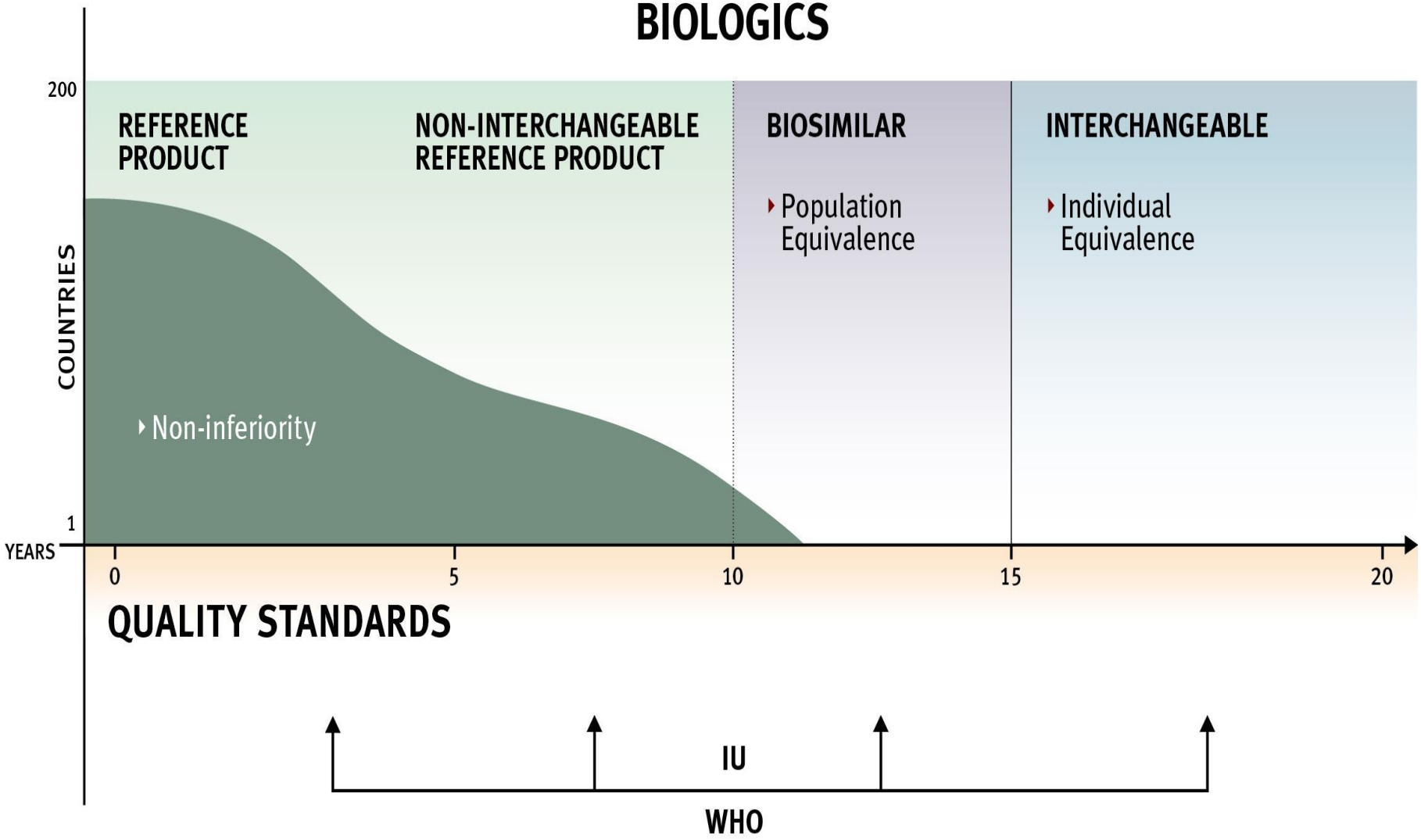
Certification MARKS

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**

Pharmacope(o)ial Discussion Group

- **European Pharmacopoeia (Ph.Eur.), Japanese Pharmacopoeia (JP), and the United States Pharmacopoeia (USP)] met US September 12 – 13 2017.**
- **Changes to work structure**
- **Move to bilateral discussions/adopt-adapt**
- **Excipient monographs**
- **International Pharmaceutical Excipients Council (IPEC) Federation meets in association**
- **Meets twice yearly, once by videoconference, next meeting October 2-3, 2018 in Strasbourg, France**

