A Regulatory Perspective on Characterization and Control of Process-Related Impurities

Christopher Downey, PhD
FDA/CDER Office of Biotechnology Products
CASSS Bay Area Discussion Group June 2017

Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies

Themes

- Control strategy for process-related impurities should be risk-based
- Development, small-scale, and validation studies need to 1) accurately represent production process and 2) capture worst-case scenarios for clearing impurities
- Good impurity control requires good assays for impurities
- Good communication can reduce regulatory burden

Regulation and Guidance

- 21 CFR 610.13 Purity: “Products shall be free of extraneous material except that which is unavoidable…”
- ICH Q3C Impurities: Guideline for Residual Solvents, Class 1, 2 and 3.
- ICH Q6B Specifications for Biotechnology Products
- ICH Q8 Pharmaceutical Development
- ICH Q11 Development and Manufacture of Drug Substances

Impurities are potential critical quality attributes (ICH Q11)

- Biotechnology product impurities defined in ICH Q6B:
  - Product-related: molecular variants arising during manufacture or storage that do not have properties comparable to those of the desired product (*e.g*. aggregates, fragments, oxidized or deamidated species)
  - Process-related: derived from the manufacturing process (e.g. reagents, starting materials, leachates)
  - Contaminants: adventitiously introduced materials not intended to be part of the manufacturing process (e.g. adventitious viral and microbial agents, endotoxin, mycoplasma)
- Impurities identified as CQAs should be within an appropriate limit, range, or distribution to ensure desired product quality

Process-related impurities for biotechnology products

- Cell substrate-derived (e.g. host cell proteins and DNA, virus-like particles)
- Cell culture-derived (e.g. insulin, methotrexate, anti-foam, antibiotics, metal ions)
- Downstream processing-derived (e.g. buffers, protein A or metal ion capture column leachate, equipment or storage container leachate, reagents or reaction byproducts)

Regulatory concerns for process-related impurities

- Process-related impurities may pose direct risk to safety and efficacy
  - Direct clinical safety risk (e.g., toxicity, hypersensitivity, endotoxin shock, biological activity of impurity).
  - Immunogenicity
    - Impurities may be direct targets of immune response or adjuvant activity inducing or augmenting anti-drug antibody
    - Safety impact of immune response or efficacy impact (e.g. reduced PK)
- Impurities that do not pose a direct risk for the patient may still affect the overall safety or efficacy profile of a product

Case study: poor clearance of "inert" impurity

- PEGylation reaction uses large molar excess of PEG reagent
- Clearance of unreacted PEG highly variable
  - 50–fold lot-to-lot range of residual PEG
  - maximum levels on the order of 1% of total solution
- Sponsor's rationale:
  - Adequate safety margin for PEG toxicity
  - Lots for non-clinical and proposed clinical studies made by same process
- Need to consider impact to product profile (in this case, essentially an uncontrolled, highly variable excipient)
  - Potential to impact stability (PEG could be stabilizing or destabilizing, effect leaching power of solution)
  - Ability to detect DS degradation
  - Variable matrix for QC assays (e.g. potency assay)
  - Indicative of inadequately controlled purification process

Process-related impurities may impact product stability

- Proteases
- Lipases
  - Case study: residual host cell protein degrades polysorbate 20 yielding free fatty acid particles
- Glycosidases
- Metal ions
- May affect process intermediates in addition to bulk DS or DP

Stability program is important part of process-related impurity control program

- Difficult to detect impurities may affect stability profile
- Changes in degradation profiles may be indicative of underlying changes in impurities
  - Changes in impurity load from new raw materials
  - Process changes that affect clearance
  - Process drift
- Accelerated or stressed conditions may be especially informative
- Don’t forget stability of critical raw materials

Assessing risk for process-related impurities

- Potential clinical risk: Toxicity, biological activity, immunogenicity
- Potential impact to product activity or stability
- How late in process is it introduced?
- Does the impurity co-elute with the product?
- Is clearance mechanism and process capacity for clearance understood?
- Does development data and process experience cover worst-case?

