Challenges and Opportunities for Innovation in Complex Generic Drug Product Development

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Toward an Improved Understanding of Complex Drug Substances and Complex Formulations Through GDUFA Regulatory Research Program
CRS Annual Meeting 2018

Outline

- Introduction to generic drugs
- FDA's considerations on demonstrating equivalence of complex generic drug products
- GDUFA regulatory research on complex drug products
- GDUFA regulatory research outcomes

The Generic Drug User Fee Act (GDUFA) is a law designed to speed access to safe and effective generic drugs to the public, and reduce costs to industry.

Generic Drugs – what are they?

- Are "copies" of brand-name drugs
- Are the same as those brand-name drugs in dosage form, strength, route of administration, quality, performance characteristics, and intended use.

From FDA website – Abbreviated New Drug Application (ANDA)
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/default.htm

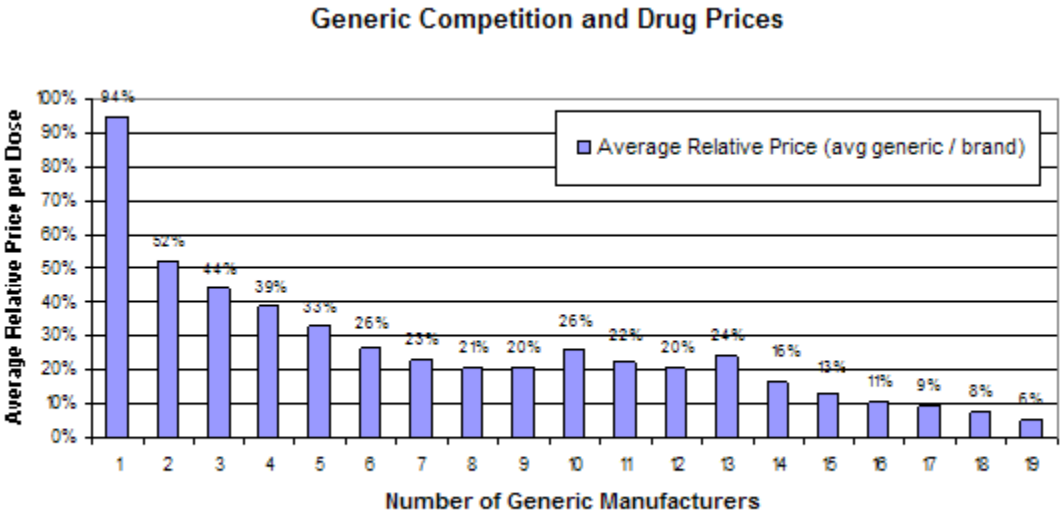
Promises about Generic Drugs

- FDA approved generic drugs are **Therapeutically Equivalent**
- They can be substituted for the RLD (brand product)
- Generics and their RLDs have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling

RLD: Reference Listed Drug

Generic Drugs Cost Less

- Generic drugs cost less to develop because generic sponsors generally do not need to include preclinical and clinical data to establish safety and effectiveness as the RLD. Instead they demonstrate **Pharmaceutical equivalence** and **Bioequivalence** to the RLD.



Source: FDA analysis of retail sales data from IMS Health, IMS National Sales Perspective (TM), 1999-2004, extracted February 2005

Equivalence Concepts

- **Pharmaceutical Equivalence (PE)**
  - Same active ingredient(s) and
  - Same dosage form and
  - Same route of administration and
  - Same strength and more …
- **Bioequivalence (BE)**
  - No significant difference in rate and extent of drug at site of action
- **Therapeutic Equivalence (TE) of Generic Products**
  - Generics must demonstrate PE and BE to the RLD
  - Generics rely on the safety and efficacy of the RLD
  - TE products can be substituted freely

New Drug Application (NDA) vs. Abbreviated New Drug Application (ANDA)

