Control Strategies for Particles Arising from HCP-mediated Degradation of Polysorbate: A Regulatory Perspective

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The views expressed in this presentation are those of the presenter and do not convey official Health Canada policy.
Presentation Overview

• Overview
  – Particles, polysorbate, HCP

• Regulatory Expectations
  – Investigation and studies

• Control strategy
  – Particles
  – Polysorbate
  – HCP
Particle Formation

• USP <787-790> and <1178> provide guidance on particles in injectables

• Particles can be classed as;
  – Extrinsic
  – Intrinsic
  – Inherent

• The concerns regarding particles include;
  – Potential risk to patient safety
  – Potentially immunogenic
  – Potential impact to product quality
  – Potential impact to processes (filters)
Polysorbate Overview

- Polysorbate is a common surfactant used to protect biopharmaceuticals against interfacial stresses experienced during manufacture, transport, and storage
- Function to prevent protein aggregation
- Sorbitan group with polymerized ethylene oxide groups and partial esters of fatty acids

Taken from Dwivedi et al., Int. J. Pharm, 2018
Degradation Mechanisms

- Polysorbate can degrade through oxidative or hydrolytic mechanisms
  - Oxidation is typical due to the presence of oxygen and the product contact material
  - Hydrolysis can be either chemical or enzymatic
- The degradation products are indicative of the mechanism of degradation

Taken from Dwivedi et al., Int. J. Pharm, 2018
HCPs

• ‘Hitch-hiker proteins’ co-elute by binding to the product
  – Binding has been localized to the CDR in the Fab region
  – Binding has been characterized as weak
  – Binding is mAb-dependent

• Examples of HCP known to co-elute with mAbs include;
  – Triacylglycerol lipase
  – Phospholipase B-like 2 (PLBL2)
  – Lipoprotein lipase
  – Lysosomal phospholipase A2
  – Carboxyl ester hydrolase
HCPs and polysorbate degradation

• Typical narrative for uncovering particles arising from HCP-mediated degradation of polysorbate
  – Out-of-specification or out-of-trend result is observed at 12-18 months for drug product on stability under long-term storage conditions of 2-8°C
    • Particles – Visible (VP) or subvisible (SVP)
    • Clarity - turbidity
  – Polysorbate levels are observed to have decreased over the same period
Regulatory Expectations

• Demonstrate that the manufacturing process is capable of consistently producing product with the desired qualities and with very low levels of impurities

• Investigations and studies are expected to be provided when polysorbate degradation and/or particle formation have been observed

• Results of the investigations and studies are used to inform the manufacturing process changes and control strategies
Investigation – Particle Composition

- Composition of the particles can be indicative of the root cause of the particle formation
  - SVP and VP containing FA esters, aldehydes, and ketones are likely due to oxidation
  - SVP and VP composed primarily of FFA and free of protein are likely due to enzymatic degradation of polysorbate
  - SVP and VP composed of proteinaceous components likely result from factors other than HCP-mediated degradation of polysorbate
Investigation – Root Cause

• Source of degradation – Enzymatic
  – Protein dilution studies
    • HCP assay – no change in result with sample dilution
    • Polysorbate degradation assay – decrease in result with sample dilution
  – Lipase inhibitor studies

• Quantification and Identification of lipolytic HCPs
  – Quantify level of the contaminating HCP
    • Low levels (<LOQ of the assay) v. high levels (~100 ppm)
  – Identification of the lipolytic HCP
    • Sensitive identification methods
Investigation – Questions

• Was the increase in particles the result of a process change?
  – Change in cell line
  – Removal of HIC chromatography step
  – New supplier of polysorbate

• Was the increase in particles the result of a test method change?
  – Previous methods not sensitive to SVP particles
  – Previously not monitoring polysorbate levels
Additional Assessments

• Toxicological Assessment
  – FFA from particles
  – Immunogenicity of the contaminating HCP

• Establish the minimum effective level for polysorbate to ensure CQAs of the product are maintained at release and over the shelf life of the drug product
Control Strategy

• The aim of the control strategy should be to minimize the contaminating HCP and to decrease particle formation in response to degradation of polysorbate

• Polysorbate should be defined as a critical excipient if changes in polysorbate levels are observed over the shelf life and result in an increase in the formation of particles

• A control strategy is required when particles arise from HCP-mediated degradation of polysorbate
Control Strategy

• Control of Raw Materials
  – Testing of polysorbate to ensure quality
  – Selection of polysorbate starting material
    • Customized polysorbates with higher contents of shorter chain FA
      – Shorter chain FA are more soluble and are less likely to form particles
      – Potential to change prevent degradation of polysorbate
Control Strategy

• Control during manufacturing process
  – Lipase-free cell line
  – Addition of a HIC chromatography step
  – In-process control for HCP / identified HCP-lipase
  – In-process control to ensure correct amount of polysorbate is added
    • Based on manufacturing process development and formulation development studies that identify the level of polysorbate required to ensure product quality
Control Strategy

• Controlling particles and polysorbate for release and stability of the drug product
  – Controlling VP and SVP particles should be included in the stability protocol and as part of the long-term, accelerated, and stressed stability studies
  – Polysorbate content should be controlled as part of the stability protocol with an appropriate specification

• Use of an in-line filter prior to administration to remove particles
Health Canada

• We welcome regulatory questions via pre-CTA meetings or pre-NDS meetings in-person or via teleconference
• Contact Office of Regulatory Affairs

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