

Regulatory Considerations in Demonstrating Complex API Sameness

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Outline



- Introduction.
- Challenges to determine API sameness of complex APIs in generic drug product.
- Approach to establish API sameness in Complex APIs.
- Three Examples of complex APIs.

Equivalence of Generic Drugs


**Pharmaceutical
Equivalence**

+

Bioequivalence

=

**Therapeutic
Equivalence**

- 
- Contain **same active pharmaceutical ingredients** (APIs)
 - Same dosage form and route of administration
 - Identical in Strength and/or concentration

Sameness of APIs



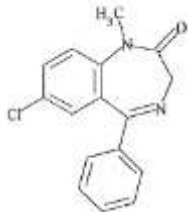
- Same Physical and Chemical characteristics as the RLD.
- Same stereochemical characteristics
- Same solid state form, where relevant.
- Impurity profile per current regulations.

Ref: [Determining Whether to Submit an ANDA or a 505\(b\)\(2\) Application Guidance for Industry](#)

Simple and Complex APIs

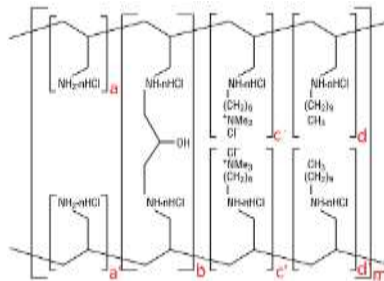
Simple APIs

- Small molecules with defined molecular weight.
- Characterized with current conventional methods.
- Impurity profile can be determined by traditional analytical methods.
- Example: Diazepam



Complex APIs

- Heterogenous mixtures of molecules, No defined MW.
- Product specific analytical techniques are required.
- Establishing impurity profile is challenging.
- Example: Colesevelam HCl



Sameness of Complex API

**Manufacturing
Process**

+

**Orthogonal
Characterization**

+

**Biological
Properties**

Starting material,
Intermediates,
CQAs and CPPs.

Structure confirmation,
Structure signature analysis,
Physicochemical properties,
impurity profile.

Comparative
biological activity
analysis, if
necessary

Literature support/justification for methods used.