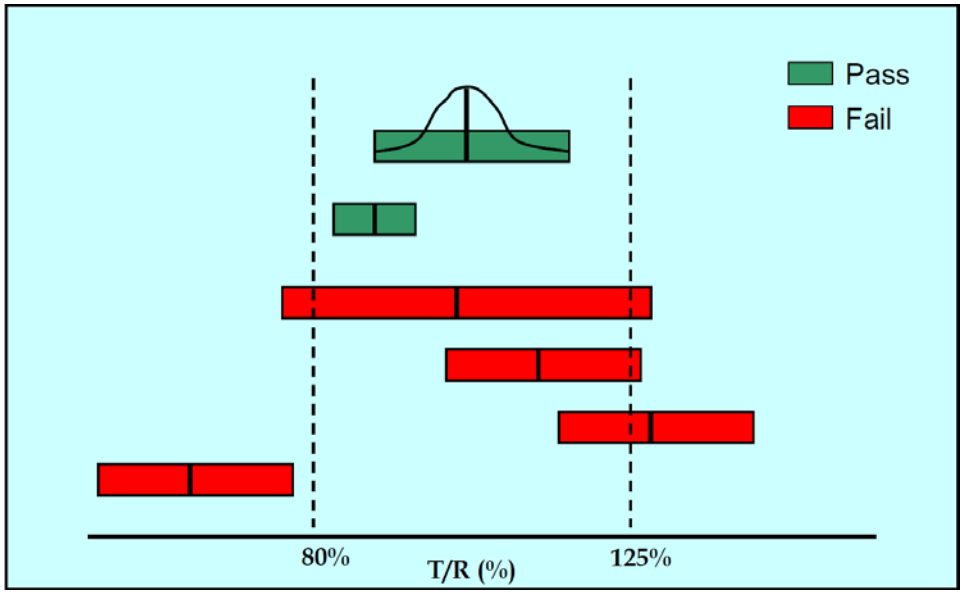
NDA	ANDA
1. Chemistry, Manufacturing & Controls (CMC)	1. Chemistry, Manufacturing & Controls (CMC)
2. Testing	2. Testing
3. Labeling	3. Labeling
4. Inspection	4. Inspection
5. Animal Studies	
6. Bioavailability	5. Bioequivalence
7. Clinical Studies	

Bioequivalence

- ***Bioequivalence*** is the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study … …

21 CFR 314.3

An Example of Bioequivalence



AUC and Cmax of T/R: 90% Confidence Intervals (CI) must fit between 80% - 125%

T = average of Test drug product

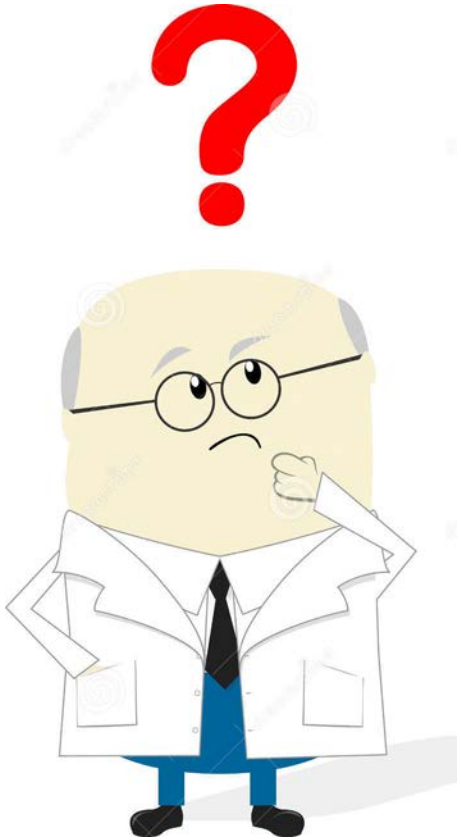
R = average of Reference drug product

Complex Products under GDUFA II

- Complex active ingredients
  - Complex mixtures of APIs, polymeric compounds, peptides
- Complex formulations
  - Liposomes, suspensions, emulsions, gels
- Complex routes of delivery
  - Locally acting such as ophthalmic, otic, dermatological and inhalational drugs
- Complex dosage forms
  - Long acting injectables and implantables, transdermals, MDIs
- Complex drug-device combinations
- Other products where complexity or uncertainty concerning the approval pathway or other alternative approach would benefit from early scientific engagement

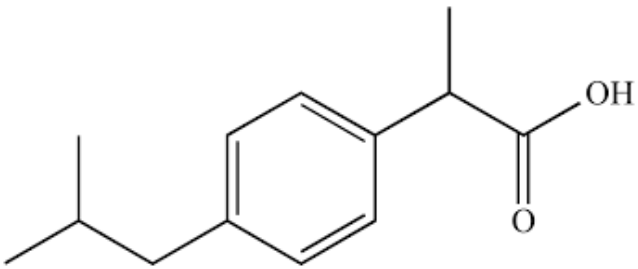
https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf

Equivalence Determination
"Simple" vs "Complex"



