SBIA-DMF Drug substance workshop

March 3 & 4, 2021 (Virtual)

Regulatory Considerations for Synthetic and Semi-synthetic Oligosaccharide Complex APIs in Generic Products

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Division of Lifecycle API/Office of New Drug Products/Office of Pharmaceutical Quality/CDER/FDA
March 3 & 4, 2021
Virtual

PURPOSE

Synthetic and semi-synthetic oligosaccharides [e.g. Low molecular weight heparins (LMWH), Pentosan polysulfate sodium (PPS)] are a group of complex APIs with heterogeneous mixtures of oligosaccharide components. LMWHs are produced by depolymerization of the unfractionated heparin (UFH) from porcine intestinal mucosa. Their molecular weights are generally below 9000 Da. Currently, Enoxaparin sodium, Dalteparin sodium, and Tinzaparin sodium are approved for the treatment of deep venous thrombosis (DVT) in the United States. Pentosan polysulfate sodium (PPS) is a semi-synthetic heparin-like macromolecular carbohydrate derivative, containing complex mixture of oligosaccharides (4000 to 6000 Da) prepared from naturally-occurring xylan extracted from the beenchwood tree. It is indicated for the relief of bladder pain or discomfort associated with interstitial cystitis. This poster will present the Agency's current thinking on the review of oligosaccharide complex APIs.

METHOD(S)

LMWH – PE FIVE CRITERIA

1. Equivalence of physicochemical properties
2. Equivalence of heparin source material and mode of depolymerization
3. Equivalence in disaccharide building blocks, fragment mapping, and sequence of oligosaccharide species
4. Equivalence in biological and biochemical assays
5. Equivalence of in vivo pharmacodynamic (PD) profile

PPS – PE THREE FOCUS

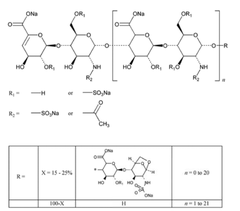
1. Source of naturally-occurring starting material
2. Physicochemical properties – molecular weight distribution, characteristic fingerprints equivalence including sulfaction degree, sodium content, Raman/IR.
3. Equivalence of monosaccharide building block composition and chain branching – xylose units, sulfation pattern, glucuronic acid groups, linkage, and anomeric configurations.

RESULT(S) – LMWH REVIEW ISSUES

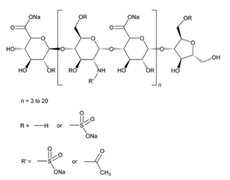
Comparison of LMWHs available in the United States

	Enoxaparin Sodium	Dalteparin Sodium	Tinzaparin Sodium
Brand name	Lovenox	Fragmin	Innohep
Innovator	Sanofi-Aventis	Pfizer	Leo
Depolymerization mechanism	Alkaline β-elimination of the benzyl ester derivative of heparin	Controlled nitrous acid depolymerization	Heparinase digestion
Weight-average molecular weight (Mw)	4,500 Da (ranges between 3800 – 5000 Da)	6,000 Da (ranges between 5600 – 6400 Da)	6,500 Da (ranges between 5500 – 7500 Da)
Molecular weight distribution	< 2000 Da: ~ 16% (12.0 – 20.0%) 2000 – 8000 Da: ~ 74% (68.0 – 82.0%) > 8000 Da: < 18.0%	< 3000 Da: 3.0 – 15% 3000 – 8000 Da: 65.0 – 78.0% > 8000 Da: 14.0 – 26.0%	< 2000 Da: < 10% 2000 – 8000 Da: 60 – 72% > 8000 Da: 22 – 36%
Anti-Xa/Anti-IIa ratio	3.3 – 5.3	1.9 – 3.2	~ 2.8
Anti-Xa activity (IU/mg)	90 – 125	110 – 210	~ 100

Enoxaparin Sodium



Dalteparin Sodium



Sample Comparison:

1. Compare at minimum 3 commercial scale batches with multiple reference listed drug (RLD) lots.
2. The Agency can not evaluate sameness comparison data with other approved generic LMWH. Per 505(j) and the citizen petition response, the demonstration of sameness can only be done using the RLD.