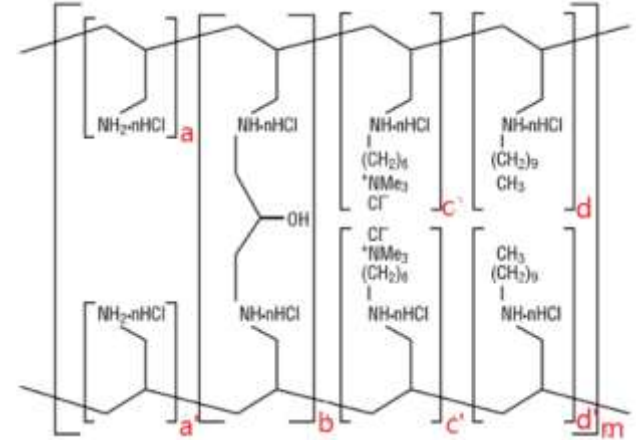
The Totality-of-the-evidence Approach

Examples of Complex APIs

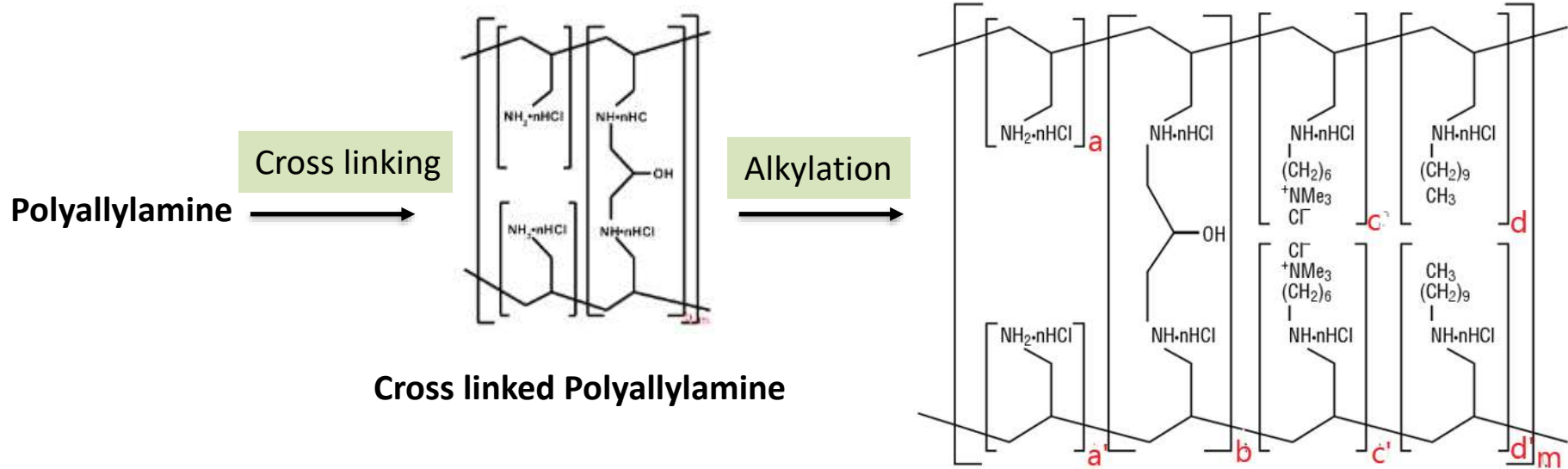
- Cross linked polymers: e.g. Colesevelam HCl
- Naturally-derived mixtures: e.g. Conjugated estrogens
- Semi-synthetic mixtures: e.g. Enoxaparin
- Synthetic peptides: e.g. Linaclotide
- Other complex drug substances, such as iron-carbohydrate complexes, synthetic nucleotides

Colesevelam Hydrochloride

- Bile acid sequestrant used for treatment of hyperlipidemia
- It is cross linked polymer with alkylated side chains.
- It is insoluble heterogenous polymeric mixture.
- Not absorbed from the gut, not metabolized, and is excreted in unchanged form with the feces.



Manufacturing of Colesevelam

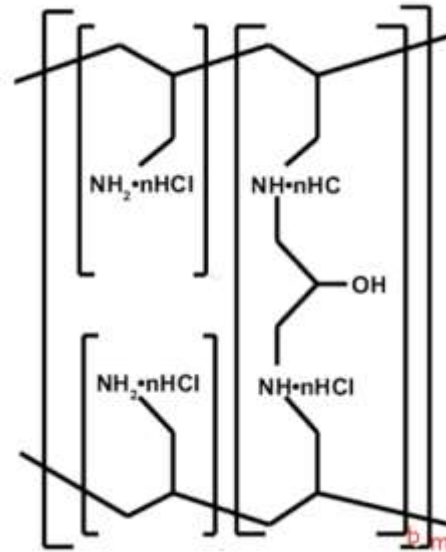


Structure signature analysis

Where: $a=a'=2$; $b=1$; $c+c'=7$; and $d+d'=6$
 'm'=amount of extended polymeric network

Characterization of Intermediate

- Polyallylamine: Molecular weight, etc
- Cross linked polyallylamine (b):
Epichlorohydrin, Degree of cross linking
by ^{13}C solid state NMR, Elemental
Analysis, Total titratable amines, DSC,
TGA, swell index, etc.
- The degree of alkylation (c, d).
- Impurity profile



Cross linked Polyallylamine

Characterization of Colesevelam

- Structure signature analysis : ^{13}C solid state NMR, FTIR, Raman, Elemental Analysis, Total titratable amines, swell index, etc.
- Solid state properties: Particle size distribution (MW), XRPD, DSC, TGA, Swell index, etc.
- Impurity profile: Related substances, PGIs, etc.
- In vitro bile acid binding capacity: Glycocholate, Glycochenodeoxycholate, Taurochenoxycholic acid and Total binding capacity.
- Compare multiple batches of Test and referenced API.

