

Introduction to Complex Products and FDA Considerations

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Demonstrating Equivalence of Generic Complex Drug Substances and Formulations
October 6th, 2017

Reducing the Hurdles for Complex Generic Drug Development

Posted on [October 2, 2017](#) by [FDA Voice](#)

By: Scott Gottlieb, M.D.

Earlier this year, I announced our [Drug Competition Action Plan](#) to advance new policies aimed at bringing more competition to the drug market. My goal was to improve access consumers have to the medicines that they need. I consider access to medicine a matter of public health. If consumers are priced out of the drugs they need, that's a public health concern that FDA should address, within the scope of its mandate and authorities.



While FDA doesn't control drug pricing, our policies do affect competition in the market. This is the nexus of our current efforts on drug pricing.

Our plan has a number of different domains. Among them is a compilation of efforts to improve the efficiency of the generic drug approval process; and another is a group of

Formal Meetings Between FDA and ANDA Applicants of

ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin

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DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.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be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance.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 <https://www.regulations.gov>. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 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) Xiaohui Jiang at 240-402-7964.

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

October 2017
Generics



This guidance

Comments and
publication in
guidance. Sub
comments to t
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the docket num

For questions:
402-7930.



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 dermatological and inhalational drugs
- Complex dosage forms
 - Long acting injectables and implantables, transdermals, MDIs
- Complex drug-device combinations

Scope of this Workshop

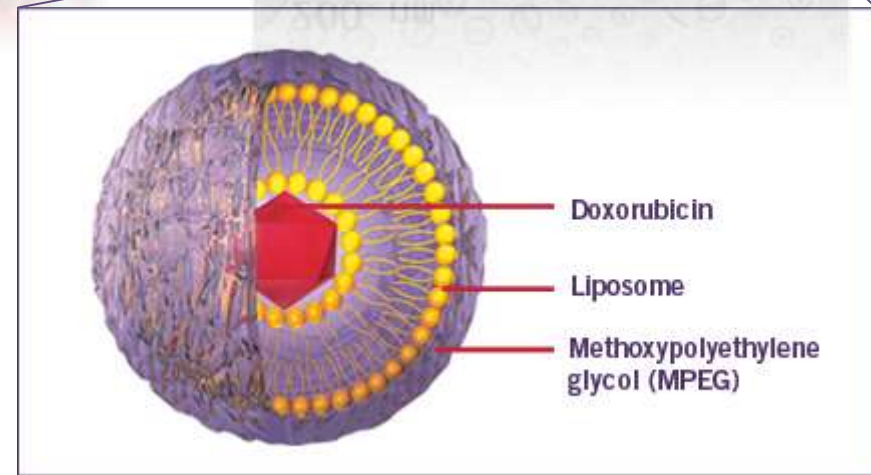
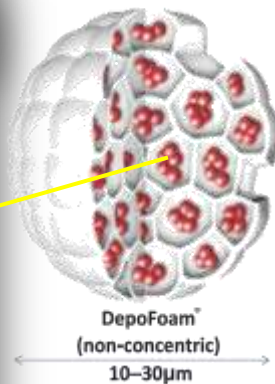
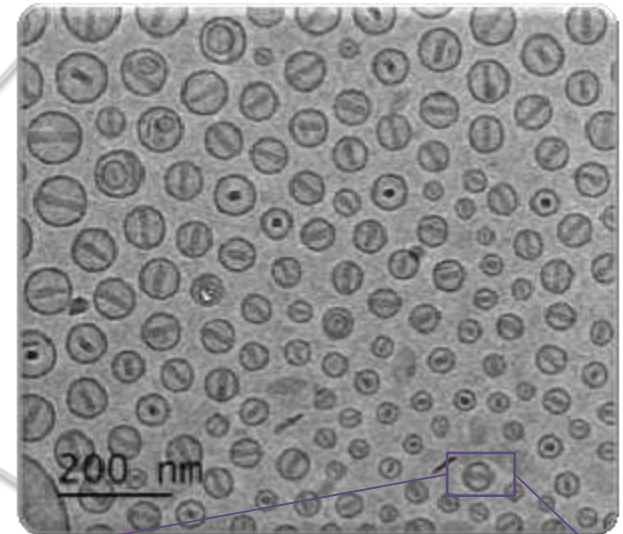
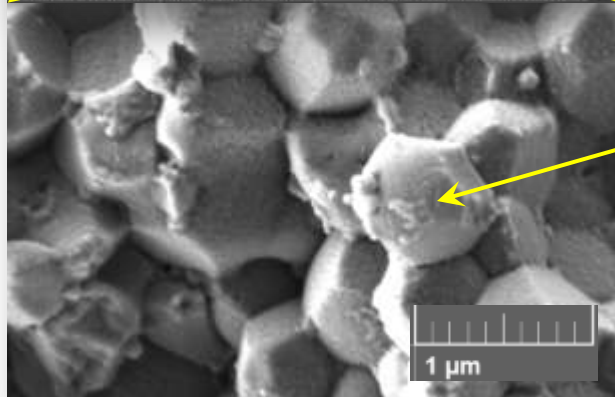
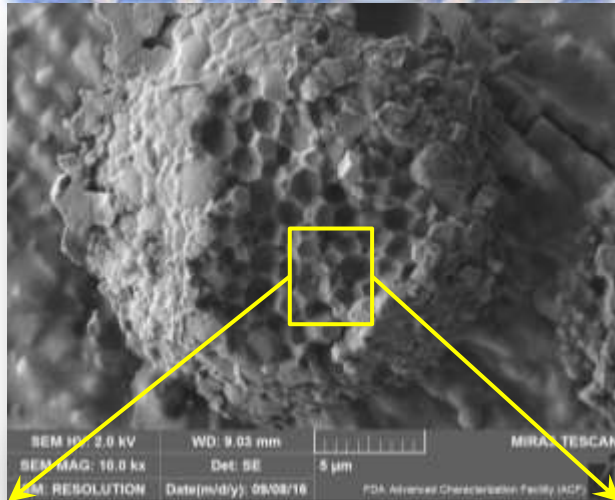
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Examples of Complex Products for this Workshop