Manufacturing:

1. Fulfill Criterion #2, equivalent heparin source material and same mode of depolymerization. Manufacturing details impact the composition and the MWD of the final LMWH. The resulting composition and content of the oligosaccharides are critical for pharmaceutical equivalence to the RLD.
2. Process parameters should be evaluated for criticality and the acceptance range should be determined based on the sameness per PE Criteria 1 and 3. Correlation of Critical process parameters (CPPs) to critical quality attributes (CQAs) should be studied thoroughly.
3. In addition to the USP requirements for Heparin Sodium, the Agency requires characterization of the building blocks, because they have an inherent direct impact on the final sameness of LMWH to the RLD:
   - Test for major disaccharides and tetrasaccharides in the Heparin sodium specification.
   - Tests for 1,6-anydro building blocks, content of trisaccharides, content of tetrasaccharides including the "linkage isomer" (ΔGlyser).
   - Establishing acceptance criteria based on analysis of multiple batches of Heparin Sodium USP.

Primary Characterization Methods:

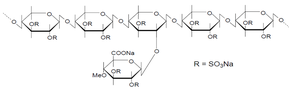
1. Develop a combination of low and high resolution techniques to characterize the structural signatures of LMWHs. High resolution methods include, but are not limited to, chain mapping/disaccharide building block/fragment mapping by SAX-HPLC (strong anion exchange), composition fingerprint quantitation by NMR, etc.
2. Quantitative Comparison Criteria (use Enoxaparin as example):
   - Peaks comprising more than 10.0% of the total peak area: 90% $_{\text{Lovenox min}}$ to 110% $_{\text{Lovenox max}}$
   - Peaks greater than 1.0% but less than 10.0%: 75% $_{\text{Lovenox min}}$ to 125% $_{\text{Lovenox max}}$
   - Peaks above the LOQ of the method up to 1.0%: a qualitative peak comparison is acceptable
   - In DBB, a specific tri-sulfated ΔIS should be controlled at 95% $_{\text{Lovenox min}}$ to 105% $_{\text{Lovenox max}}$
3. To ensure drug substance quality, selected primary characterization tests should be included in the DS release/stability specification.

Negative Controls:

1. In order to demonstrate the specificity and sensitivity of the primary characterization methods with respect to the structural fingerprints, it is important that applicants develop sufficient negative controls that cover all the manufacturing process parameters which can potentially affect the structural fingerprints.
2. They are expected to meet and/or marginally pass the basic criteria of all USP requirements, such as MWD, 1,6-anhydro content, and bioassays specified in the RLD labeling, but should fail at least some of the sameness characterization tests (e.g. chain mapping, chemical composition by NMR fingerprint, DBB mapping, etc) that capture the process signatures of individual manufacturing process steps.
3. Negative control should be applied to all the sameness characterization tests.
4. Results of negative controls should be compared to multiple RLD lots.

RESULT(S) – PPS REVIEW ISSUES

Pentosan Polysulfate Sodium



Sample Comparison:

1. Compare at minimum 3 commercial scale batches with multiple reference listed drug (RLD) lots.
2. The RLD drug product formulation (capsule) contains API PPS (as a complex mixture polymer) and excipients. Extraction of PPS from RLD is necessary. Complete and clean recovery (per label claim) of PPS from RLD should be demonstrated so that the analytical results represent all PPS components within RLD.

Manufacturing:

1. Source material sameness: the natural raw material used for manufacturing should be specified. The identification of the plant species should be up to the cultivar.
2. The essential structural features of the API can be impacted by the natural source and the manufacturing mechanism. Thus, manufacturing details and all process parameters should be reported.
3. Detailed process developmental study on the correlation of CPP ranges to CQAs is requested.

Primary Characterization Methods:

1. Full characterization and comparative data against the RLD are required for sameness for all structural features (i.e. building blocks, types and positions of linkages and their order). This should be achieved by a combination of low and high resolution techniques.

Negative Controls:

1. To demonstrate the specificity and sensitivity of the analytics with respect to the structural fingerprints, sufficient negative controls should be developed to cover all the manufacturing process parameters that can potentially affect the structural fingerprints. It is recommended that the test results on negative controls is compared to the equivalence criteria established based on at least three RLD lots.

CONCLUSION(S) *– COMMON DEFICIENCIES*

1. Manufacturing CPP ranges are not justified by CQA tests.
2. Negative control batches were not developed properly.
3. Insufficient data is provided to establish drug substance sameness.
4. Primary characterization methods are not validated properly.
5. Drug substance specification doesn't include any primary characterization tests to ensure quality.

