Regulatory updates from the EU

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[AGES logo]
Content

• Update on biologicals
  • Process validation and ICH
  • Biosimilars
  • Pharmacovigilance activities
• Further EU Regulatory activities
  • Promoting early access to medicines
  • NTC Training center
• Transparency → separate presentation
Quality questions raised by Rapporteurs/BWP in dossiers submitted in 2015

- Major objections are the exception rather than the rule
- Major Objections identified in manufacturing process description, potency assay, manufacturing process development, comparability
- In general, recombinant proteins have slightly more questions (however this is based on a small sample size)

Slide provided by Seán Barry
Distribution of other concerns

Based on 20 MAA applications for mAbs and recombinant proteins received in 2015
The three most consistent areas for questions are:

- Process Development (S.2.6)
- Process validation (S.2.5)
- Specifications (S.4.1, S.4.5, P.5.1, P.5.6)
VALIDATION = consistency

• Required for Marketing Authorisation
• Validated manufacturing process under appropriate control
• Ensure to obtain a active substance and final product with a defined profile – purity, functionality
• Ensure and control impurities to the minimum
• Ensure that each patient is administered with the product as authorised
• Aseptic process validation from start of clinical development
<table>
<thead>
<tr>
<th>Aspect</th>
<th>Minimal Approaches</th>
<th>Enhanced, Quality by Design Approaches</th>
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| Overall Pharmaceutical Development | • Mainly empirical  
• Developmental research often conducted one variable at a time | • Systematic, relating mechanistic understanding of material attributes and process parameters to drug product CQAs  
• Multivariate experiments to understand product and process  
• Establishment of design space  
• PAT tools utilised |
| Manufacturing Process         | • Fixed  
• Validation primarily based on initial full-scale batches  
• Focus on optimisation and reproducibility | • Adjustable within design space  
• Lifecycle approach to validation and, ideally, continuous process verification  
• Focus on control strategy and robustness  
• Use of statistical process control methods |
| Process Controls              | • In-process tests primarily for go/no go decisions  
• Off-line analysis | • PAT tools utilised with appropriate feed forward and feedback controls  
• Process operations tracked and trended to support continual improvement efforts post-approval |
| Product Specifications        | • Primary means of control  
• Based on batch data available at time of registration | • Part of the overall quality control strategy  
• Based on desired product performance with relevant supportive data |
| Control Strategy              | • Drug product quality controlled primarily by intermediates (in-process materials) and end product testing | • Drug product quality ensured by risk-based control strategy for well understood product and process  
• Quality controls shifted upstream, with the possibility of real-time release testing or reduced end-product testing |
| Lifecycle Management          | • Reactive (i.e., problem solving and corrective action) | • Preventive action  
• Continual improvement facilitated |
ICH Q8, Q9, Q10, Q11 now Q12

• ICH Q8 – formulation development of final product – focused on chemicals – defines QbD

• ICH Q9 – Introduces the risk analysis approach – required to understand process validation under QbD – Document seen only in inspection

• ICH Q10 – Sets the pharmaceutical quality system: process performance - state of control ensured - continual improvement … verified in inspection

• ICH Q11 – Process development and manufacture of active substances based on ICHQ9 – Chem + Biotech – for MA assessment

• ICH Q12 started – Selected fixed specifications from MA by analogy with the product specification file of IMPD – inspection
Active Substance consistency – for MA

From process development (ICH Q11) to validation

Draft guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission

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<th>Download document</th>
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Flexibility to reduce MAA verification requirements e.g. accelerated access, urgent need, protocols, multi-facility
Guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission
Process evaluation

Studies, performed at small and/or commercial scale, should provide evidence that the complete manufacturing process and each step/operating unit have been appropriately designed and are controlled to obtain a product of the intended quality.

DoE and RBA are important tools to define and control acceptable process variability.

Process verification

Studies which should confirm that the final manufacturing process performs effectively and is able to produce an active substance or intermediate meeting its predetermined acceptance criteria, on an appropriate number of consecutive batches produced with the commercial process and scale.