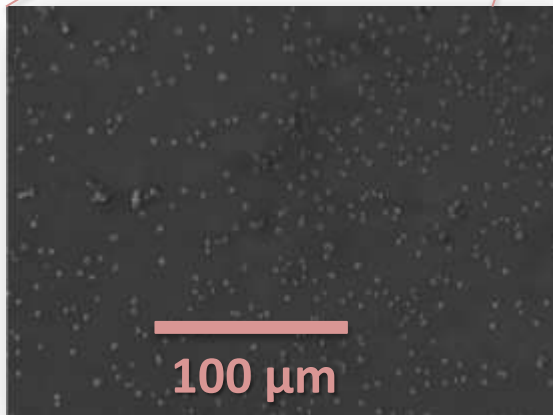
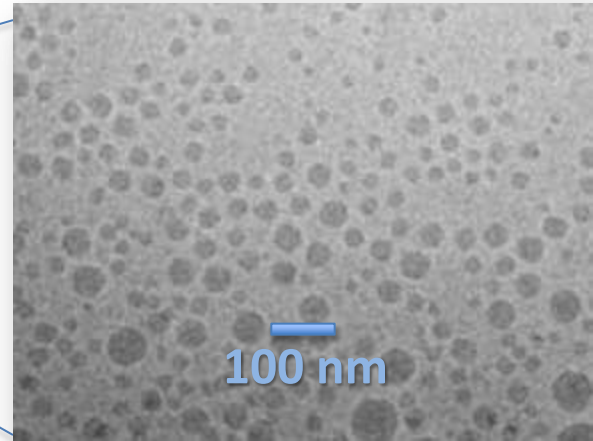
- Complex API
 - Glatiramer acetate, teriparatide, conjugated estrogens, pentosan polysulfate, sevelamer, iron sucrose
- Long acting injectable
 - PLGA: risperidone, octreotide, exenatide
 - Suspension: medroxyprogesterone, paliperidone
- Other products
 - Abraxane, Mirena, Lumason

Liposomal Products



Sources:
<http://stmedia.starttribune.com/images/exparel.jpg>
https://www.researchgate.net/profile/Kenneth_Cummings2/publication/232226382/figure/fig/2/AS:203040624779269@1425420065756/Cross-sectional-diagram-of-DepoFoam-containing-bupivacaine-image-supplied-courtesy-of.png
<https://l.pining.com/736/dc/54/b0/d654607a354e3c0b8759243f15468d40-chemotherapy-drugs-side-effects.jpg>
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<https://www.doxil.com/sites/default/files/images/hcp-mm-mechanism-of-action-img1.jpg>

