Considerations in Demonstrating Complex API Sameness

Complex Generic Drug Product Development Workshop
Session 2: Complex Active Pharmaceutical Ingredients (APIs)

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Disclaimer

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Outline

- Introduction: API Sameness for an ANDA
- Considerations in Demonstrating Complex API Sameness: Totality of Evidence
  - Starting Material
  - Reaction Scheme
  - Structural Signature Analysis
  - Physicochemical and biological properties/impurities

Generic Drugs and API Sameness

A generic drug must be therapeutically equivalent* to the reference listed drug (RLD)

- Approved as safe and effective
- **Pharmaceutical equivalent**
- Bioequivalent
- Adequately labeled
- Manufactured in compliance with cGMP regulations

*For definition, see 21 CFR 314.3(b)

Generic Drugs and API Sameness

Pharmaceutical Equivalence (PE):

- **Contains same active pharmaceutical ingredient(s) (API)**
- Uses same dosage form and route of administration
- Is identical in strength or concentration
- PE product meets the same or compendial standards for strength, quality, purity and identity

API sameness is a requirement for generic drugs

Simple API vs Complex API

Examples of Simple API	Examples of Complex API
Small molecules with defined structure	Peptides
	Natural and synthetic polymers
Mixture of a few small molecules in a fixed ratio	Heterogenous mixture of small molecules
	Macromolecular complexes

Simple API vs Complex API

Characterizations of Simple API	Characterizations of Complex API
HPLC, MS, NMR, IR and other spectroscopic analysis if needed	MW or MW distribution, polydispersity
	Spectroscopic analysis, other physicochemical analysis if needed
PXRD, TGA, DSC, particle size distribution	Distribution of mixtures, structural signature analysis
	Biological activity and impurity analysis if needed

Complex API Sameness: Considerations

- Source of starting material
- Reaction scheme
- Structural signature analysis
- Physicochemical and biological properties/impurities

FDA takes these factors into consideration when developing product-specific guidances (PSGs) and reviewing ANDAs for products with complex APIs

Examples of Complex APIs

- Low Molecular Weight Heparins (LMWHs): Enoxaparin and Dalteparin
- Colesevelam Hydrochloride: A Synthetic Polymer

LMWHs: Enoxaparin and Dalteparin

Source of Starting Material

- LMWHs: Indicated for the prevention of deep vein thrombosis (blood clots)
  - Both Enoxaparin and Dalteparin LMWH are derived from porcine heparin*
  - Even though clinically similar, bovine heparin cannot replace porcine heparin to be used as starting material for LMWHs

* Enoxaparin and Dalteparin Labeling

Source of Starting Material

- ^{1}H NMR comparison of bovine (blue) and porcine (red) heparin

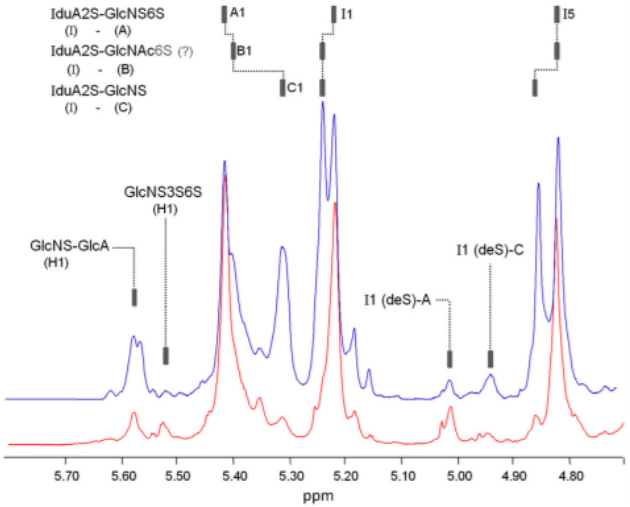
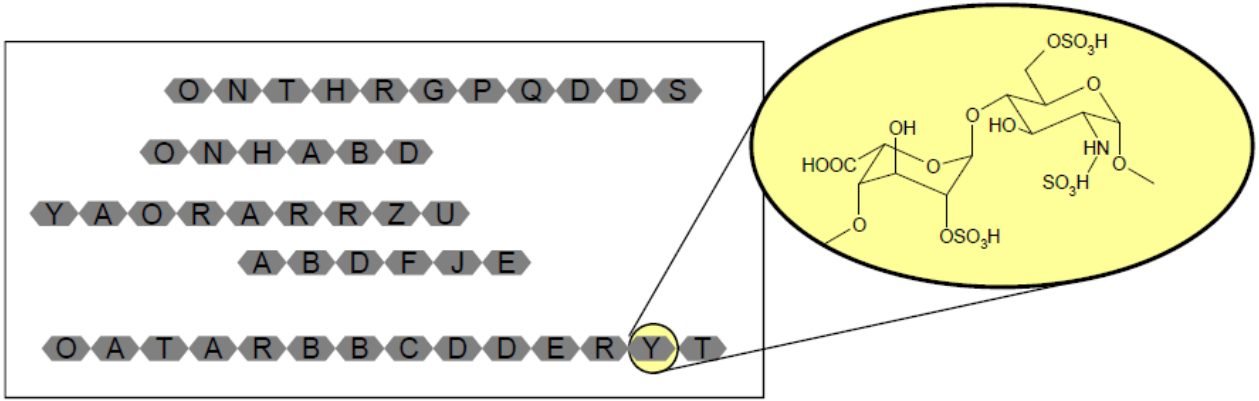


