Risk Assessments for Host Cell Protein Control Strategies: CDER Experiences

Laurie Graham
FDA/CDER
Office of Pharmaceutical Quality (OPQ)
Office of Policy for Pharmaceutical Quality (OPPQ)
Disclaimer

The views and opinions expressed should not be used in place of regulations, published FDA guidance, or discussions with the Agency
HCP Control Strategy Risk Assessments

- The risk assessment of the HCP control strategy includes consideration for
  - The critical quality attribute impact assessment (i.e., the potential impact on safety and efficacy)
  - Process understanding
  - Analytical performance

- Generally expect HCP testing to be included at Phase I as a DS release test
HCPs as CQAs
Critical Quality Attributes (CQAs)

- A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality (ICH Q8)

- Per ICH Q11: Impurities are considered potential CQAs. For biotechnology products this includes process- and product- related impurities as well as contaminants as defined in ICH Q6B.
Impurities and Biotechnology Products: ICH Q6B

- **Product-related** = ‘…molecular variants arising during manufacture and/or storage, which do not have properties comparable to those of the desired product …’(e.g. aggregates, fragments, oxidation, deamidation).

- **Process-related** = ‘…those that are derived from the manufacturing process, cell culture or downstream processing’ (e.g. HCP, DNA, insulin, methotrexate, anti-foam, leachables).

- **Contaminants** = ‘…all adventitiously introduced materials not intended to be part of the manufacturing process’ (e.g. adventitious viral and microbial agents, endotoxin, mycoplasma etc).
Impact of HCPs

HCPs as Critical Quality Attributes (CQAs)

- Expect some information at Phase 1 with continued refinement during development

- Impact on potency, PK, safety, and immunogenicity, for example:
  - Direct clinical effect (hypersensitivity, immediate toxicity, biologically active impurity, etc)
  - Impact on the overall safety and efficacy profile of the product
  - Induce or augment anti-drug antibodies or induce an immune response to an endogenous protein
Impact of HCPs

HCPs as Critical Quality Attributes (CQAs)

In vitro, animal, and clinical data, patient factors, product factors, prior knowledge, and published information used to assess impact on PK/PD, potency, immunogenicity, and safety

For factors to consider in immunogenicity risk assessments: see FDA guidance of Industry “Immunogenicity Assessments for Therapeutic Protein Products”
Process Characterization
Process Characterization of HCP

- As development proceeds, process understanding would include consideration for factors such as:
  - Validation of removal at commercial scale
  - Small scale removal studies (may include spiking)
  - Process characterization studies
  - Product stability
Host Cell Protein Assays

- Assays generally rely on the ability of an anti-HCP anti-serum to detect HCP impurities.

- Performance of the assay is tightly linked to the quality of the anti-HCP antiserum.

- To provide assurance that the HCP assay accurately reflects the HCP impurities present, data needs to be provided estimating the approximate percent of potential HCP impurities that are recognized by the HCP antiserum.
Provide a summary description of the assay and the source (in-house or commercial) of the antiserum used for detection of host cell protein impurities (HCPs). The anti-HCP antiserum needs to be qualified for its ability to detect potential HCP impurities. This assessment should include 2D SDS-PAGE gels of the range of HCPs detected by a sensitive protein stain, such as silver stain, compared to the range detected by western blot analysis using the antiserum employed in the assay. It is possible to use a similarly sensitive and discriminating assay in lieu of the 2D SDS-PAGE assay. If an alternative pathway is pursued, consultation with the Agency is recommended. These data should be used to determine the approximate percent of potential HCP impurities that are recognized by the HCP antiserum. It is the Agency’s experience that analysis of HCP coverage by a 1-dimensional SDS-PAGE gel method is not sufficiently informative for this purpose.
HCP Analytics

➢ To improve coverage of assay, often see change in control strategy from general (e.g. commercial kit) assay to process-specific assay during development

• Commercial assay: The anti-HCP antiserum was raised against host cell proteins derived from a ‘generic’ cell line (CHO, NSO, E. coli).