Control of process-related impurities

- Identify and characterize all potential process-related impurities
- Develop and implement an appropriate control strategy
  - Raw material sourcing and testing
  - Control of introduction into the process (e.g. agents added to the bioreactor on an ‘as needed’ basis)
  - Leachable/extractable studies
  - Small scale removal studies (may include spiking or load “challenge”)
  - Process characterization
  - Validation of removal at commercial scale
  - In-process or release tests
  - Control of product stability

Control of process-related impurities needs good assays

- If the assay to detect the impurity does not sensitively and accurately detect the impurity, data supporting removal or control may not be meaningful
- Would you see it if it were there?
- Assay qualification or validation data demonstrating effective assays will strengthen the case to regulators for the control strategy

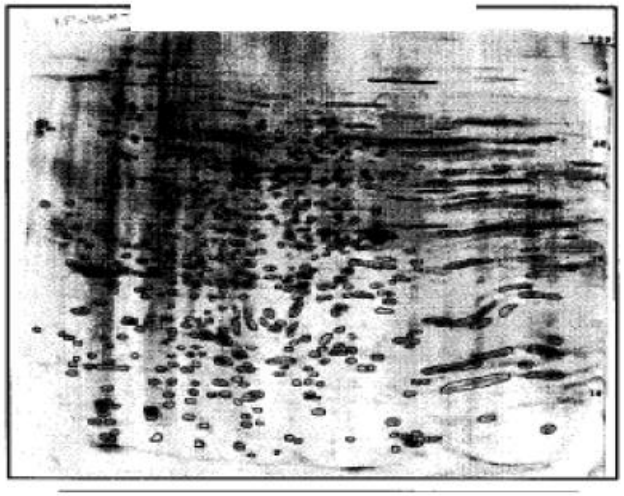
Host cell protein (HCP) impurities represent a unique challenge because of their complexity and diversity

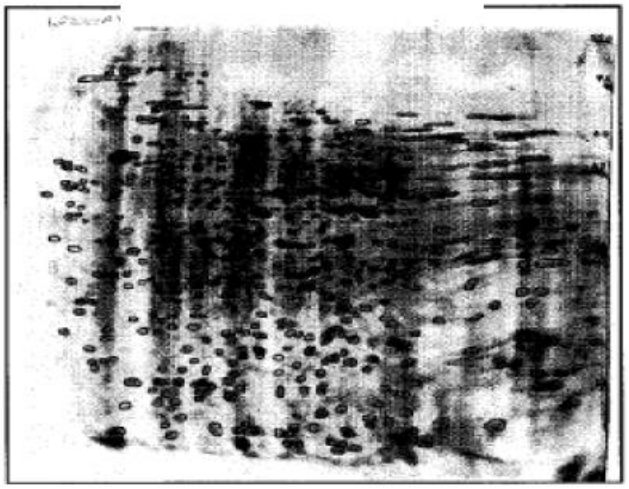
- The ELISA platform typically used for drug substance release/IPCs relies on the ability of an anti-HCP antiserum to detect HCP impurities
- The performance of the assay is tightly linked to the quality of the anti-sera
- The assay data will not accurately reflect the level of HCP if:
  - The antiserum does not recognize a majority of the potential HCP impurities
  - The signal is dominated by antibodies against one or a few proteins present in the sample being tested

Many products use commercial assay early in development and implement process-specific assay later in development

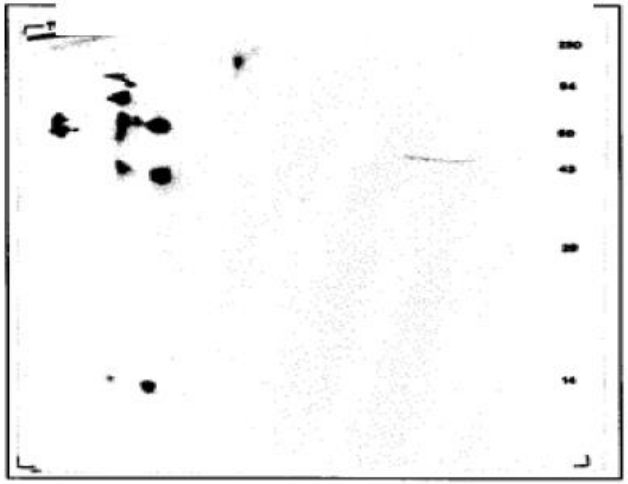
- Commercial assay: HCP antiserum raised against host cell proteins derived from a “generic” cell line (e.g. CHO, *E. coli*)
- Process-specific assay: HCP antiserum raised against a harvest or early downstream process pool derived from the cell line used for production (generally an empty vector transfected parental cell line is used)