Figure 1 Analysis of the pharmaceutical preparations of bovine (in blue) and porcine (in red) heparin by 1D ^{1}H NMR spectroscopy at 800 MHz. The signals designated as A1 correspond to H1 of *N*,6-disulfated α-glucosamine units; B1 and C1 to H1 of *N*-acetylated and

Tovar AMF, et al *BMC Research Notes*, **2013**, *6*, 230

Source of Starting Material

- Heparin structure:



- Disaccharides are the building block of heparin
- The arrangement of disaccharides is controlled by the biosynthetic pathway
- Heparin from the same source and meeting the compendial standards (USP monograph) would have very similar building blocks and arrangement.

Reaction Scheme

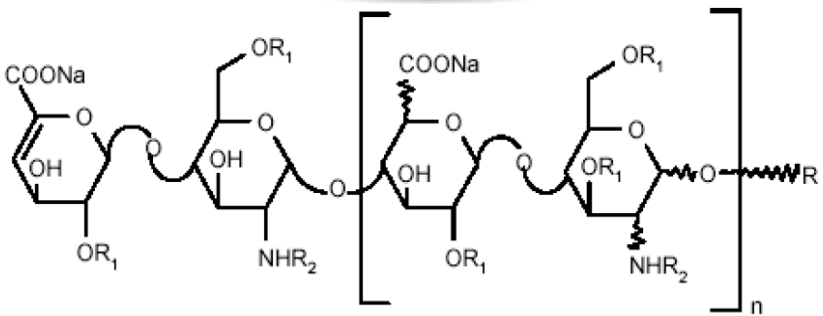
Porcine heparin

Alkaline depolymerization

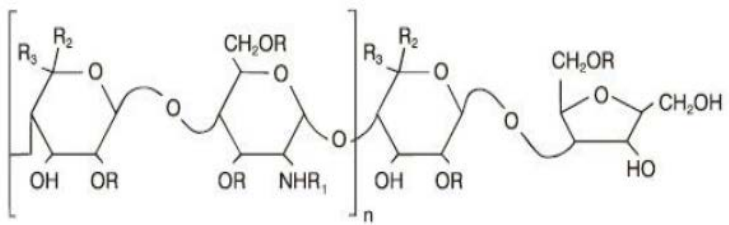
Nitrous acid depolymerization

Enoxaparin

Dalteparin



R_1 = H or SO_3Na and R_2 = SO_3Na or $COCH_3$



R = H or SO_3Na
R_1 = $COCH_3$ or SO_3Na
R_2 = H R_3 = COONa
or
R_2 = COONa R_3 = H

n = 3–20

From labeling information of Enoxaparin and Dalteparin

Reaction Scheme

- Enoxaparin and Dalteparin are all derived from porcine heparin, but through different chemical depolymerization reactions
- Same mode of depolymerization as used by RLD needs to be utilized to generate highly similar “modified” terminal building blocks for generic products

Structural Signature Analysis

- Structural signature analysis is performed in addition to physicochemical property characterizations
- There is no standard method for structural signature analysis → it is product-specific
- Structural signature analysis is an important tool to evaluate process signature

Structural Signature Analysis

- Enoxaparin:
  - Structural signatures: disaccharide building blocks, fragments after enzymatic cleavage, oligosaccharide sequence
  - Structural signatures are linked to factors such as starting heparin structures and depolymerization process parameters

Other Sameness Characterizations

- Physicochemical properties
  - Overall composition, spectroscopic data, certain USP tests
- Biological (in vitro/in vivo) activities
  - In vitro Anti-Factor Xa activity, Anti-Xa/IIa ratio
  - In vivo pharmacodynamic (PD) profile

API Sameness: Totality of Evidence Approach

- Equivalent starting material
- Equivalent reaction scheme
- Equivalent structural signature
- Equivalent physicochemical and biological properties/impurity profiles

Lee S, et al *Nature Biotech*. **2013**, *31*, 220-226

Enoxaparin PSG: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM277709.pdf

Colesevelam Hydrochloride:

A Synthetic Polymer

Starting Material and Reaction Scheme

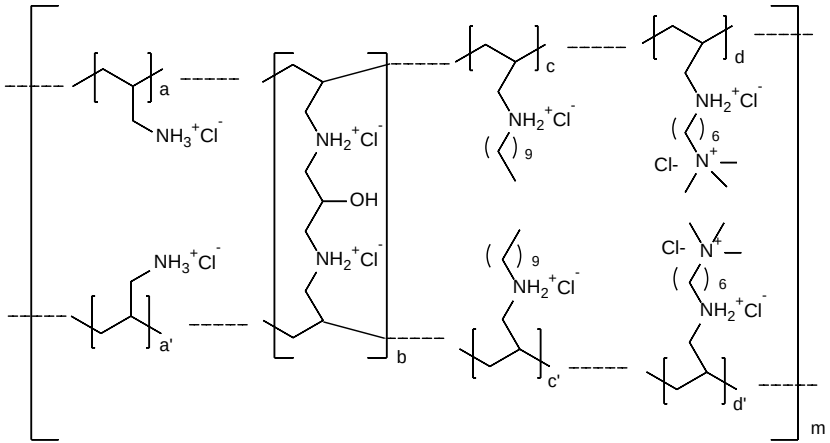
- Colesevelam Hydrochloride: Bile acid sequestrant used for the treatment of hyperlipidemia

Poly(Allylamine HCl)*

↓ Cross-linking*

Cross-linked intermediate

Alkylations*



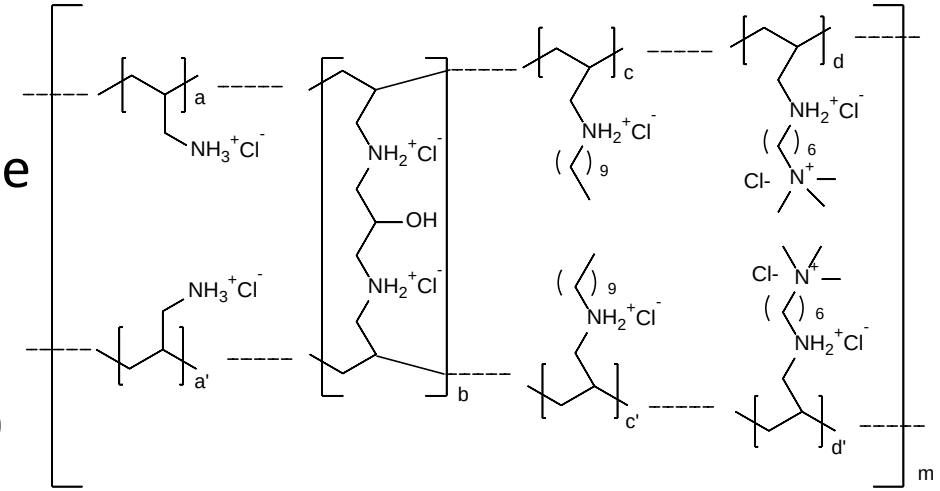
Colesevelam HCl**

*Labeling information of Colesevelam hydrochloride

** PSG on Colesevelam hydrochloride

Structural Signature Analysis

- Colesevelam HCl:
  - Define the descriptive (a+a’), b, (c+c’), and (d+d’) value; should be consistent with the structure drawn on the right
  - Analysis of cross-linked intermediate (related to b value)
  - Alkylation studies: quantify the degree of alkylations: (c+c’) and (d+d’) values



a + a’ = 2; b = 1
c + c’ = 7; d + d’ = 6
m = amount of extended polymeric network

Physicochemical Characterizations

- Spectroscopic properties (^{13}C SSNMR, FT-IR, Raman, etc.)
- Particle size distribution (related to MW)
- Solid state properties (DSC, TGA, swelling index)
- Functional group/elements (EA, Cl, Br, amines)

API Sameness: Totality of Evidence Approach

- Equivalent starting material
- Equivalent reaction scheme
- Equivalent structural signature
- Equivalent physicochemical properties

Colesevelam HCl PSG:
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm083337.pdf
And https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM224204.pdf

First Generic Approved: Tablet: 5/16/2018; Powder for Suspension: 7/16/2018

Complex API Products and PSGs

- A Complex API Product-Specific Guidance (PSG)
  - Reflects Agency's current thinking and where applicable, recommendations on complex API sameness
  - Applies the "Totality of Evidence Approach" principle with consideration of product-specific needs
  - May provide a roadmap for similar future complex API products without a PSG

Summary

- Complex API sameness can be demonstrated through a comprehensive, totality of evidence approach
- Applicant needs to evaluate product-specific issues and apply the principles accordingly
- To characterize API sameness, applicant should provide necessary literature support or justifications when new analytical methods are used and avoid data dumping

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