Ophthalmic Suspension and Emulsion



Sources:

<http://b.kwikweb.co.za/brianroosopti/photos/eyedrop1.jpg>

https://www.restasis.com/Content/Images/MDPF/AboutMultiDose_Comparison_img.png

GDUFA Complex Products Workshops



- Oct 6th, 2017: Demonstrating Equivalence of Generic Complex Drug Substances and Formulations
- Oct 20th, 2017: Topical Dermatological Generic Drug Products: Overcoming Barriers to Development and Improving Patient Access
- Jan 9th, 2018: New Insights for Product Development and Bioequivalence Assessments of Generic Orally Inhaled and Nasal Drug Products

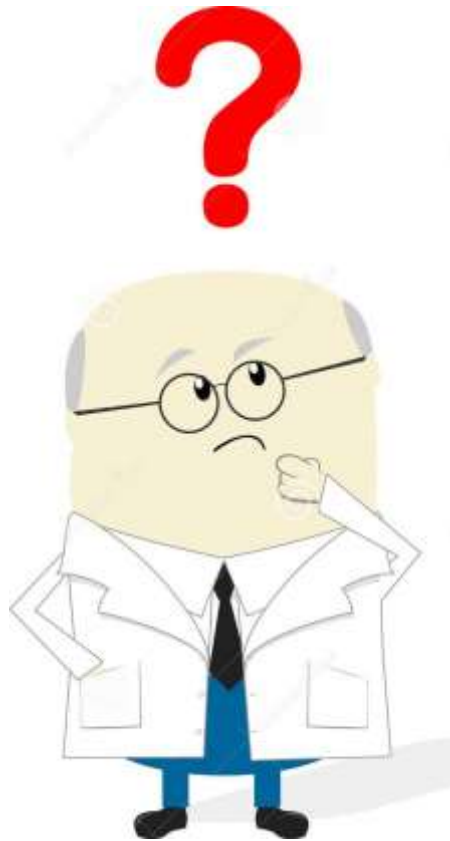


Today's Agenda

- Introduction and FDA Considerations
- Demonstrating Complex API Sameness
- Characterization of Complex Excipients and Formulations
- Novel IVRT for Complex Formulations
- Panel Discussion – Audience's Questions

Equivalence

“Simple” vs “Complex”



Promises about Generic Drugs



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

Therapeutic Equivalents

- *Therapeutic equivalents* are approved drug products that are pharmaceutical equivalents for which bioequivalence has been demonstrated, and that can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.

Considerations for Complex Generics

- Active ingredient sameness
 - Distributions for “mixtures”
- Pharmaceutical equivalence
 - Including inactive ingredients*
 - Including impurities if needed
- Bioequivalence
- **Same clinical effect and safety profile**
 - inactive ingredients, impurities and other allowed differences in the proposed drug product that do not affect the safety or efficacy of the proposed drug product
 - device



