Risk Assessments and Control Strategies for Host Cell Proteins: FDA Expectations and Experiences

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Disclaimer

• *Our comments are an informal communication and represent our own best judgment. These comments do not bind or obligate FDA.*
Regulatory framework for HCP control

- 42 USC 262 – “The biological product ...is safe, pure, and potent”
- ICH Q6B – HCPs are defined as process-related impurities and guidance for setting specification is outlined
- ICH Q8 – HCPs fit the definition of Critical Quality Attribute and HCP levels should be controlled accordingly
Importance of controlling HCPs

• Clinical safety
  – Potential immunogenicity
  – Potential adjuvant effect
  – Undesired activity in humans
  – Unknown potential risks

• Manufacturing process consistency
  – Purification process efficiency
HCP assay requirements

- Sensitivity
  - Should be able to detect low levels of HCPs expected in the product

- Specificity
  - Should perform well in the presence of large amount of therapeutic protein

- Coverage
  - Should have demonstrated the ability to detect the majority of the HCPs present in the product
  - Should have demonstrated quantitative relationship to the amount of HCPs in the product
Considerations for HCP control

• Use orthogonal purification modes (e.g., IEX and affinity chromatography)
• Archive samples from early stages of process and assay development to demonstrate comparability
• Re-qualify the assay after major manufacturing process changes
• Develop process-specific assay
Considerations for HCP control (contd.)

- Start HCP assay development early
- Use orthogonal methods to demonstrate assay capabilities (2D-PAGE, etc.)
- Develop clinical assay for anti-HCP antibodies in parallel with HCP assay
- Ensure the long-term availability of the critical reagents
- Use upstream process intermediate for the development of anti-HCP antibodies
Strategies for HCP ELISA development

Using upstream process intermediate for assay development potentially reduces assay sensitivity but improves process control and allows process changes to be made easier.
HCP control over regulatory lifecycle

**Pre-IND**
- Commercial assay may be used
- Studies in relevant animal models to confirm safety

**IND**
- By Phase I the coverage of the HCP assay is demonstrated
- Assay is in place to detect anti-HCP antibodies in patients
- Relevant antigens and reference standards are developed and qualified
- Samples are archived

**BLA**
- Validated assay with demonstrated process-specific performance
- Comparability of product manufactured by validated process to investigational product is established
- Information on the development and qualification of the assays and the reagents are included
Setting Specification for HCP

- Product class
- Indication
- Dose
- Clinical benefits
- The levels of HCPs in product lots used in clinical trials
- Animal studies
- Clinical trials
- HCP assay performance parameters (LOQ & LOD, etc.)
Some regulatory considerations for HCP specification

• Risk/Benefit analysis
• Are there similar products on the market?
  – Levels of HCPs in similar products
  – Does new product offer major advantages
• Are there reasons that particular HCPs should be controlled separately?
  – Known activity/high immunogenicity of a particular protein
  – Protein(s) co-purified with product at disproportionately high level
• Was sound scientific reasoning used in method development and specification setting?
HCP specifications in approved blood coagulation factor products

• No specific guidelines for HCP levels
• Usually for drug substance only
• Different formats
  – ppm
  – ng/mg
  – ng/1000 U
  – Some products use more than one format
• Wide range of approved specifications
Perspectives

• Use of state-of-the-art technologies is encouraged.

• Emerging technologies may be used if their capabilities are proven adequate.
  – There are no restrictions in the types of methodologies used in assaying HCPs, i.e., not limited to antibody-based assays.

• Seek FDA feedback
  – We recommend sponsors to discuss HCP control strategy early in product development.