Sameness of Colesevelam HCl

Manufacturing Process

Characterization of intermediates,
Impurity profile in intermediates,
Amount of cross linking agent
Amount of alkylating agents

Orthogonal Characterization

Intermediate: Cross coupling with ^{13}C -SSNMR, elemental analysis, TTA, Sell index, DSC, TGA, etc.
API: ^{13}C -SSNMR, elemental analysis, TTA, Sell index, DSC, TGA, IR, etc.
Particle size distribution (MW), XRPD, DSC, TGA, Swell index, etc.

Biological Properties

Bile acid binding assay (GC, GCDC, TCDA and Total binding)

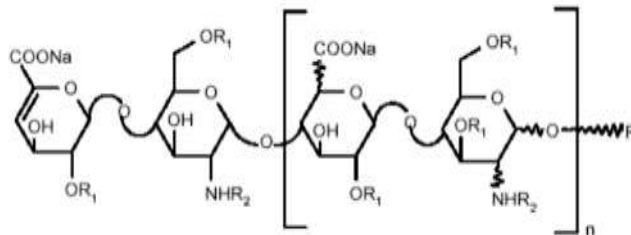
Compare at least three batches of Test and referenced API

Ref: Product specific guidance

Enoxaparin



Enoxaparin is a low molecular weight heparin which has antithrombotic properties.



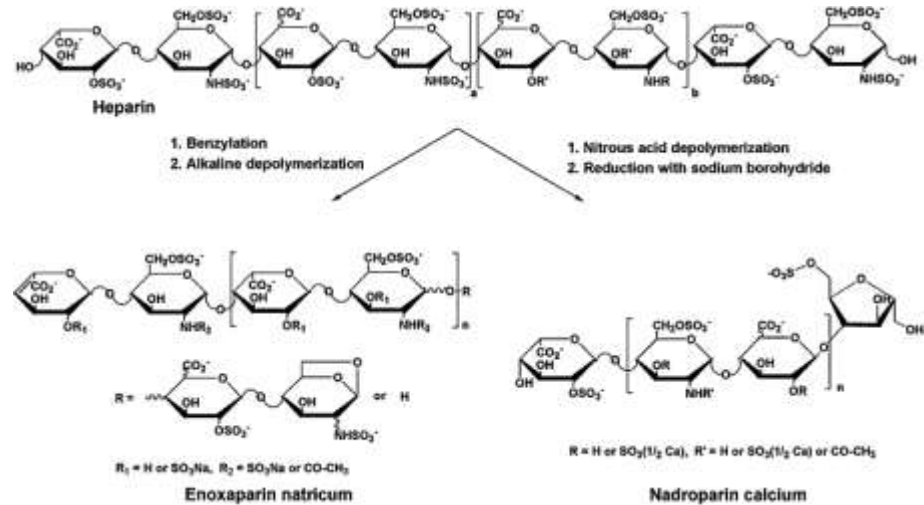
$R_1 = \text{H or SO}_3\text{Na}$ and $R_2 = \text{SO}_3\text{Na or COCH}_3$

R	$X^* = 15 \text{ to } 25\%$		$n = 0 \text{ to } 20$
	$100 - X$	H	$n = 1 \text{ to } 21$

*X = Percent of polysaccharide chain containing 1,6 anhydro derivative on the reducing end.

Manufacturing Process

- Identify CQAs and CPPs,
- Source of Heparin
- Depolymerization method
- Negative controls.