**Comprehensive
Characterizations**

* If required under 21 CFR 314.94(a)(9) or recommended by a PSG

Bioequivalence

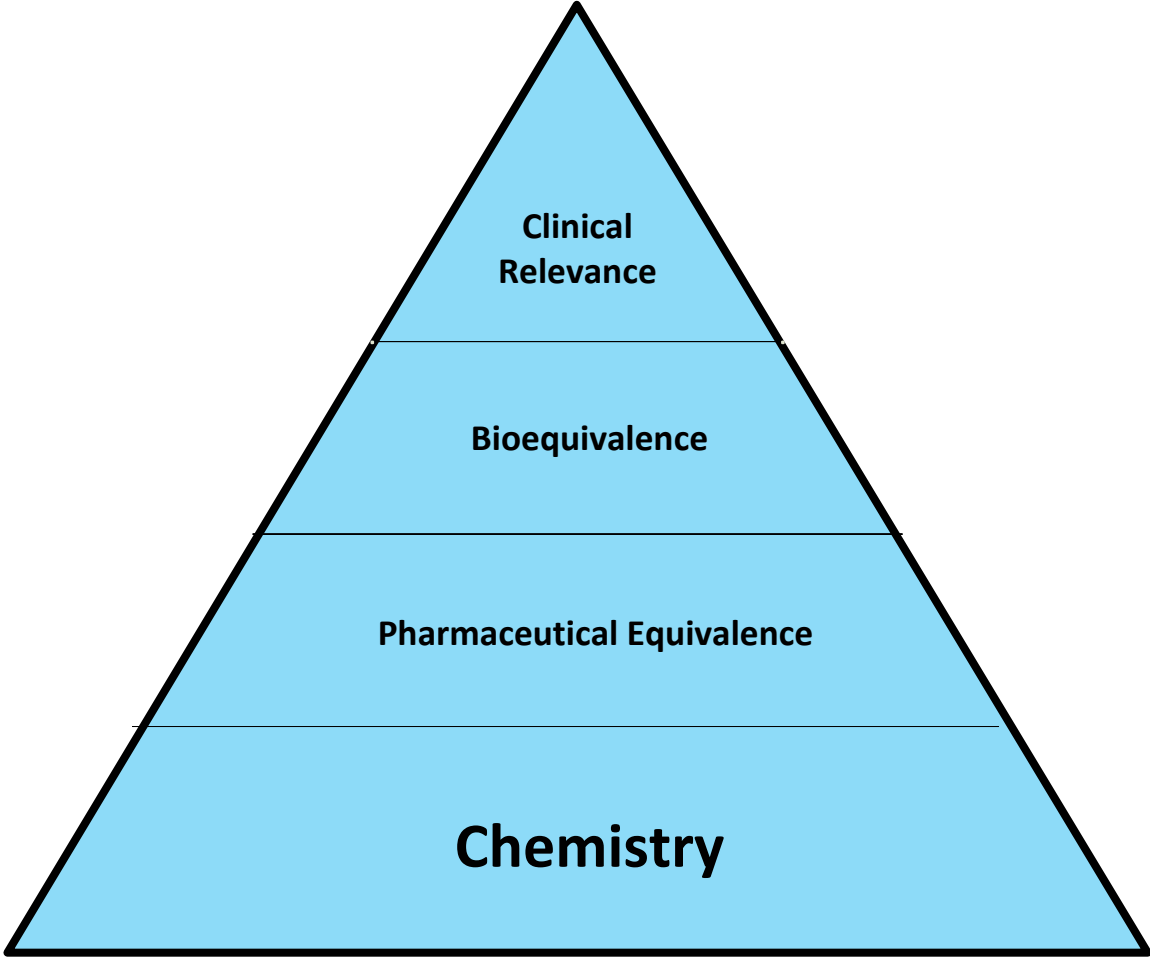
- *Bioequivalence* is the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions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

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

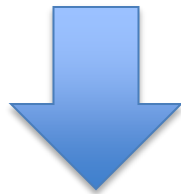
Evaluations of Generic Drugs



GDUFA Regulatory Science Priorities



- Post-market Evaluation of Generic Drugs
- Equivalence of Complex Products
- Equivalence of Locally Acting Products
- Therapeutic Equivalence Evaluation and Standards
- Computational and Analytical Tools



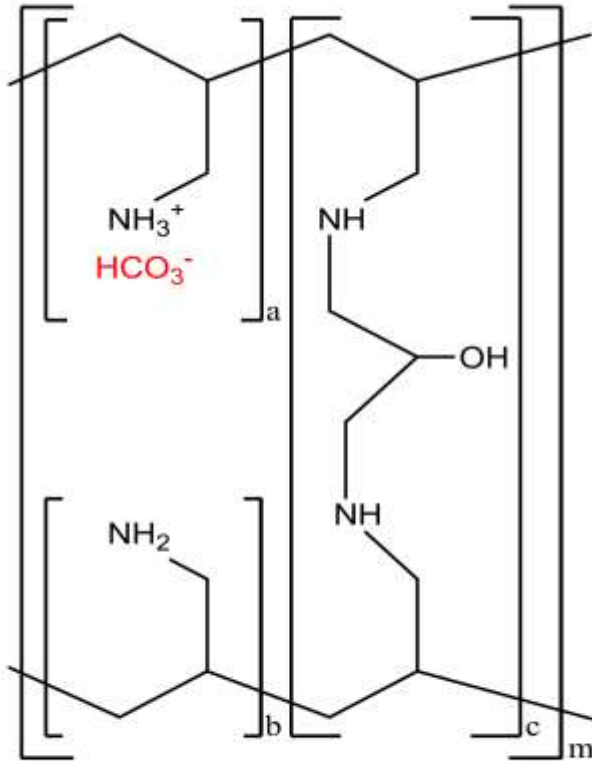
Product-specific guidance (PSG) development
ANDA review and approval

