



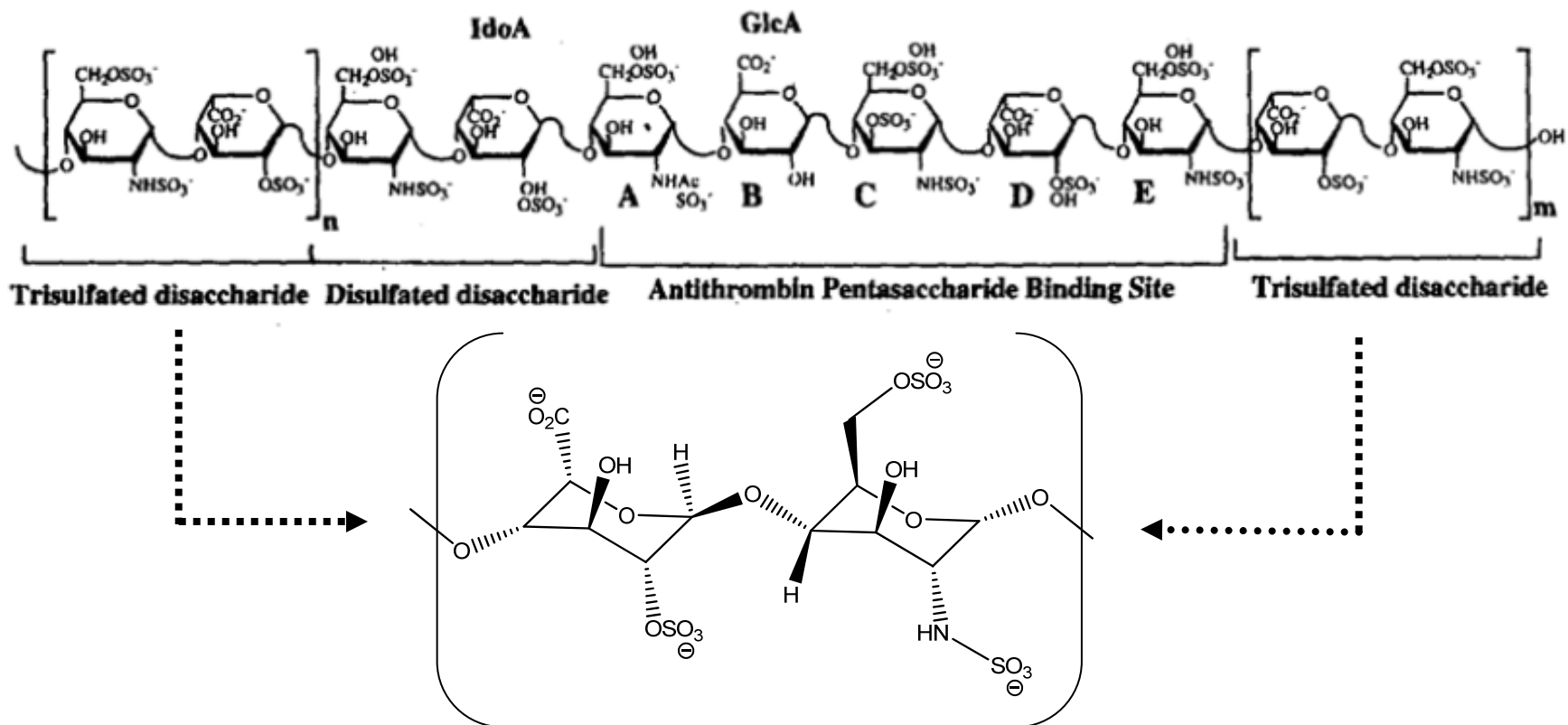
Impact of the Heparin Crisis on Regulatory Requirements and Review Process

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Introduction

- Heparin is a Polydisperse polysaccharide mixture (various chains length, different degree of sulfation and isomerization).