Traditional Approach for Establishing Equivalence of an ANDA

- Active ingredient sameness — API characterizations
- Pharmaceutical equivalence — Same dosage forms …
- Bioequivalence — PK study …



Challenges for Complex Generics

- Active ingredient sameness
  - Characterizing mixture of APIs
- Pharmaceutical equivalence
  - Characterizing complex formulation
  - Comparing inactive ingredients if needed*
  - Comparing impurities if needed
- Bioequivalence
  - Locally acting …

➢ Same clinical effect and safety profile

How to demonstrate inactive ingredients, impurities and other allowed differences in a proposed drug product do not affect its safety or efficacy???

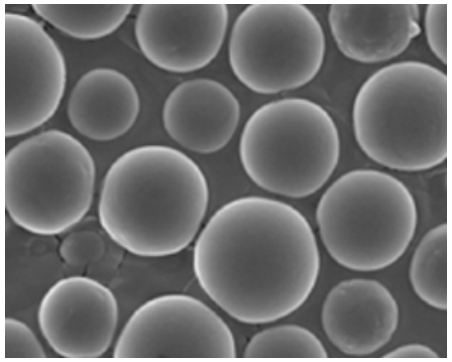
* If required under 21 CFR 314.94(a)(9) or recommended by a product specific guidance