Ref: BMC Res Notes 6, 230 (2013); Carb. Poly, V 99, 2014, P 339-344

Structure Signature Analysis



- Equivalent Disaccharide building blocks
- Equivalent Sequence of oligosaccharide species
- Fragment mapping, etc
- Equivalent Physicochemical properties (MW, etc)
- Equivalence in *in-vitro* biochemical assays (Coagulation)
- Evaluate impurity profile

Sameness of Enoxaparin



Manufacturing Process

Source of starting material
Depolymerization method

+

Orthogonal Characterization

Structure fingerprint analysis, which involves extensive chromatographic separation, mass spectrometry, and 1D and 2D NMR studies.
Equivalence of physicochemical properties (MW, etc)

+

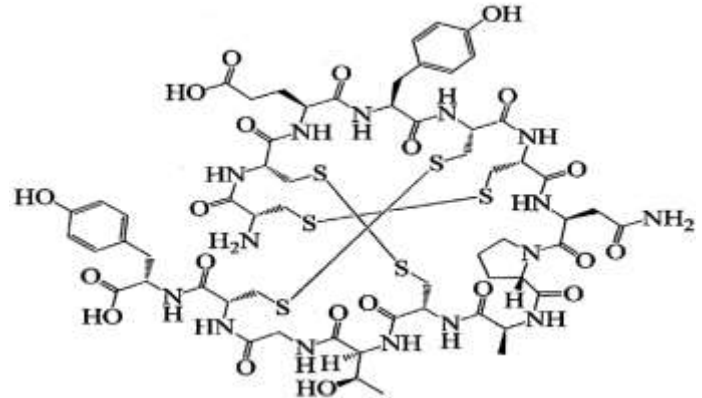
Biological Properties

Invitro biological assay

Linacotide

- An oligo-peptide agonist of guanylate cyclase 2C, approved for the treatment in adults of constipation-predominant irritable bowel syndrome and chronic idiopathic constipation.

L-cysteinyl-L-cysteinyl-L-glutamyl-L-tyrosyl-L-cysteinyl-L-cysteinyl-L-asparaginyl-L-prolyl-L-alanyl-L-cysteinyl-L-threonyl-glycyl-L-cysteinyl-L-tyrosine, cyclic (1-6), (2-10), (5-13)-tris(disulfide).



API sameness of Linaclotide



- Manufacturing process
- Primary peptide sequence and stereochemical properties
- Configuration of the three disulfide bonds
- Impurity profile
- In vitro biological activity (e.g., binding, functional assays)

Totality of evidence Approach is used

*Ref: Product specific guidance,
ANDAs for Certain Highly Purified Synthetic Peptide Drug Products that Refer to
Listed Drugs of rDNA Origin*

Summary



- Through a comprehensive, totality of evidence approach.
- Each complex API has its own challenges, apply the recommendations and required principles as needed.
- Establish CQAs and CPPs in manufacturing process.
- Developing negative controls.
- Characterize multiple lots for both the proposed generic drug product and reference product.
- Provide all the required data and literature support.

Resources-1

- Product specific guidance (PSG) for FDA, Compendial monographs, Scientific literature
- Meeting with ANDA applicants like
 - Product development meeting
 - Pre-submission meetings
- Teleconferences to clarify deficiencies



Resources-2

Controlled Correspondence Related to Generic Drug Development Draft Guidance for Industry:

<https://www.fda.gov/media/109232/download>

Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA Guidance for Industry:

<https://www.fda.gov/media/107626/download>

Product-specific Guidance:

<https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development>

DMF Website:

<https://www.fda.gov/drugs/forms-submission-requirements/drug-master-files-dmfs>



Acknowledgements

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Thank You!



Please refer to the following posters for cross-referenced materials:

- Synthetic Therapeutic Polymers: Recommended documentation for API sameness by Bapu Gaddam
- Synthetic Peptide APIs of generic complex drug products: Recommendations for API sameness by Manivannan Ethirajan
- Regulatory Considerations for Synthetic and Semi-synthetic Oligosaccharide Complex APIs in Generic Products by Keduo Qian

If you have any questions, please type them into the Q&A box in the bottom right hand corner of your screen so that we can address them during the scheduled Q&A panel after this presentation.

If you have a question on this presentation after this workshop is over, send them to DMFworkshop2021@fda.hhs.gov by March 19th for inclusion in the Follow-on webinar on April 9th.