• Process-specific assay: The anti-HCP antiserum is raised against a host cell protein pool that is derived from the cell line used for production. Generally a vector transfected parental cell line is used.
HCP Analytics

3 of 8 BLAs approved by DMA in 2014 included PMC for development of a host cell protein assay with improved coverage.
Host Cell Protein Control Strategy
Risk Assessment Case Studies
Case Study 1

- Phase I IND placed on hold because
  - There was insufficient information provided to demonstrate that the commercial HCP assay used (mouse cell line) would provide adequate coverage of the potential HCP impurities from the production cell line (human B cell/murine hybridoma).
  - The HCP assay appeared to cross-react with the product.
  - The sponsor did not perform an adequate CQA assessment.
## Case Study 2: Change from Commercial to Specific Assay

<table>
<thead>
<tr>
<th></th>
<th>Current process</th>
<th>Previous process</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial HCP assay</td>
<td>&lt;LOQ</td>
<td>&lt;LOQ</td>
</tr>
<tr>
<td>Specific HCP assay</td>
<td>47-76 ppm</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Current process</th>
<th>Previous Process</th>
<th>Historical process</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial HCP assay</td>
<td>&lt;LOQ</td>
<td>&lt;LOQ</td>
<td>5-13</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>20-74</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4-106</td>
</tr>
<tr>
<td>Specific HCP assay</td>
<td>47-76</td>
<td>39-123</td>
<td>83-146</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>154-303</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>290-644</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>421-1256</td>
</tr>
</tbody>
</table>
Anti-HCP Antiserum Coverage: Case Study 3

- At time of licensure, the HCP assay was found to be deficient with regard to HCP impurity coverage and the sponsor committed to developing a new assay.

- The new assay was implemented with significant changes to drug substance (DS) manufacturing.

- The new HCP assay indicated that the post-change DS had a higher level of HCP than the pre-change material.

- The new process had to be modified to include an additional HCP clearance step. The process had to be re-validated prior to the submission of a supplement.
Anti-HCP Antiserum Immuno-reactivity: Case Study 4

- HCP ELISA assay results indicated no clearance of HCP by Protein A column. However, it was determined that this was due to the presence of one co-eluting highly immuno-reactive protein that was not identified during assay development/qualification. The co-eluting protein was identified and found to be cleared by subsequent steps.

- The ELISA results, therefore, did not accurately reflect the ability of the Protein A column to remove HCPs. The sponsor developed an orthogonal assay to assess the lifetime performance of the Protein A columns with regard to HCP clearance.

- Other case studies have revealed HCPs co-purifying with the product and the identified HCPs having the potential to impact safety and efficacy.
Replacing the anti-HCP antiserum: Case Study 5

- After licensure, with the implementation of a new DS manufacturing process, a sponsor also had to replace the anti-HCP antiserum in the process specific assay.

- DS lots from the previous manufacturing process were tested with the old and new HCP methods. The new HCP antiserum detected a reduced range of proteins compared to the old antiserum.
Replacing the anti-HCP antiserum: Case Study 5

The data suggest that the new antiserum detects reduced levels of HCP impurities compared to the original method.

<table>
<thead>
<tr>
<th>DS Lot</th>
<th>HCP ng/mL Old method</th>
<th>HCP ng/mL New Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>47.1</td>
<td>13.1</td>
</tr>
<tr>
<td>2</td>
<td>37</td>
<td>7.10</td>
</tr>
<tr>
<td>3</td>
<td>54.2</td>
<td>22.3</td>
</tr>
<tr>
<td>4</td>
<td>35.5</td>
<td>5.00</td>
</tr>
<tr>
<td>5</td>
<td>26.2</td>
<td>25.3</td>
</tr>
<tr>
<td>6</td>
<td>39.6</td>
<td>13.5</td>
</tr>
<tr>
<td>7</td>
<td>25.9</td>
<td>17.5</td>
</tr>
</tbody>
</table>

A CR was issued because of possible DP stability issues and concerns about the potential role for a new HCP impurity.
General Considerations for Replacing an Existing Analytical Method

- Performance parameters of the new assay should be the same or better than the existing assay

- If new process related impurities are seen with the new assay, information from retain samples should be provided demonstrating that the variants/impurities are not new

- If making a major change in how a quality attribute is measured:
  - Assess consistency and comparability across multiple lots
For HCP Assays.....

- Multiple factors need to be considered during the analytical lifecycle.

- Assay qualification needs to include data demonstrating that the anti-HCP antiserum adequately detects potential HCP impurities.

- Assay qualification should be done early in development so that the final control strategy can be adequately justified.