Forensic Analysis of PLGA Microparticles

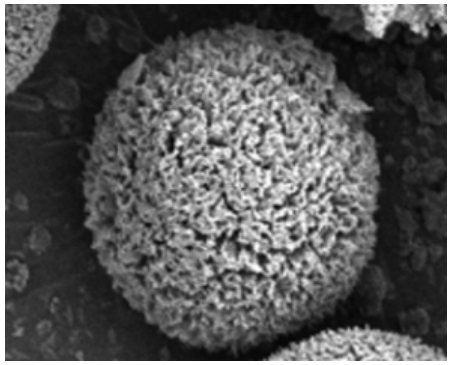
Surface Morphology

Keohane 2014 IJP Wang 2015 IJP Lu 2014 IJP Bile 2015 IJP

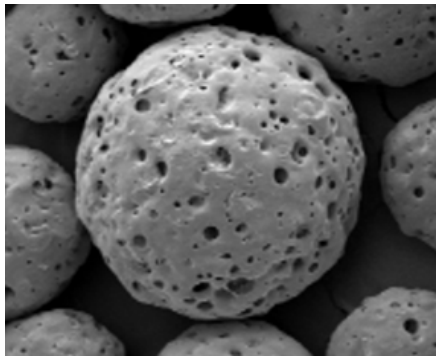
Smooth



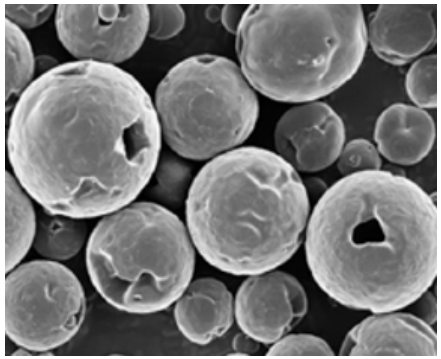
Spongy

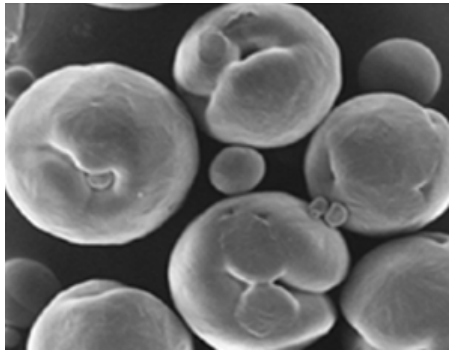


Porous

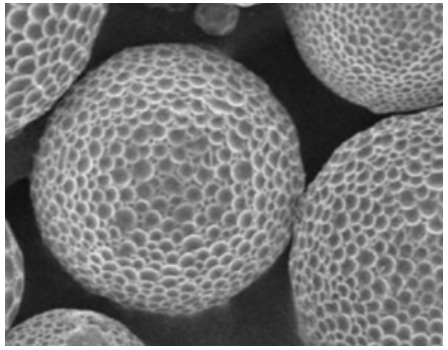


Holey

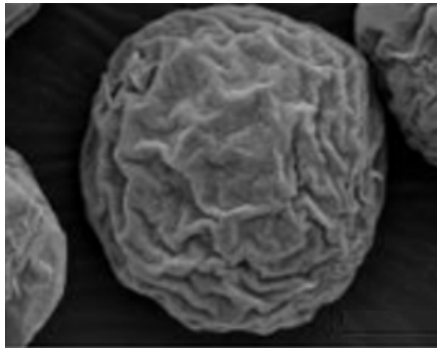




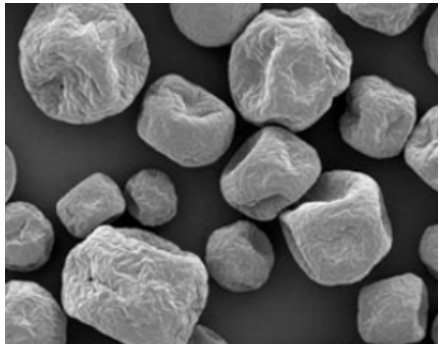
Scarred



Dimpled



Wrinkled

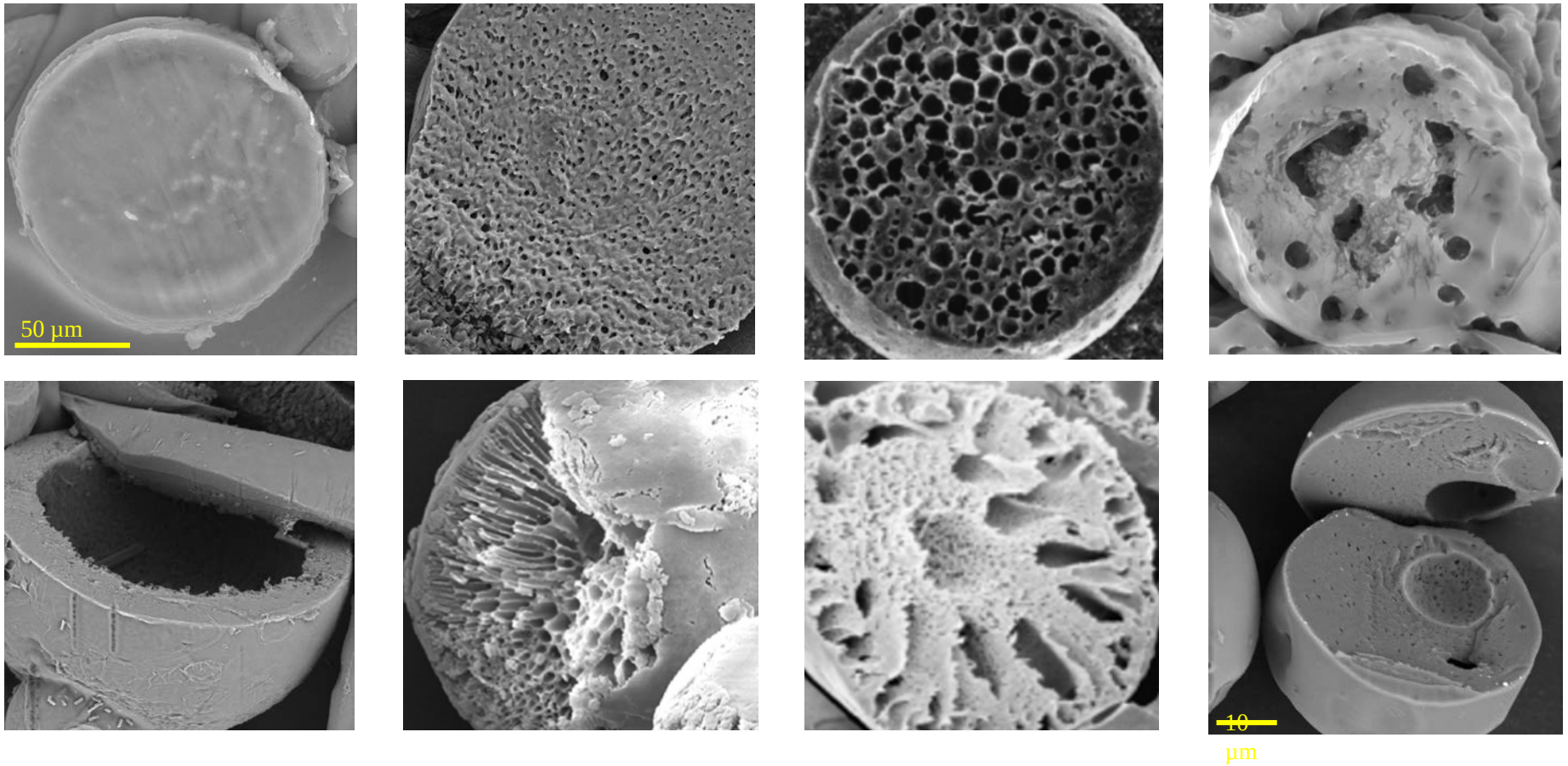


Irregular