Case Study: Sevelamer Carbonate



- RLD: Renvela (sevelamer carbonate)
- Initial U.S. approval: 2007
- Dosage forms: tablets and powder for oral suspension
- Indications: a phosphate binder indicated for the control of serum phosphorus in patients with chronic kidney disease on dialysis

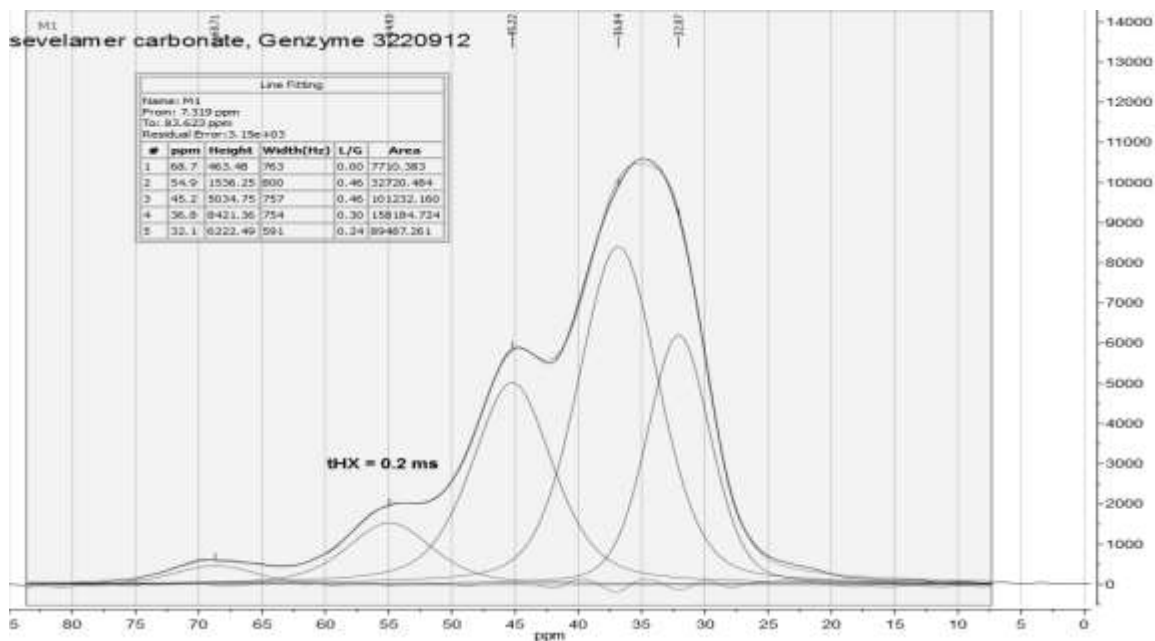
Sevelamer: Complex API



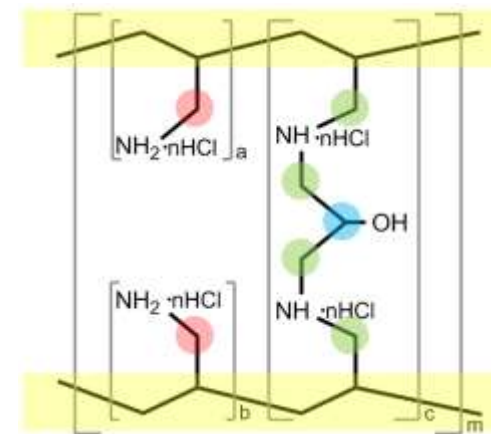
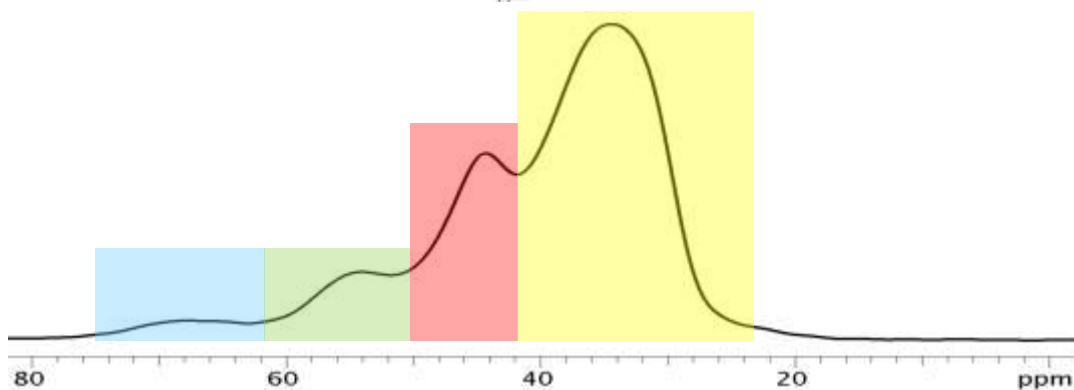
- Crosslinked polymers polyallylamine cross-linked with epichlorohydrin
- 20+ ANDAs submitted
- Internal FDA study performed on API characterizations