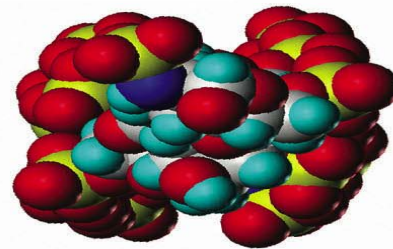
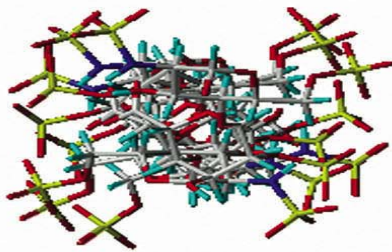
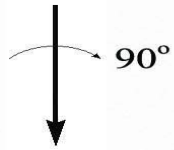
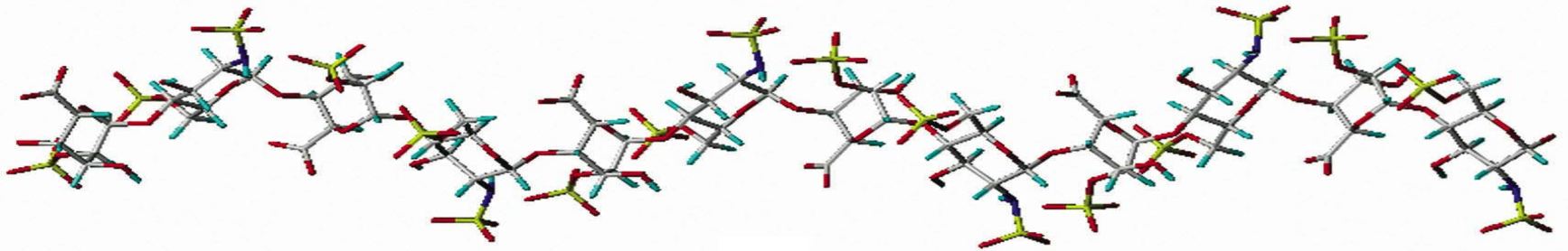


Major repeating unit consists of iduronic acid and glucosamine residues 2

Heparin Sodium

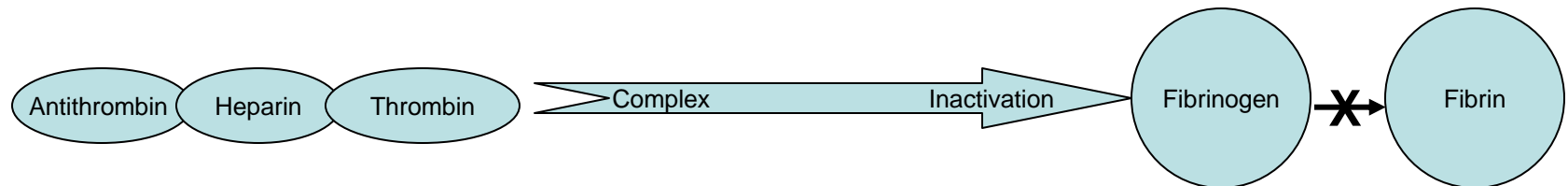
- **Polydisperse** (various chain lengths, heterogeneous mixture, large number of isomers)
- **Highly sulfated polysaccharides**
- **Repeating units** of 1→4 linked hexuronic acid residues (L-iduronic acid and D-glucuronic acid) and glucosamine sugar residues (N-sulfated, O-sulfated and N-acetylated)
- **Specific pentasaccharide sequence** in 30% of heparin that is bound by a unique site in anti-thrombin III.
- **Other structures** account for a **variety** of biological activities which are little understood.