From Dr. Kinam Park: A Long Walk to PLGA, CRS Annual Meeting 2018

Forensic Analysis of PLGA Microparticles

Inner Morphology



From Dr. Kinam Park: A Long Walk to PLGA, CRS Annual Meeting 2018

Bioequivalence Approaches

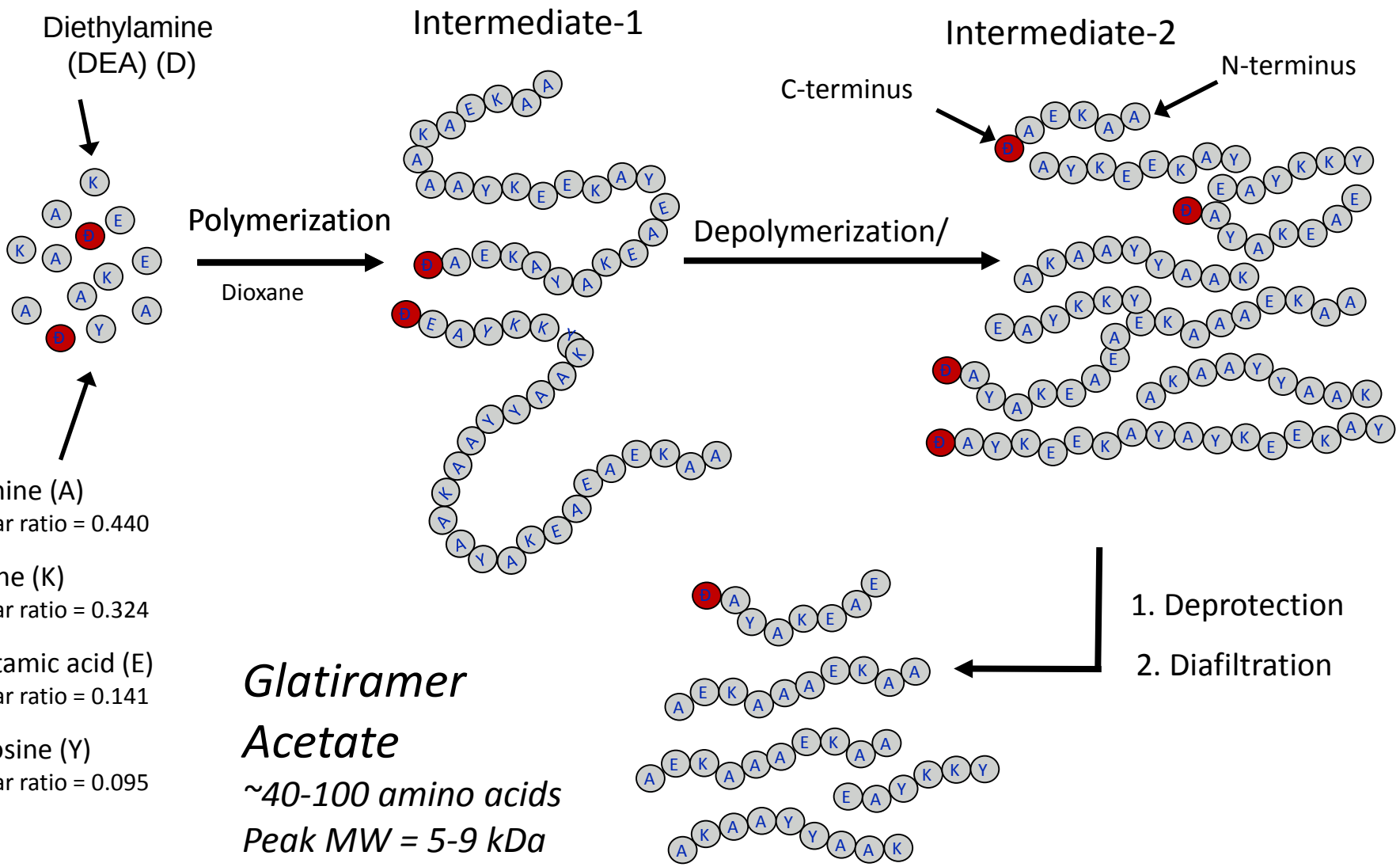
- In vivo PK study or a correlated in vitro study
- In vivo urine study
- In vivo PD study
- In vivo clinical BE study
- In vitro test acceptable to FDA (usually dissolution rate test)
- Any other approach deemed adequate by FDA to measure bioavailability or establish bioequivalence