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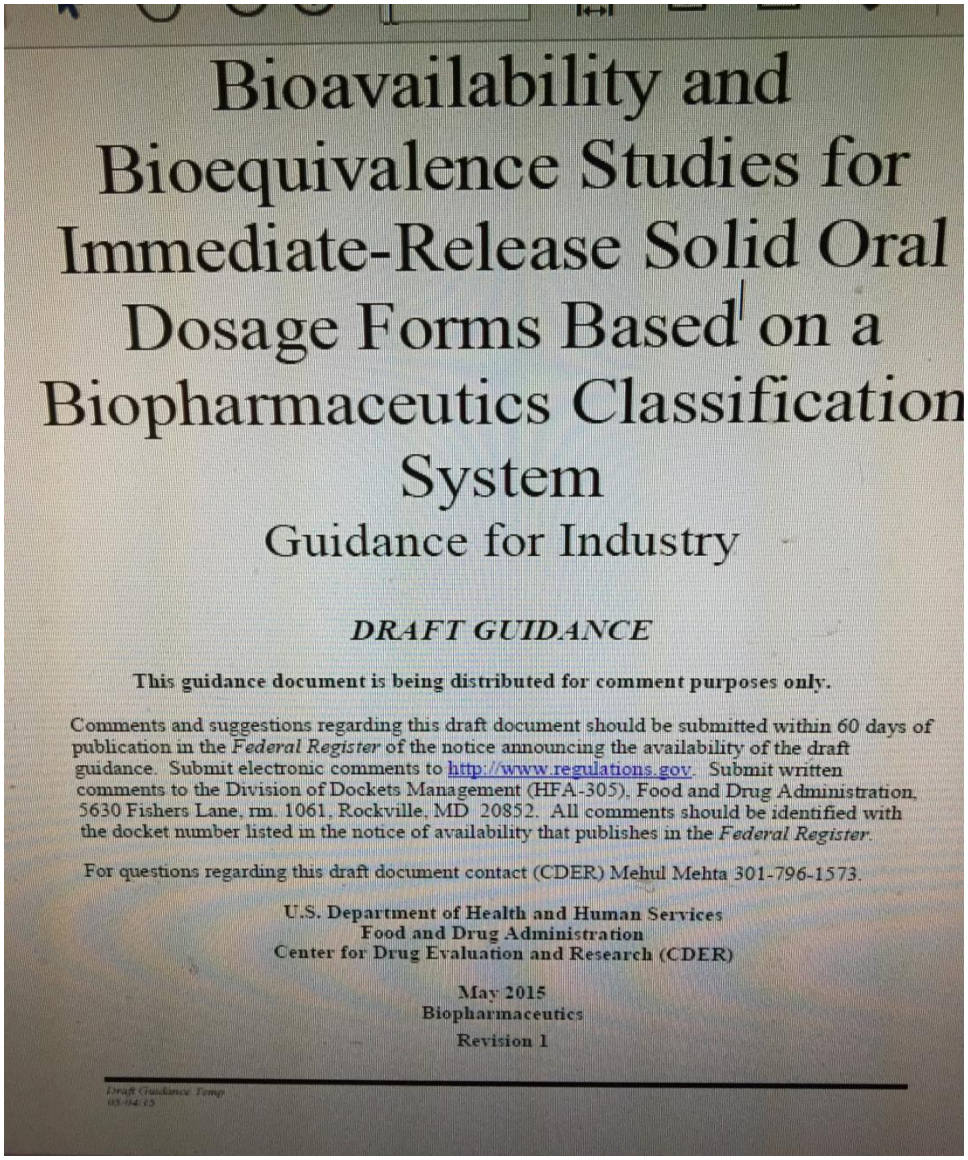

Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System

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

BCS Challenges

- **Permeability difficult**
- **Why repeat**
  Could information become public: FDA (no), EMA (EPAR)—yes?
  If available, put in product specific guidance
  RLD labeling (yes)
  ? Pharmacop(o)eias)
- **Q1/Q2 Class III—difficult for Q2**
  ? Impact on BA
  ? Known interactions
  ? Transporters

Topics

- **Past to Present**
  1. **FDA**
  2. **ICH and IGBA**
  3. **USP**
  4. **BCS**
- **Discussion**

Success!

- UFAs (but)
- Regulatory Research—Guidances
- Complex Drugs
- Reference Scaling (Not IBE)
- ICH (? India)
- IGBA (? India)
- USP Pending and Flexible
- BCS

No Success

- **Comparable Biologics in US**
- **Interchangeable Biologics in US (none)**
- **USP more independent of donors (Medicine Compendium failed)**
- **USP Verification/Certification**
- **Individual BE**
- **USP Biologics/India**

India

- **Drug substance**
- **Drug product (interchangeable)**
- **505b2 (improvement)**
- **NCE ?**
- **New biologics?**
- **Bioequivalence in India**

Thank you!