Regulatory Considerations for Synthetic and Semi-synthetic Oligosaccharide Complex APIs in Generic Products

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– Chemist

Division of Lifecycle API
Office of New Drug Products
Office of Pharmaceutical Quality, FDA/CDER

Purpose(s)

Synthetic and semi-synthetic oligosaccharides: Low molecular weight heparins (LMWH), Pentosan polysulfate sodium (PPS), etc

- In order to assist applicants preparing an abbreviated new drug application (ANDA), the Agency has published product specific draft guidance on Enoxaparin sodium, Dalteparin sodium, and Pentosan polysulfate sodium (PPS).
- We will present the Agency's current thinking on the active ingredient sameness assessment of oligosaccharide complex APIs in generic and reference products.
- Topics on the source material equivalence; sample preparation; CPP and CQA; primary characterization methods; and negative controls will be covered.

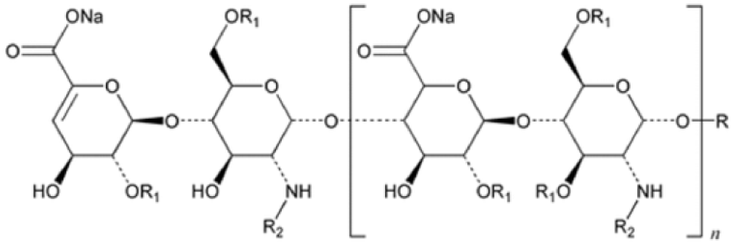
Low Molecular Weight Heparins (LMWH)

LMWH products are anticoagulants that are produced by depolymerization of unfractionated heparin. In comparison with heparin, LMWH has the advantage of lower adverse event of heparin-induced thrombocytopenia (HIT), which can be fatal.

Currently, Enoxaparin sodium (Lovenox®), Dalteparin sodium (Fragmin®), and Tinzaparin sodium (Innohep®) have received US Food and Drug Administration (FDA) approval for the treatment of deep venous thrombosis (DVT) in the United States.

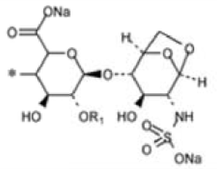
Low Molecular Weight Heparins (LMWH)