21 CFR 320.24(b)

Copaxone (glatiramer acetate injection)

- Immunomodulator complex drug product for treatment of relapsing-remitting multiple sclerosis
- Mechanism of action is highly complex and not fully understood
- Synthetic amino acid copolymers
  - Mix of peptides formed from four amino acids at a defined molar ratio
  - With batch-to-batch variations
- NDA approved in 1996

Glatiramer Acetate Synthesis



Konfino, E. et al. *Copolymer-1 improvements in compositions of copolymers* (1999), U.S.Pat. 5,981,589.

FDA Performed Studies on Glatiramer Acetate

Anal Bioanal Chem (2015) 407:8647–8659
DOI 10.1007/s00216-015-9057-8

PAPER IN FOREFRONT

Modern analytics for synthetically derived complex drug substances: NMR, AFFF–MALS, and MS tests for glatiramer acetate

Sarah Rogstad[1] · Eric Pang[1] · Cynthia Sommers[1] · Meng Hu[2] · Xiaohui Jiang[2] · David A. Keire[1] · Michael T. Boyne II[1]

Received: 27 June 2015 / Revised: 10 September 2015 / Accepted: 16 September 2015 / Published online: 12 October 2015

FDA Published Product Specific Guidance on Glatiramer Acetate

Recommendations to demonstrate API sameness of a proposed generic product:

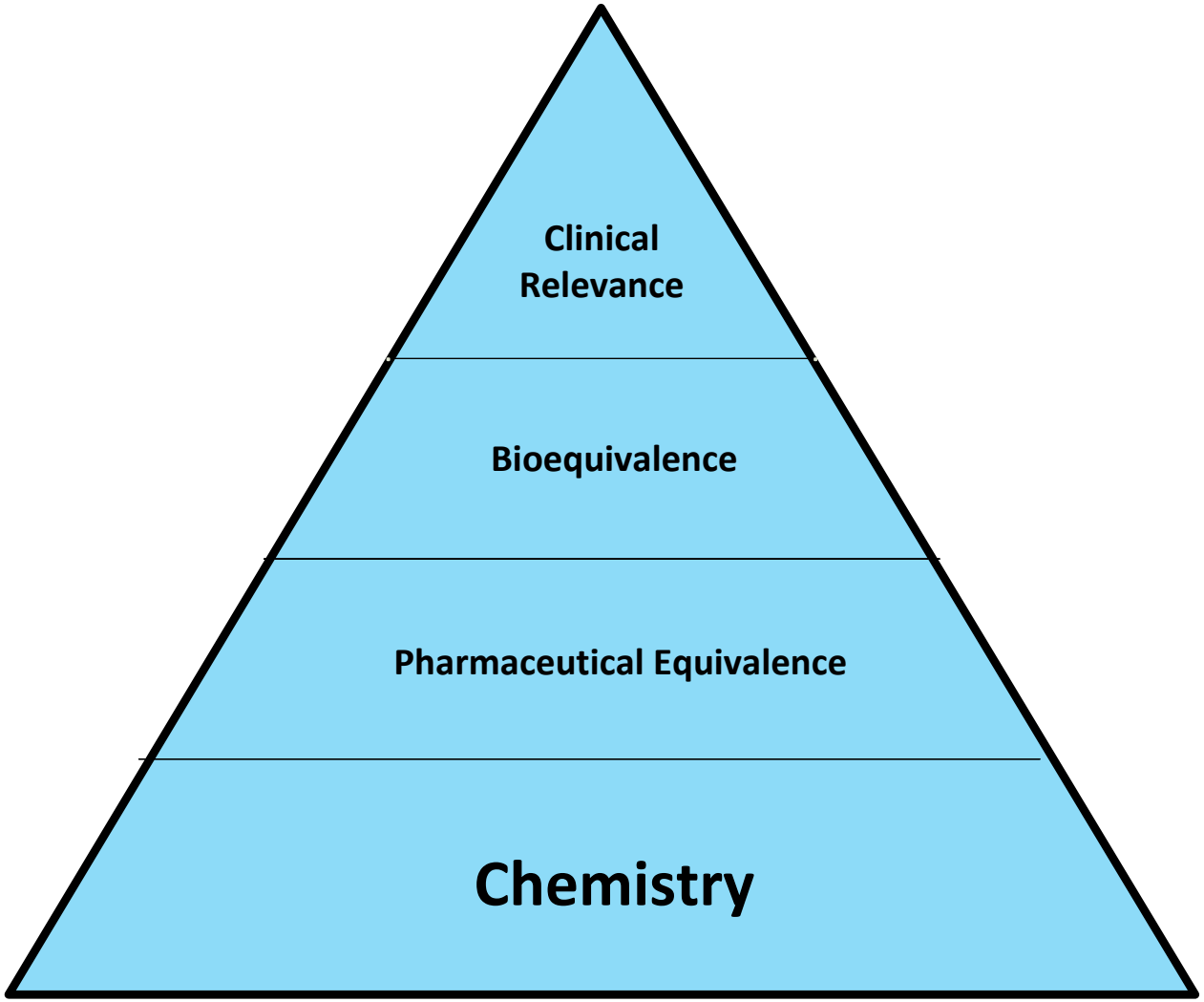
- Fundamental reaction scheme
- Physicochemical properties including composition
- Structural signatures for polymerization and depolymerization
- Results in biological assays