Helical Structure

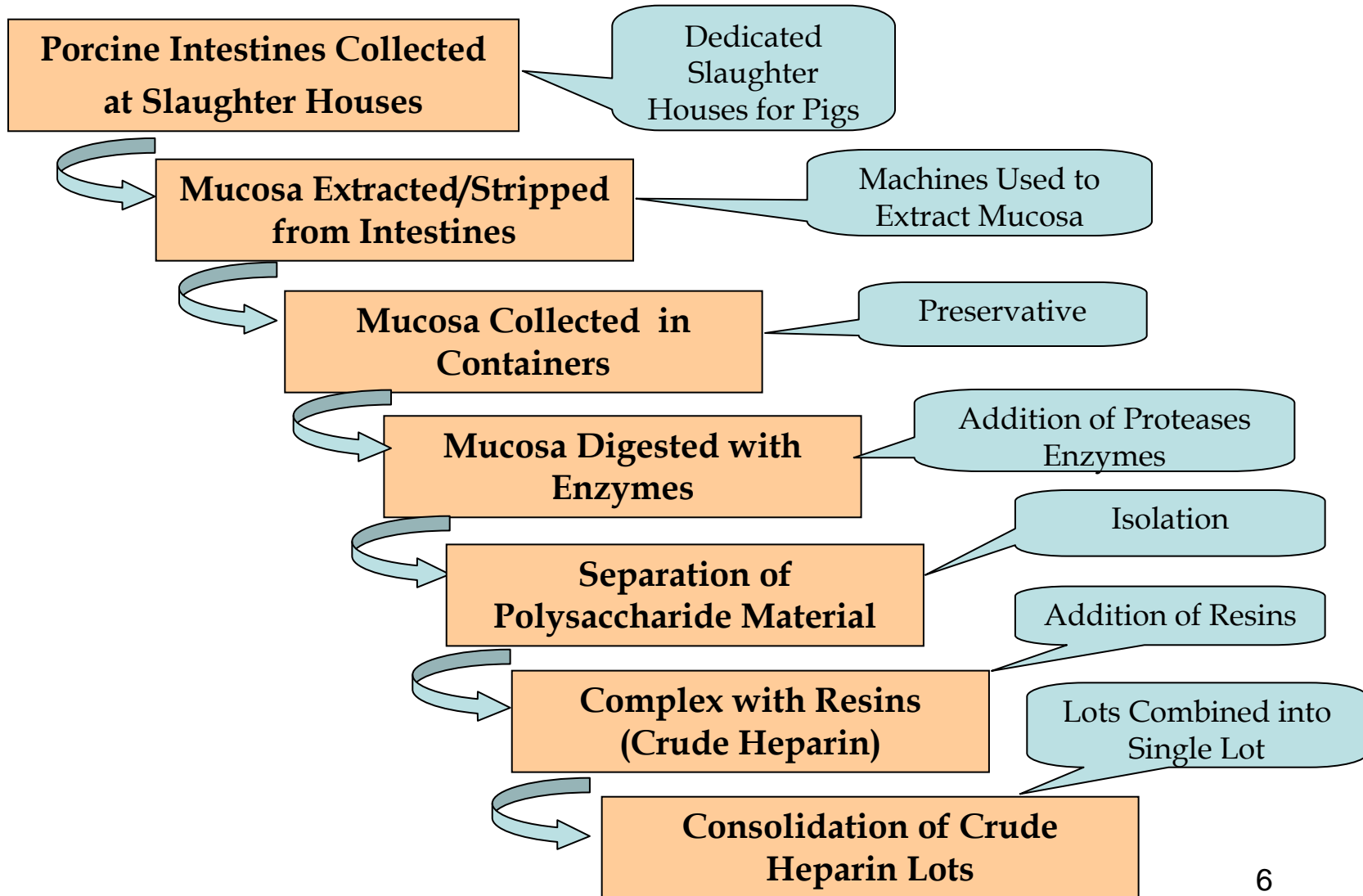


Activities

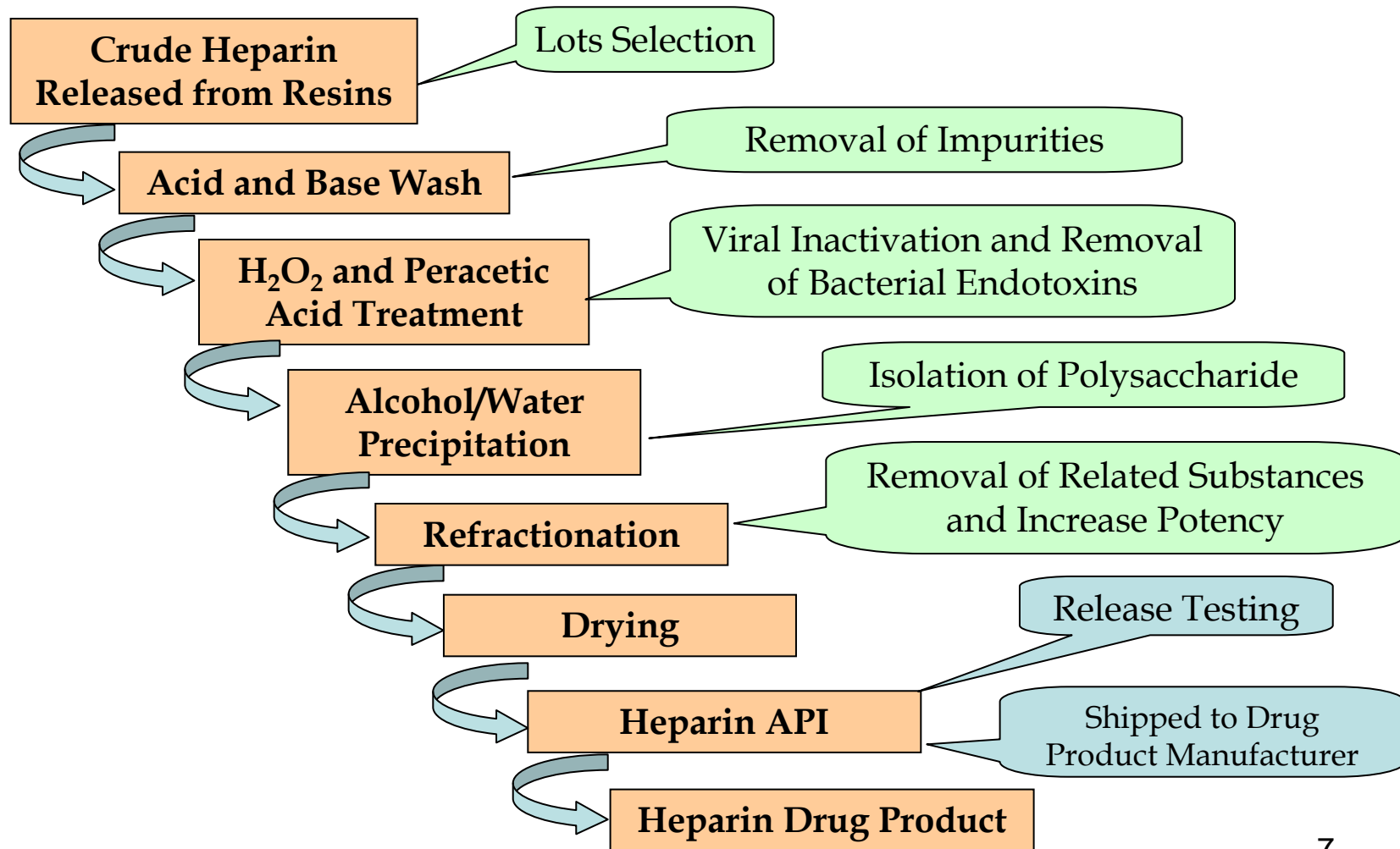
The anticoagulant activity of heparin results from its binding to the serine protease inhibitor, antithrombin and thrombin. Heparin binding causes a conformational change in antithrombin that results in enhanced inhibition of thrombin and other serine proteases involved in the blood clotting cascade. Therefore, the formation of this complex between antithrombin, thrombin, and heparin results in accelerating the rate of thrombin inactivation. Indications include **Kidney Dialysis, Surgery, especially Cardiac-Invasive, Heart Attack, Cardiac Arrhythmia, Acute Coronary Syndrome, Pulmonary Embolism, Stroke, Deep-vein Thrombosis, Blood Clot Prevention**, etc.



