European Regulatory Experiences and Expectations of HCP Analysis and Control

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The views presented here are my own and do not necessarily reflect the views of the Paul-Ehrlich-Institute or any other European regulatory body.
Recombinant Blood Products (rFVIII, rFIX, …)

Regulatory framework – Marketing authorization

Goal: ensure production of safe biotechnology products with regard to the risk of residual process-related impurities: HCPs, host cell DNA…

General guidelines/monographs

- Guideline 3AB1A - Production and quality control of medicinal products derived by recombinant DNA technology (1995)
- EP monograph 0784 – Products of Recombinant DNA technology (01/2008)
Specifications


Specification versus validation approach

- CPMP/BWP/382/97 - Position statement on DNA and Host Cell Protein impurities, routine testing versus validation studies (1997)
Recombinant Blood Products (rFVIII, rFIX, …)

Comparability exercise after process changes

- ICH Q5E (CPMP/ICH/5721/03) NfG on biotechnological/biological products subject to changes in their manufacturing process (2005)

Biosimilarity exercise

- EMA/CHMP/BWP/247713/2012 - Similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (rev. 1, effective 01.12.2014)
Recombinant Blood Products (rFVIII, rFIX,...)

Clinical Drug Development Phase I-III

- EMEA/CHMP/BWP/534898/08 - Requirements for quality documentation concerning biological investigational medicinal products in clinical trials (2012)

- EP monograph regarding Immunological Assays/Validation
  EP 2.7.1 (20701) – Immunochemical methods (01/2008)
European Pharmacopoeia – HCP assay

- for HCP assays currently no specific EP monograph available
- suitable HCP assays are required due to the heterogeneous nature of HCPs in medicinal products, dependent on the specific manufacturing process

EDQM (European Directorate for the Quality of Medicines & HealthCare) has recently initiated a working party to draft a monograph on general considerations/recommendations on HCP testing and characterization

- Publication in ‘Pharmeuropa’ in April 2015
  - Talk by Kowid Ho
Requirements for HCP testing/characterization

Summary of guideline requirements:

- a sensitive assay (e.g. immunoassay) capable of detecting a wide range of host cell protein impurities should be used
- test system should be validated
- the active substance is tested for process-related impurities including HCPs
- control of HCPs are typically part of the drug substance specification
  - the upper impurity level should be defined, limit decision is made on case by case basis
Requirements for HCP testing...

- Specification setting for HCPs  \((EMA \ Guideline \ ICH \ Q6B)\)
  - specifications are linked to the manufacturing process
  - specifications should be based on lots used in pre-clinical and clinical studies
  - prerequisite: material used in pre-clinical and clinical studies is representative of the commercial process
  - linked to analytical procedures – confirm that data generated during development correlate with data generated at the time of filing the marketing authorization
Requirements for HCP testing…

Upper safety limits for HCP impurities are not defined

_{CPMP/BWP/382/97 - Position statement on DNA and host cell protein impurities, routine testing versus validation studies (1997)}

- not possible to set a common limit for different products
- qualitative and quantitative HCP pattern depends on the individual manufacturing process

- **Regulatory requirement:**

  Reduction of host cell impurities to an acceptable level (as much as possible) in a consistent and reproducible manner using a well-controlled manufacturing process
Case studies – Blood Products

General aspects for HCP testing:

- No examples for platform production / platform HCP assays
- HCP assay development as in-house and as commercial assay
- Validation approach not used – HCP testing performed at the drug substance level
- HCP clearance studies performed across different manufacturing steps
- Drug substance specification limits for HCPs are usually in discussion – should reflect the range tested in clinical studies and the routine process
- Successful marketing authorization application: mostly with in-house process-specific HCP assays
Case study 1 - Drug substance, 1/3

- CHO HCP testing (sandwich ELISA) implemented as part of the Drug Substance Specification
- Development of Host Cell Protein assay (CHO) explained – same in-house assay used for all stages of development
- Analytical procedure, reagents, standards, antibodies… described in detail
- CHO reference material (pooled CHO antigens from supernatant of fermentation process)
- Preparation of different polyclonal antibodies using antigens obtained by different culture/harvesting methods – multispecific antibody
Pooling of polyclonal antibodies performed to improve HCP coverage (tested/selected on ELISA basis)

- Same polyclonal antibody used for capture and detection

- Validation of analytical in-house test provided (ICH Q2 (R1))

- HCP coverage shown by different test methods: 1D-SDS PAGE – Coomassie, Silver stain and Western blot

- Estimated HCP coverage: ~ 80 %

- All batches tested for HCP levels – clinical, validation and commercial batches

- HCP levels around X000 ppm observed
HCP levels around X000 ppm observed – initially proposed limit

- considered too high when compared to the HCP batch results for routine and clinical batches (after improved manufacturing process)
- about X0 batches were tested - only few batches with high ppm values found

Tightening of HCP specification limit according to the DS batch analysis data (for routine and clinical batches) was requested

- HCP specification limit was reduced to X000/2 ppm
  - represents improved routine manufacturing process
  - covered by clinical trials
Marketing authorization application – not successful

- CHO HCP testing performed using a commercial ELISA assay (same polyclonal antibody for capture and detection)
- Problem low sensitivity for HCPs (different commercial assays used during clinical development until MAA)
- Estimated coverage (generic assay, test kit): ~ 60 to 80 %
- ELISA, 2D electrophoresis (silver stain) and Western blot
- During the MAA procedure, a new process-specific HCP ELISA was developed with up to 30 to 50-fold higher sensitivity – thus much higher HCP levels were observed, validation pending
Clinical studies: antibodies against CHO HCPs observed in patients (up to 1/4 of enrolled patients)

Anti-CHO-AB not associated with any clinical relevant events (no safety issues or other abnormal lab results)

Immunogenicity risk assessment – no change in risk profile accord. to company

- Baseline screening for some patients missing
- Different reactivity for different patient sample batches observed – potential explanation ? (5% to 25 %)
Clinical trial amendment and revision of risk management plan was necessary.

Additional testing of patients was proposed.

Attempts were made to identify the HCP antigen(s) to which the patient antibodies are directed (LC-MS/MS, LC-MRM).

Preventive measure: introduction of a ‘polishing step’ to reduce HCPs – change in manufacturing process during MAA.

Problem for company: additional data requirement – MAA time lines.
Problems and required steps:

- Reduction of high HCP levels (and other impurities) in the drug substance by additional ‘polishing’ step
- Due to change of the manufacturing process - additional clinical data with the impurity-reduced material were required
  - could not be performed within MAA time lines
Conclusions for HCP testing/characterization

Summary of requirements:

- A sensitive assay (e.g., immunoassay, ...) capable of detecting a wide range of HCPs should be used, preferably process-specific.
- Development of the assay, the reagents, and the standards should be described.
- A validated test system should be used.
- HCP testing should be implemented as part of the drug substance specification.
- Upper impurity level should be defined - representative of the routine process and the clinical studies (case by case).
- Identification of main impurities (?), risk assessment.