Session I: Demonstrating Complex API Sameness

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What Are Complex APIs

• Peptides
• Polymers
• Naturally-derived complex mixtures (including semi-synthetic mixtures)
• Other complex drug substances, such as iron-carbohydrate complexes, synthetic nucleotides
Peptides

• Important part of the US drug market (> 18 Billion $$ in 2016*) for the treatment of various diseases;
• Chemical synthesis of therapeutic peptides became a mature method with the advancement of SPPS technology;
• Development of new analytical technology makes characterizations of API and impurities possible;
• Evaluation of immunogenicity risk

Liraglutide: 3 billion $$ (2016*)
Glatiramer acetate: 4 billion $$ (2016*)

* Source: IMS Health, IMS National Sales Perspectives™. Years 2012-2016. Extracted August 2017
Polymers

• Mostly local GI drugs as sequestrants:
  – Inorganic ions (Potassium; Phosphate, etc.)
  – Bile acids

• Insoluble, complex nature of API hinders the development of generic versions

Sevelamer carbonate (Renvela®)
Colesevelam hydrochloride (Welchol®)

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Naturally-derived Complex Mixtures

• From plants:

South American Tree *Croton lechleri*  
Crofelemer for HIV-related diarrhea

Xylan from German Beechwood (Fagus sylvatica)  
Pentosan polysulfate sodium for interstitial cystitis

(Fagus sylvatica)
Naturally-derived Complex Mixtures

• From animals:
  - Pregnant mares’ urine
  - Porcine intestinal tissue
  - Conjugated estrogens for postmenopausal symptoms
  - Heparin and low MW heparin (enoxaparin) as anticoagulants

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Naturally-derived Complex Mixtures

- Broad sources of material
- Heterogeneous: natural compositional variabilities exist in reference listed drugs
- Challenging characterizations:
  - New analytical methods
  - Big data analysis/model building
Other Complex Drug Substances

Metal-complexes:

Fe:
Ferric carboxymaltose or iron deficiency anemia

Al:
Sucralfate for duodenal ulcers

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Demonstrating API Sameness

• Why: Critical part of the pharmaceutical equivalence:
  – Same active ingredient(s)
  – Same dosage form and route of administration
  – Identical in strength or concentration

• How: Explore and apply modern analytical and quantitative methods to characterize product-specific attributes to establish API sameness
OGD Supported Research Efforts

• External grants or contracts: To support analytical method development and application in complex API characterizations:
  – Pentosan polysulfate sodium (MIT*, Pacific Northwest Nat Lab*)
  – Crofelemer (Univ of Kansas*)

• Internal collaborations with FDA labs:
  – Component analysis of conjugated estrogens
  – Polymeric drug characterizations
  – Peptide impurity analysis and immunogenicity evaluations
  – Glatiramer acetate characterizations

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Research Outcomes

• Developed and/or revised 12 product specific guidances (PSGs) on complex API drugs

• Directly contributed to 3 First Generic approvals

• Developed *Guidance for Industry* on allowing ANDA submission of certain synthetic peptides referencing RLDs of rDNA origin

• Advanced science through publications and/or presentations
Speakers

• Professor Ram Sasisekharan (MIT)
  – Comparative characterization of highly heterogeneous drugs

• Dr. Daniela Verthelyi (FDA Lab Chief)
  – Scientific considerations for the assessment of immunogenicity risk of generic synthetic peptide products