Comparison of coverage of generic and process-specific HCP assays





Silver stain



Western blots

generic

Process-specific

FDA typically requests characterization of coverage for the HCP assay

- Estimation of the approximate percent of potential HCP impurities that are recognized by the HCP antiserum
- Comparison of silver stained (or other sensitive stain) and western blotted 2D-SDS PAGE gels
  - 1-dimensional SDS-PAGE gel method is not sufficient
- No magic number for coverage
  - <50% is likely concerning
  - >75% is more reassuring

Mass Spectroscopy is a potentially powerful tool for evaluating HCP

- Product-independent assay platform
- Avoids biases from anti-HCP sera
- Identifies individual HCP proteins
- Quantifies abundant HCP molecules (1-5ppm?)
- Provides comprehensive profiles of HCP for each unit operation during process development
- Enables more detailed risk assessments

Challenges of mass spectroscopy for evaluating HCP

- Implementation in a QC environment
  - Throughput, assay validation, feasibility of assay transfers
- Identification/quantitation of low levels of HCP in highly purified DS matrix
- Impacts on safety by individual quantifiable & identifiable HCP
- Limited bases for risk assessments: databases & prior knowledge
- Legacy Products:
  - Clinical materials no longer available
  - Bridging MS data with historical knowledge

Raw materials control is a key part of process-related impurity control strategy

- Materials themselves need to be cleared from product
- May contain material-related or process-related impurities of their own that impact process or product
  - e.g. metal ion impurities in Mg salt reagent used in cell culture impacts Fc glycoforms in mAb
- Microbial/viral/TSE risk understood and controlled
- Material stability (e.g. polysorbates oxidation)

Case study: residual protease in drug product excipient

- Plant-derived excipient contains a residual protease
- Residual protease originally uncontrolled in excipient
- Causes degradation of the drug product on accelerated and long-term stability
- Changed supplier and implemented measure of protease activity into raw material control strategy

Case study: enzymes used in downstream processing

- Downstream process used 2 enzymes to modify a protein product
- Enzyme raw material control strategy includes:
  - Activity and product-related impurity controls
  - HCP and DNA control strategy for each
  - Virus control strategy for CHO-derived enzyme
- Manufacturing and control strategy for product includes:
  - Chromatography steps to remove enzymes
  - Validation of clearance of enzymes and routine tests for residual enzymes
  - Stability tests sensitive to effects from residual enzymes
  - Assessment of immunogenicity risk from residual enzymes

Leachables and particles

- Affinity chromatography
  - Protein A
  - Metal ions
- Membranes
  - E.g wetting agents (pre-flush step required?)
- Containers
  - Single-use containers: volatile or non-volatile organics; metal ions
  - Steel tanks: metal ions, particles from corrosion
- Connections and valves
  - Particles from wear

Assessing and managing risk from leachables

- Container and product-contacting materials
- Contact time with particular container
- Extractables studies with representative worst-case solvents to identify potential leachables
- Resin and membrane lifetime studies
- Equipment selection and maintenance

Case study: non-representative extractable study for intermediate container

- Reversed-phase chromatography purification step, capture and elute operation
- Elution buffer contains high % acetonitrile
- Eluate held >1 day at room temp in disposable bags
- Bag vendor extractables study used neutral H_2O, high pH, low pH, EtOH
- No vendor or applicant-generated extractable/leachable data for representative buffer
- Inadequate data for meaningful risk assessment for leachables

Phase 1 expectations reflect relatively low knowledge of process

- Generally expect HCP and DNA testing to be included at Phase I as a DS release test
- Release tests for high risk and/or late in process impurities, for example:
  - Unconjugated drug in antibody-drug conjugates
  - Cyanide from PEGyation by reductive amination
- Prefer quantitative specs, even if relatively wide at Phase 1 (can be narrowed with increasing clinical or manufacturing experience)
  - True of all specs, not just impurities!
- Data supporting virus clearance by ≥2 process steps with orthogonal clearance mechanism
- Sufficient process description to enable an initial assessment of risk from cell-culture and downstream related impurities