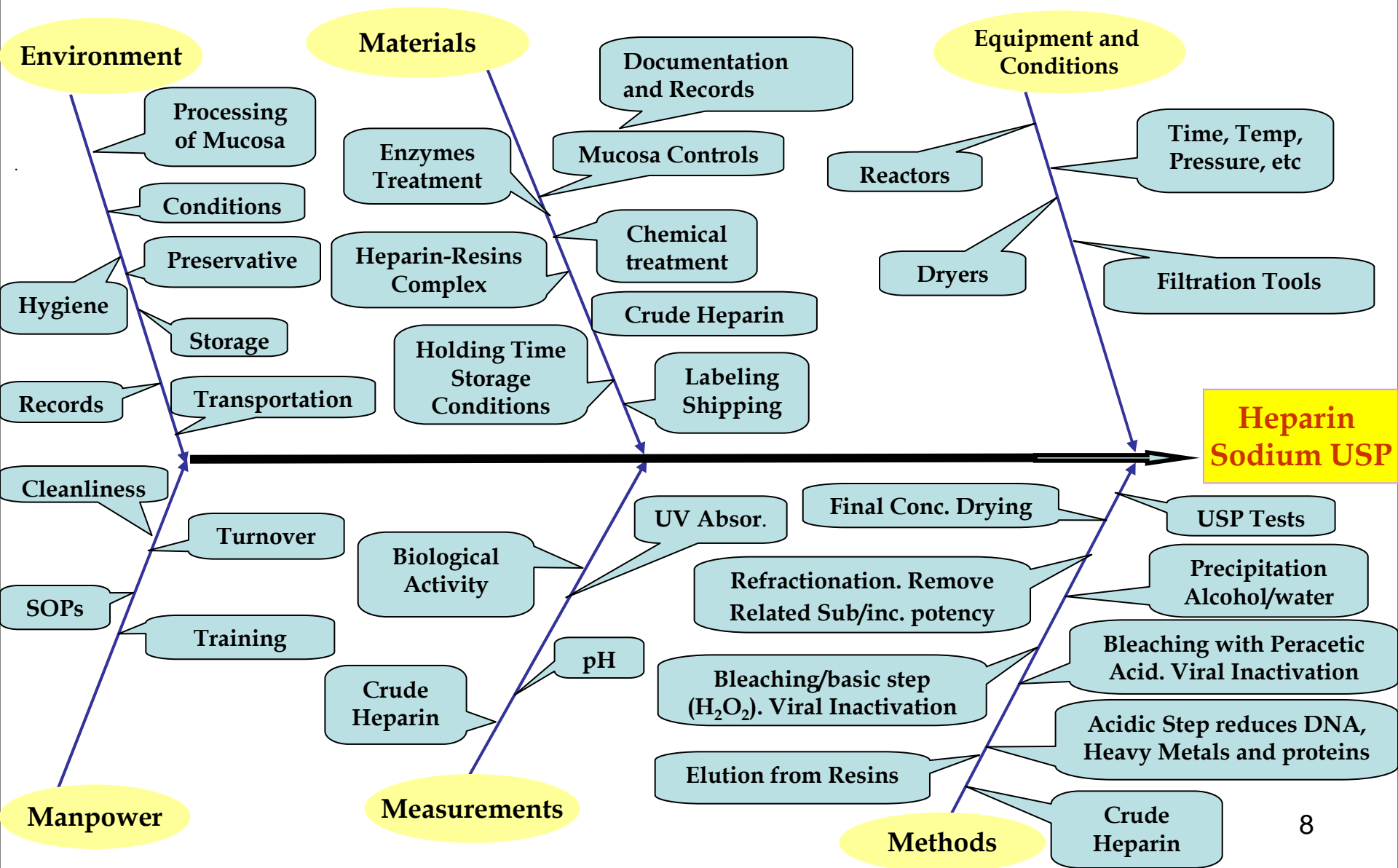
Manufacturing Process-Crude Heparin Collection



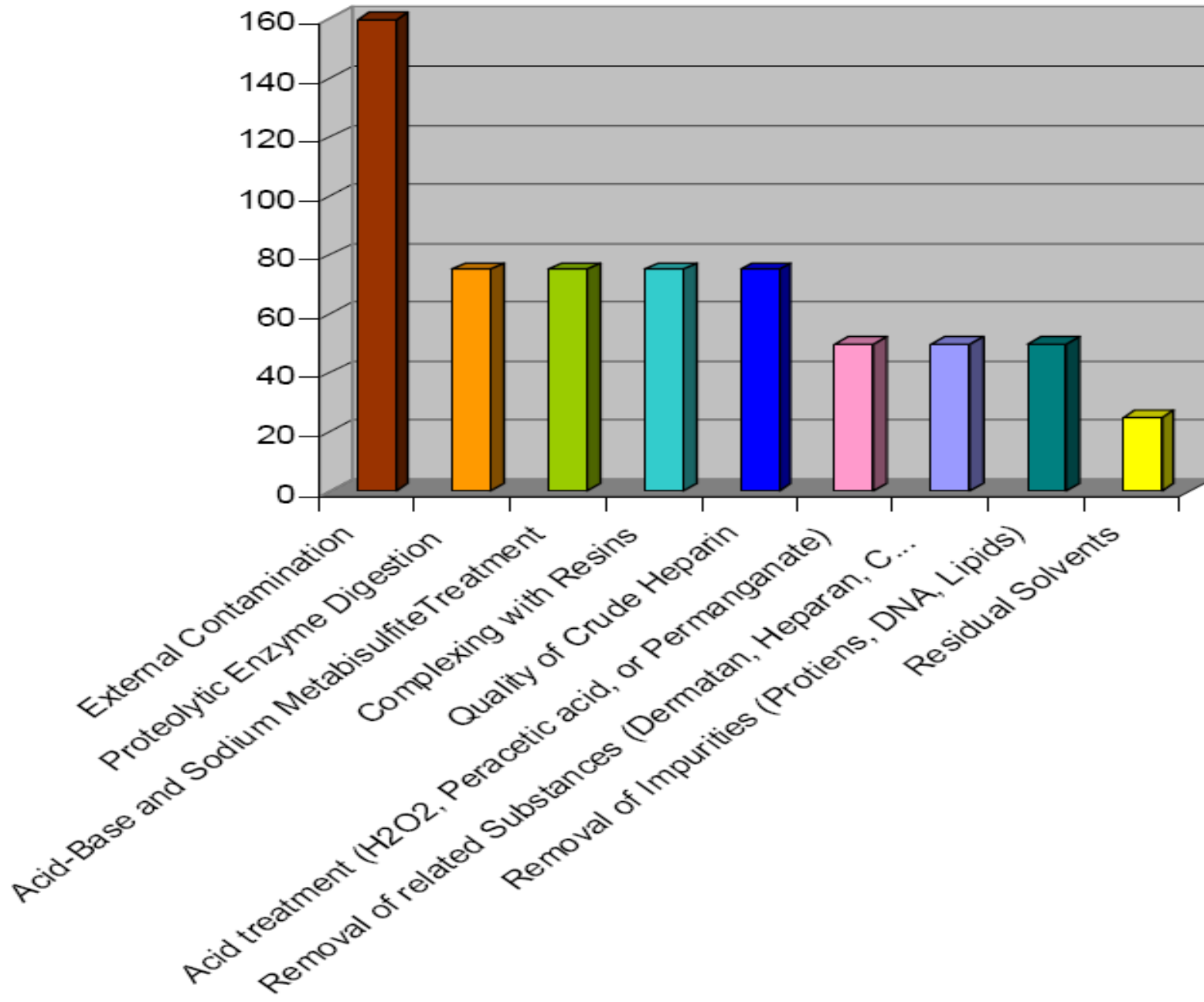
General Scheme - Heparin Drug Substance (API) Manufacturing Process