$a, b = \text{number of primary amine groups}$ $a + b = 9$
 $c = \text{number of crosslinking groups}$ $c = 1$
 $m = \text{large number to indicate extended polymer network}$

Solid-state ^{13}C NMR Analysis



- Individual peaks deconvoluted
- Peak areas calculated
- Relative peak areas are proportional to the number of carbon atoms in each electronic environment



Product Specific Guidance

Sevelamer Carbonate



- API sameness
 - Reaction scheme: same as on the RLD label
 - Characterizations
 - Degree of crosslinking (^{13}C solid-state NMR)
 - Degree of protonation
 - Total titratable amine
 - Particle size
 - Elemental analysis
 - Additional characterizations: FTIR, Raman, XRD, DSC ...

Product Specific Guidance Sevelamer Carbonate



- Bioequivalence
 - In vitro equilibrium binding study
 - In vitro kinetic binding study

Sevelamer Carbonate Timeline



- 2007: RLD approval
- 2008: Initial PSG (BE)
- 2009, 2010, 2011: PSG revisions (BE)
- 2012 – 2014: FDA internal studies
- 2015, 2016: PSG revision (API + BE)
- 2017: 1st sevelamer carbonate powder approval
- 2017: 1st sevelamer carbonate tablets approval

GDUFA I Research Outcomes



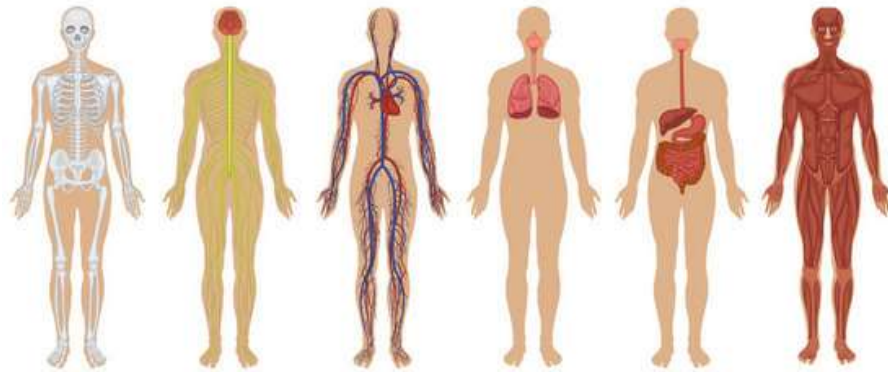
- Issued 100 of research grants and contracts
- Published 788 of PSGs (495 new and 293 revisions)
- Held 65+ pre-ANDA meetings
- Approved 4 first generic ANDAs linked to GDUFA research projects

Challenges of Analytical Characterization

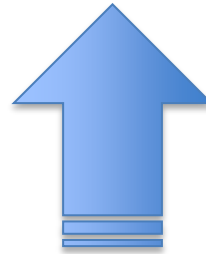


- Completeness of characterization
 - How many characterizations are needed?
- How similar is equivalent?
 - Equivalence test (statistical criteria)
 - Quality range approach (mean \pm X SD)
 - Qualitative comparison (visual displays)

Bridging in vitro and in vivo studies



In vivo performance



In vitro testing