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM495029.pdf

Generic Glatiramer Acetate Approvals

- First generic (20 mg/mL) from Sandoz (Apr 2015)
- First generic (40 mg/mL) from Mylan (Oct 2017)
- Generic (20 mg/mL) from Mylan (Oct 2017)
- Generic (40 mg/mL) from Sandoz (Feb 2018)

Evaluations of Generic Drugs



Why is Research Part of GDUFA?

- **Patient need:** To ensure affordable high quality generics are available. Need for approval pathways for complex products that lack generic competition.
- **Industry need:** To provide a clear, cost- and time-saving ANDA submission path.
  - Alternative BE approaches to avoid costly but insensitive comparative clinical endpoint studies
- **Agency need:** To ensure confidence in the approval pathway and the equivalence of any approved products.

GDUFA II
ANDA and Research Linkage

- In the last few years we have strongly focused research toward **complex generics**
  - Lack of generic versions of complex products
  - Research is needed due to the difficulty for making generic copies of complex products
  - Anticipatory to DCAP and Commissioner level priorities
  - In the GDUFA II negotiations, industry had a strong support for efforts around complex generics

DCAP: Drug Competition Action Plan

What does GDUFA Research Support?

Inputs

- External grants and contracts
  - Identification of needs and RFP
  - Peer-review
  - Collaboration/Oversight with external PI
  - Ensure safety of human subjects
- Research in labs and offices
  - ORISE Fellows
  - Supplies and equipment

Outcomes

- Standards, Guidance and Policy Development
- Effective pre-ANDA meetings
- ANDA Evaluation
- Response to Public Health Issues

GDUFA Regulatory Science Priorities

Developing efficient and modern generic drug review tools in the following categories:

- Complex active ingredients, formulations, or dosage forms
- Complex routes of delivery
- Complex drug-device combinations
- Tools and methodologies for BE and substitutability evaluation