Risk Assessment (Ishikawa Diagram)

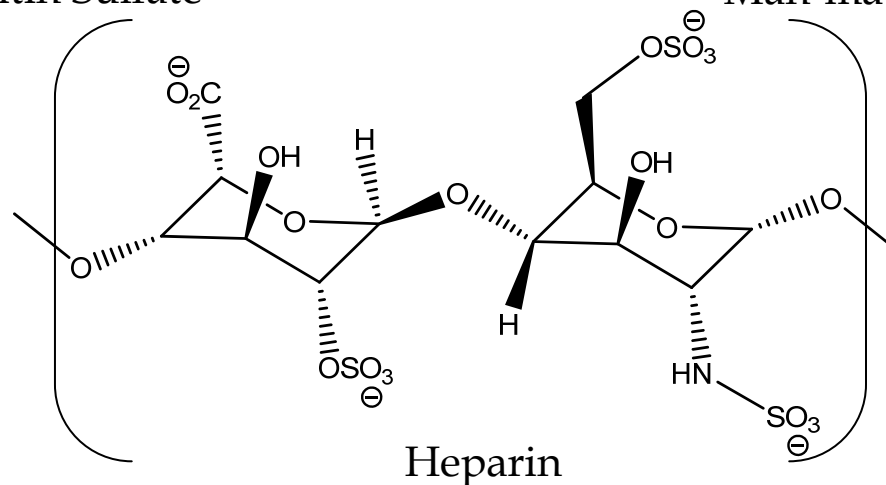
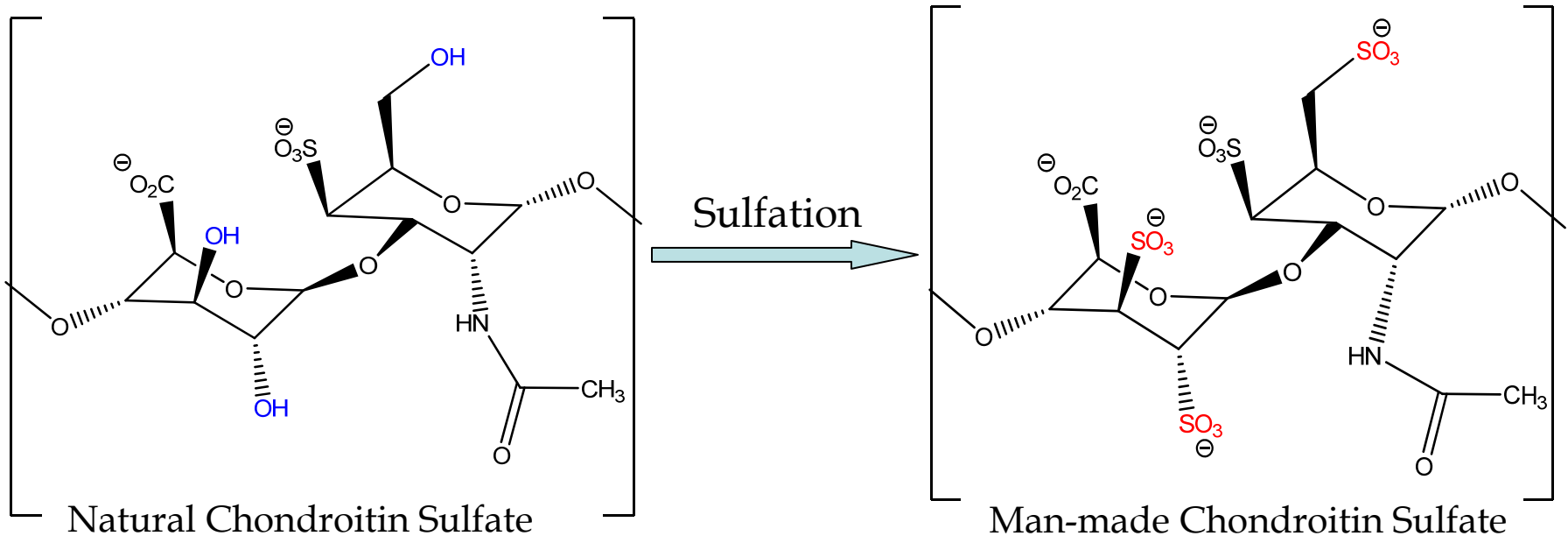