Develop assays early

- Assay development enhances process development
- Case study:
  - Development of an improved HCP assay with better coverage and sensitivity
  - Discovered a late-in-development process change had increased HCP in DS
  - Loss of clearance not detected by previous HCP assay
  - Additional purification step was added to the commercial process

Development and small-scale studies need to be representative of production scale

- Use same resins, buffers, column bed heights, flow rates, membrane materials, flow rates, etc.
- Column and membrane loads should reflect those in production
- As appropriate, include worst-case:
  - Ages of resins and membranes
  - Product/ impurity loads
  - Cell age (HCP expression may vary with age)
  - Spiking or challenge studies where suitable
- Include all sub-steps of unit operations such as membrane buffer flushes

Case study: column load too high in production process

- Adequate HCP clearance in development studies
- Process for phase 1 material had significantly higher protein load per unit resin volume
- Overloaded production column had poor clearance, clinical material had ~1000 ppm HCP
- Placed on clinical hold for uncontrolled process and potential clinical risk of high HCPs

Case study: virus clearance studies did not model process as run in production

- Virus breakthrough after pause in filtration can reduce virus clearance by a log or more
- Many processes include a flush with buffer to recover additional product
  - Pause not modeled in virus clearance studies
  - Duration is uncontrolled in manufacturing process

Commercial specifications for process-related impurities

- Lot rejection limits for impurities with relatively high risk of safety or efficacy impact
  - High potential for toxicity or immunogenicity
  - Insufficient process knowledge/experience/control to fully assure clearance
  - Novel impurity
  - High risk impurity enters product “close to the patient”, i.e. late in the process with few remaining clearance steps
  - Impurity introduced by material or process changes late in development
- In some cases criteria based on known or accepted risk, in others based on clinical and/or manufacturing experience (e.g. HCP)

Low-risk impurities with proven process capability may not need IPC or release test

- Clearance demonstrated in process validation and during development
- Well understood mechanisms of clearance (e.g. small molecule cell culture components)
- Risk of introduction is demonstrated to be low (e.g. resin lifetime studies show little risk of protein A leaching)

Justifying reduced testing category or “validating out” testing of higher risk impurities

- Measurement of clearance at scale
- Clearance capability under worst-case conditions understood
  - Effect of age of columns and membranes understood
- Small scale studies
  - Clearance for aged resins and membranes
  - Spiking or challenge studies
- In-process testing at appropriate control point
  - Direct testing of impurity
  - Surrogate tests demonstrate process performance
- Effective control strategy for raw materials (inputs understood)
- Leverage process and platform experience

Case study: column seals and column packing can affect clearance

- Sensitive HCP assay, scale-down studies, clinical lots, and process validation experience show high clearance capacity for HCP
- Poor sealing of one of the columns after repacking discovered after high residual HCP test result
- HCP assay added to the release specification

Case study: removal of impurity release test

- Toxic small molecule reagent introduced late in downstream process
- Cleared by chromatography step and UF/DF step
- Original release specification included test for the impurity
- Removal of the impurity specification approved
  - Clearance mechanism well understood (small molecule does not stick to product)
  - Process capable of clearing worst-case load
  - Sensitive assay detects levels many logs below levels that would pose safety risk (safety factor well established)
  - Sufficient process controls in-place to assure column and DF performance
  - Extensive manufacturing experience/process understanding: >100 commercial lots cleared to levels <<< specification limit

It can be challenging to set specs for accelerated development programs

- Relatively few clinical lots and relatively little manufacturing experience
- Challenge mitigated by:
  - Early identification of CQAs and risks to enable targeted process characterization and development
  - Early development of assays maximize availability of high-quality data
  - In some cases, post-marketing commitment to reevaluate and adjust specifications after specified number of commercial lots

Important to clearly communicate control strategy and supporting data

- Provide enough details about the process to present a clear picture
- Provide enough details about development studies to support that they are representative and whether they cover maximum loads/worst-case
- Describe risk assessments and mitigations that justify decisions about control strategy
- Define terms and units
- What do you know about the risks from impurities? How do you know it? How have you mitigated it? How will you know if something changes or something unexpected happens?

Acknowledgements

- Xianghong (Emily) Jing
- Joel Welch
- Juhong Liu


FDA
U.S. FOOD & DRUG
ADMINISTRATION