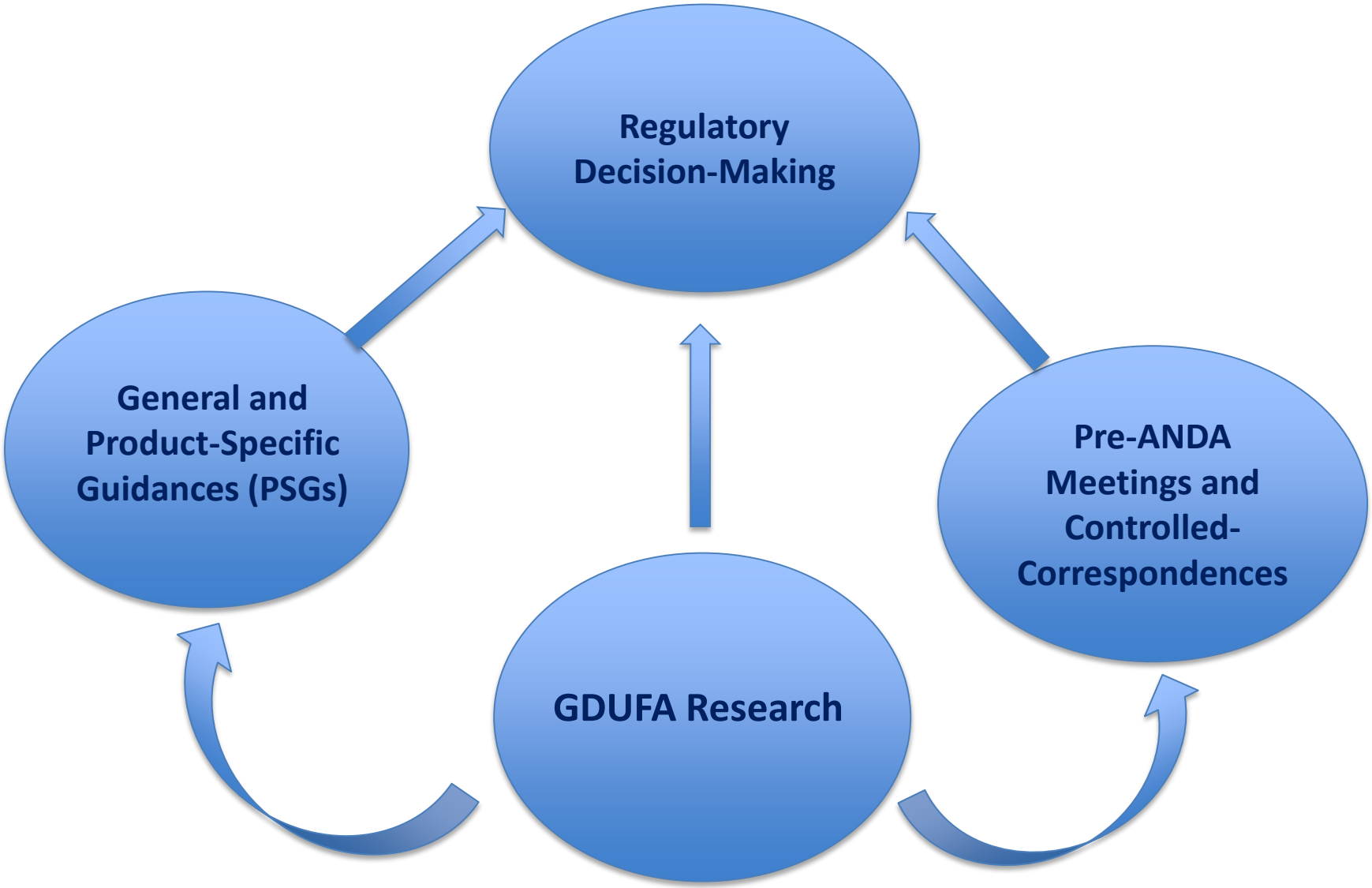
Product-specific guidance (PSG) development
Pre-ANDA meeting, ANDA review and approval

https://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/genericdrugs/ucm567695.htm

Enhanced pre-ANDA Process in GDUFA II for Complex Drug Products

- Early stage
  - Regulatory science & PSG development
  - Pre-ANDA development meeting with goals
- Mid-stage
  - Publish PSG when available
  - Pre-ANDA development meeting for alternative approaches to PSG (different class)
  - Complex control correspondence for alternative method to PSG (same class)
- ANDA submission and review
  - Pre-ANDA submission meeting with goals
  - Mid-cycle review meeting

Science Informs Regulatory Decisions



Research Outcomes

- 181 new PSGs for complex products during GDUFA I
  - 120 complex product PSG revisions
- 124 pre-ANDA meeting requests for complex products during GDUFA I
- 117 external research collaborations (grants, contracts) from OGD since GDUFA I
  - 171 peer reviewed publications

Research Outcomes: Examples

- **ANDA Approvals**
  - Glatiramer acetate, Mometasone nasal spray
- **ANDA Receipts**
  - Inhalation products including Albuterol MDIs and DPIs containing FP and SX (Advair)
- **General Guidance**
  - Abuse deterrence of generic solid oral opioids
  - Transdermal adhesion
  - Synthetic peptides referencing recombinant RLDs
- **Product-specific guidance (PSG)**
  - Conjugated estrogen
  - Cyclosporine ophthalmic emulsion
  - Acyclovir topical cream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