

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



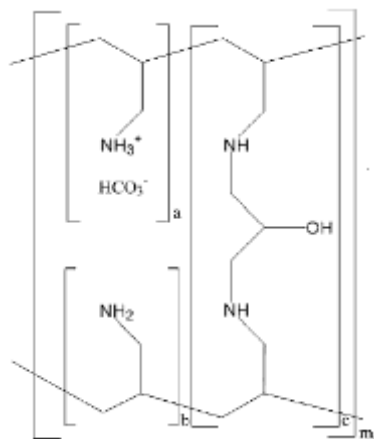
Liraglutide: 3 billion \$\$ (2016*)



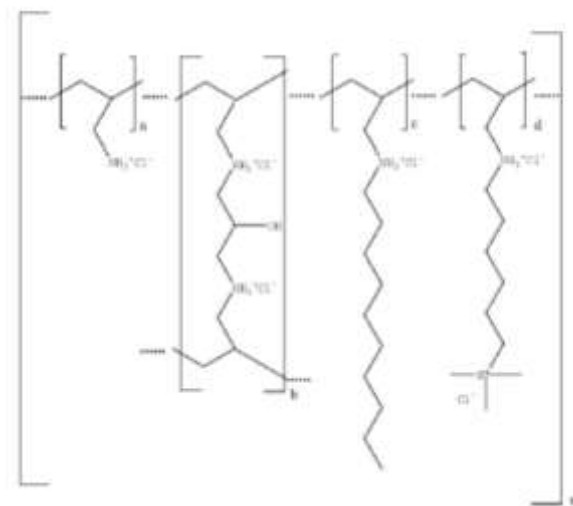
Glatiramer acetate: 4 billion \$\$ (2016*)

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



www.fda.gov Sevelamer carbonate (Renvela®)



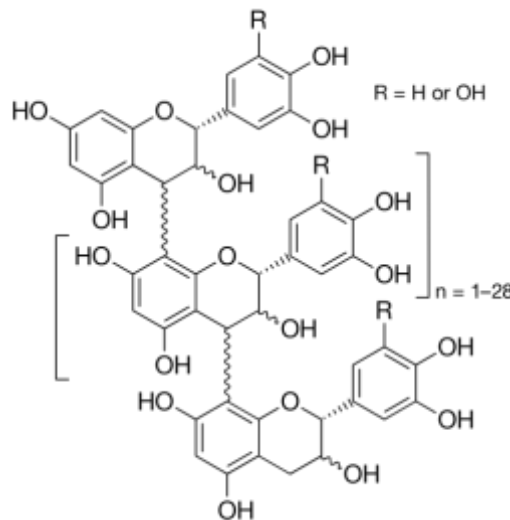
Colesevelam hydrochloride (Welchol®)⁴

Naturally-derived Complex Mixtures

- From plants:



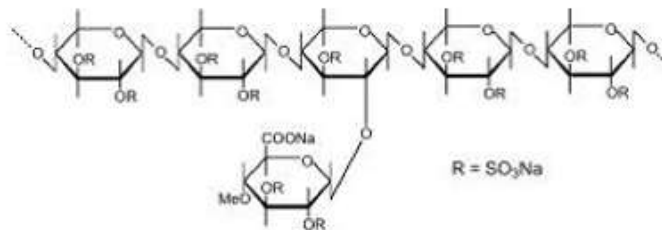
South American Tree *Croton lechleri*



Crofelemer for HIV-related diarrhea



Xylan from German Beechwood
www.fda.gov (*Fagus sylvatica*)



Pentosan polysulfate sodium for interstitial cystitis 5



Naturally-derived Complex Mixtures

- From animals:



Pregnant mares' urine



Conjugated estrogens for postmenopausal symptoms



Porcine intestinal tissue



Heparin and low MW heparin (enoxaparin) as anticoagulants

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

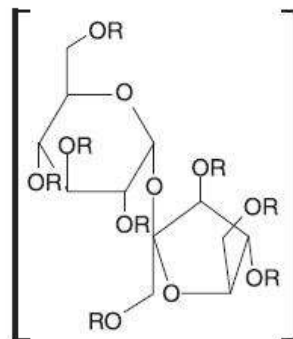
Metal-complexes:

Fe:

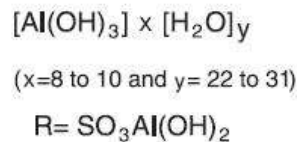


ferrous carboxymaltose
for iron deficiency
anemia

Al:



Sucralfate for duodenal ulcers



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

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*