Enoxaparin Sodium

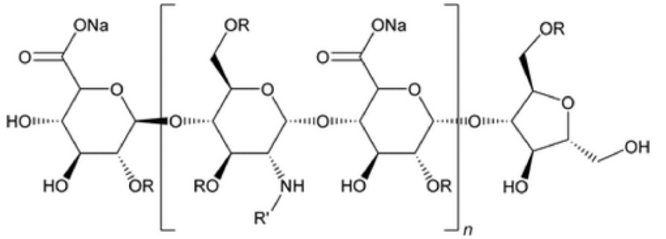


R_1 = —H or —SO_3Na

R_2 = —SO_3Na or —C(=O)CH_3

R =	X = 15 - 25%		*n* = 0 to 20
	100-X	H	*n* = 1 to 21

Dalteparin Sodium

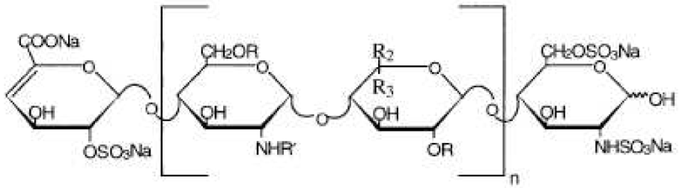


n = 3 to 20

R = —H or —S(=O)(=O)—ONa

R' = —S(=O)(=O)—ONa or —C(=O)CH_3

Tinzaparin Sodium

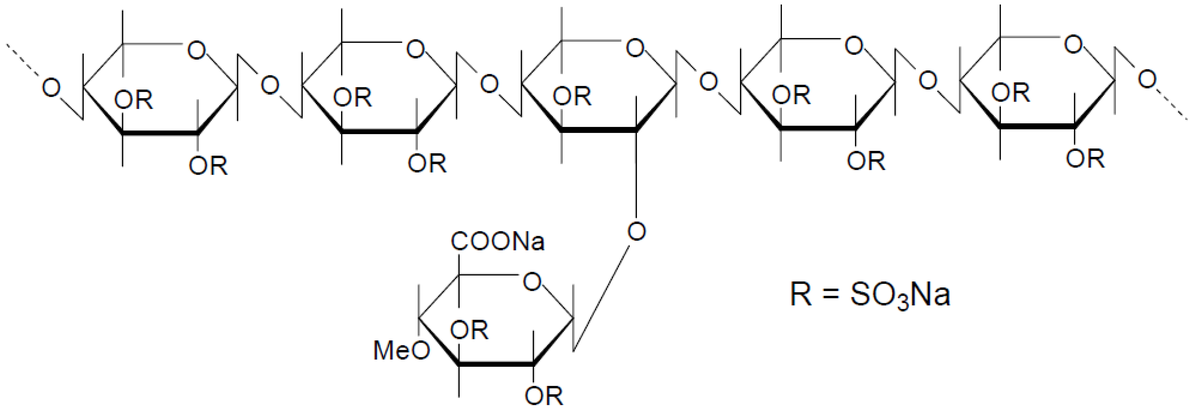


n= 1 to 25, R = H or SO_3Na, R' = H or SO_3Na or $COCH_3$
R_2 = H and R_3 = COONa or R_2 = COONa and R_3= H

Pentosan Polysulfate Sodium (PPS)

ELMIRON® (Pentosan Polysulfate Sodium Capsules, 100 mg) is indicated for the relief of bladder pain or discomfort associated with interstitial cystitis.

PPS is prepared from naturally-occurring xylan, extracted from the beenchwood tree, and has a molecular weight of 4000 to 6000 Dalton.



Complex Mixtures

LMWH and PPS are synthetic/semi-synthetic complex mixtures. In most cases, these complex mixtures are treated as a single active ingredient.

- ANDA applicants should try to characterize each component
- Acceptance ranges should be proposed for each component in the active ingredient mixture with justification
- Rationale for acceptability of any differences should be specified

Product Specific Guidance (PSG)

LMWH – Five Criteria	PPS – Three Focus
1. Equivalence of physicochemical properties	1. Source of naturally-occurring starting material – The starting material used should be the same.
2. Equivalence of heparin source material and mode of depolymerization	
3. Equivalence in disaccharide building blocks, fragment mapping, and sequence of oligosaccharide species	2. Physicochemical properties – The molecular weight distribution should be comparable, the overall structural properties or characteristic fingerprints (e.g. degree of sulfation, sodium content, Raman and IR spectra, etc) should be equivalent.
4. Equivalence in biological and biochemical assays	3. Equivalence of monosaccharide building block composition and chain branching, e.g. xylose units, sulfation pattern, glucuronic acid groups, linkages, and anomeric configurations.
5. Equivalence of in vivo pharmacodynamic (PD) profile	

Characterization Analytical Methods

A combination of validated low resolution and high resolution analytical methods should be applied in the sameness establishment:

- Weight average molecular weight and MW distribution by GPC, stoichiometry study, UV, FT-IR/Raman, etc
- Strong anion exchange HPLC (SAX-HPLC), Reversed-phase ion-pairing ultraperformance liquid chromatography (RPIP-UPLC), etc
- Chemical Composition Fingerprint Analyses by ^{1}H NMR, ^{13}C NMR, and HSQC 2D-NMR, etc.

LMWH – Review Issues

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LMWH – Review Issues

Manufacturing

1. Fulfill Criterion #2, equivalent heparin source material and same mode of depolymerization.
2. Developmental studies should be carried out to correlate critical process parameters (CPPs) to critical quality attributes (CQAs).
3. In addition to the USP requirements for Heparin Sodium, the Agency requires characterization of the building blocks, because they have an inherent direct impact on the final sameness of LMWH to the RLD:
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Need help ?

Prospective ANDA applicants may submit controlled correspondence to or request a pre-ANDA meeting with the Office of Generic Drugs to discuss their proposed methods for demonstrating sameness.

Resources

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 Guidances:

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

Immunogenicity-Related Considerations for Low Molecular Weight Heparin:

https://www.fda.gov/media/88253/download

Generic Enoxaparin Questions and Answers

https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/generic-enoxaparin-questions-and-answers

Thank You!

We look forward to seeing you at the Workshop on March 3rd and 4th

- Send questions regarding this poster to: DMFWorkshop2021@fda.hhs.gov by 2/15/2021 for inclusion in the poster Q&A session on *March 3rd.*

- Follow-on webinar for both posters/presentations is on April 9, 2021. Questions can be sent to the above email by 3/19/2021 for the webinar.