U.S. FOOD & DRUG ADMINISTRATION

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

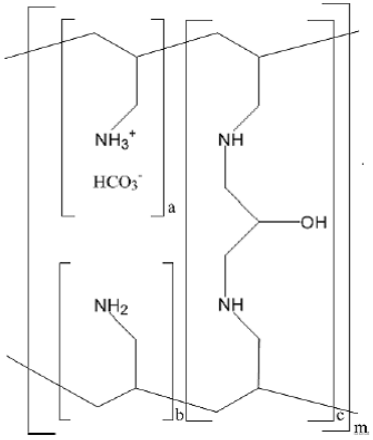
Liraglutide: 3 billion $$ (2016*)

Glatiramer acetate: 4 billion $$ (2016*)

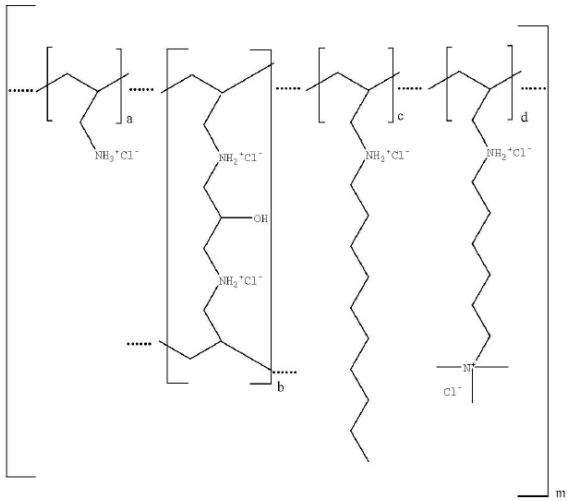
* Source: IMS Health, IMS National Sales Perspectives™. Years 2012-2016. Extracted August 2017

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®)

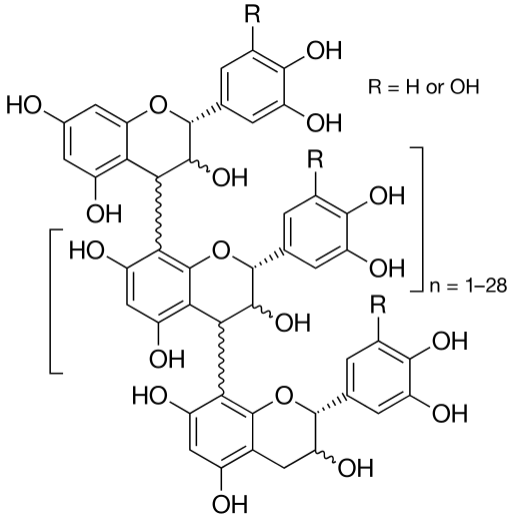


Colesevelam hydrochloride (Welchol®)

Naturally-derived Complex Mixtures

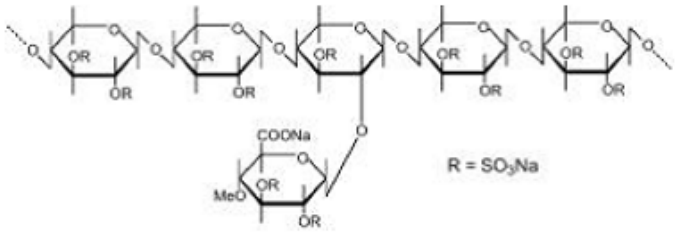
- From plants:

South American Tree *Croton lechleri*



Crofelemer for HIV-related diarrhea

Xylan from German Beechwood (Fagus sylvatica)



Pentosan polysulfate sodium for interstitial cystitis

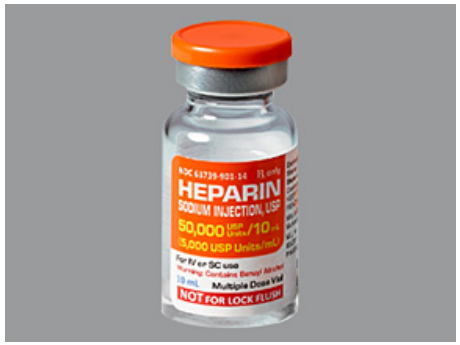
Naturally-derived Complex Mixtures

- From animals:

Pregnant mares' urine

Conjugated estrogens for postmenopausal symptoms

Porcine intestinal tissue



Heparin and low MW heparin (enoxaparin) as anticoagulants

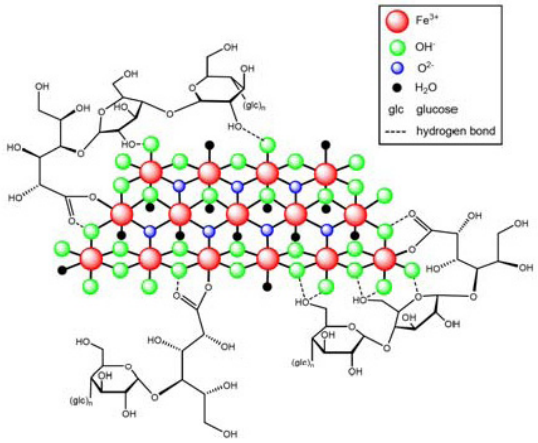
Naturally-derived Complex Mixtures

- 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

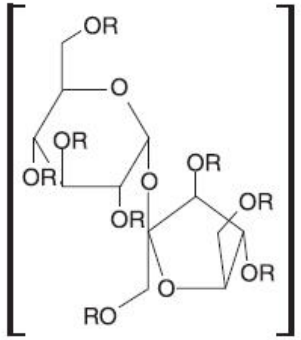
Metal-complexes:

Fe:



Ferric carboxymaltose for iron deficiency anemia

Al:



$[Al(OH)_3] \times [H_2O]_y$

(x=8 to 10 and y= 22 to 31)

$R= SO_3Al(OH)_2$

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

* Grants jointed supported by OGD and OPQ. Grant number: MIT: 1U01FD005291; PNNL: 1U01FD005288 and KU: 1U01FD005285

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*