Risk Prioritization



Oversulfated Chondroitin Sulfate

After extensive laboratory investigation, the presence of Oversulfated Chondroitin Sulfate (OSCS), as a contaminant, was identified in batches that produced Adverse Events. Chemically, OSCS is a heparin like material.



Two Key Issues

- **Updating the Compendial Standards for Heparin**
- **Improvement of the CMC Review Process**



Old USP Public Standards for Heparin Sodium

- Packaging and storage
- Labeling
- USP reference standard
- Bacterial endotoxins
- pH
- Loss on drying
- Residue on ignition
- Protein
- Heavy metal
- Antifactor Xa activity
- Nitrogen content
- Assay

OSCS contaminated heparin batches passed the above standards!

Updated USP Standards for Heparin Sodium

H-1 Nuclear Magnetic Resonance (NMR)
Viral Inactivation USP <1050>
SAX-HPLC Method
Anti Factor Xa/IIa ratio
Limit on Galactosamine (1%)
Residual Solvents (USP 467)



New

Potency (NLT 180 U/mg)
Protein Impurity
Nucleotide Impurity



Improved

Importance of the Updated Public Standards

- Provide better assurance of the quality of marketed Heparin products by using appropriate and modern analytical methods.
- Prevent fraudulent suppliers from adding components that in the past have eluded existing identity tests due to similar properties
- Provide significant improvement to the safety nets that keep substandard drugs from reaching the marketplace.

Improvement of the CMC Review Process

- Implementation of Quality by Design (QbD)
 - Extensive evaluation of pharmaceutical development and manufacturing information
 - Quality Risk Management (QRM)
 - Evaluation of QRM information in submissions
 - Risk-based review
 - Assessment of Proposed Control strategies
 - Identification of Critical Quality Attributes (CQA)
 - Not limited by only end product testing
 - More Focus on:
 - Control of Raw Materials and supply chains (crude heparin)
 - In-Process control and testing
 - Assessment of Critical Process Parameters in the manufacturing process and their operating ranges (Design Space)

Conclusion

- **Updating the Compendial Standards for Heparin**
- **Implementation of Quality by Design Approach (QbD) for Reviewing Heparin Pharmaceutical Preparations:**
 - Quality Risk Management (QRM). Risk-based review and subsequent evaluation
 - Identification of Critical Quality Attributes (CQA)
 - Control of Raw Materials and Supply Chains (crude heparin)
 - In-Process control and testing
 - Assessment of Critical Process Parameters in the manufacturing process and their operating ranges