Generally predefined testing of 3 consecutive batches – statistically valid.
Process validation should not be viewed as a one-time event. Process validation incorporates a lifecycle approach linking product and process development, validation of the commercial manufacturing process and maintenance of the process in a state of control during routine commercial production.
Figure 1: Approach to Implementing Quality by Design for obinutuzumab
Similar but not identical
BIOSIMILAR COMPARABILITY

- The same reference product should be used in all studies including the comparability exercise.
- Similarity to be established at finished product level.
- Publicly available reference standards (e.g. Ph. Eur.) cannot be used as the reference medicinal product for demonstration of biosimilarity.
- Minor differences in quality may be acceptable but need to demonstrate not to impact on the performance of the product.
- Remove impurities instead of qualifying them with preclinical testing.
- Acceptable criteria for biosimilarity defined within reference product ranges – handled separately from release criteria.
- Quality attribute values which are outside the range(s) of variability measured in the different profiles of the reference product should be justified.
- Once MA granted biosimilarity no longer needed – changes trigger comparability.
PHYSICOCHEMICAL AND BIOLOGICAL CHARACTERISATION

- Aminoacid sequence should be identical or part of microheterogeneous pattern of the reference product.
- N- and C- terminal aminoacid, free SH or disulfide bridges compared
- Truncation / modification quantified
- overall glycan profile, site-specific glycosylation patterns as well as site occupancy should be compared.
- Unusual glycosylation (unusual monosaccharides, linkages or sequences) or variants not observed in the reference product require appropriate justification.
- measure of biological activity with complementary approaches - comparison of affinity of the products to the intended target - sufficiently discriminatory to actually detect changes in biological activity
IMMUNOCHEMICAL PROPERTIES – specific for monoclonals

- Monoclonal antibodies or related substances (e.g. fusion proteins based on IgG Fc), the immunological properties to be fully compared.
- Binding affinity of the Fc to relevant receptors (e.g. FcγR, C1q, FcRn) should be compared. (part of in vitro NC program)
- Compare the ability to induce Fab- and Fc-associated effector functions

PURITY AND IMPURITIES

- Product related substances and product-related impurities compared qualitatively and quantitatively
- Similarity of the degradation profile in stress conditions useful
- Process-related impurities (e.g., host cell proteins, host cell DNA, reagents, downstream impurities, etc.) not part of comparability.
EU – Position on statistics

• Currently EMA does not require or recommend any specific statistical method – approaches to be justified
• The final conclusion on analytical biosimilarity can not be drawn only based on statistical analyses
• Consider impact of sample size, acceptance ranges/significance levels, risk of false positive conclusion
• Similarity ranges based on tolerance intervals can lead to wide ranges with little (or no) clinical relevance
• If inferential statistics is used, testing for equivalence is generally preferred

Adapted from N. Ekman
Purity – similar / differences
• SEC-HPLC – minor higher aggregates but monomer >99%.
• CE-SDS (non-reduced) - array of six IgG molecular variants: higher variant 2HC-1LC with no impact on TNFα binding affinity and in vitro TNFα neutralising activity.
• IEF - pI ranges
• IEC-HPLC - six peaks different relative proportions. Oxidized forms slightly higher. Each with similar potency by in vitro TNFα neutralisation analysis, TNFα binding affinity (by ELISA) and FcRn binding affinity (SPR) + C1q binding but lower FcγRIIIa binding affinity

High order structure – similar / no differences
• disulphide bonds , free thiol/mole IgG , DSC three transition temperatures, Fc domains comparable 3-D structures

Primary structure – similar / differences
• amino acid analysis, peptide mapping (MS/MS), sequencing LC-ESI-MS
• C- terminal Lys – CT-P13 with >K0 HC-IgG and <K1 HC-IgG

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INFLIXIMAB BIOSIMILAR
Inflectra / Remsima

Stability – similar / no differences
• Long term profile
• Increase in oxidized variants in long term, accelerated (25 ± 2° C/60 ± 5% RH) or stress conditions (40 ± 2° C/75 ± 5% RH)

Glycosylation – similar / differences
• Asn300 - only site of N-glycosylation G0F and G1F. No O-Glycans, no new glycans
• higher levels of G1FNeuGc and G2FNeuGc
• monosaccharide molar ratios content of neutral and amino sugars. NeuGc levels.
• afucosylated glycans levels, Man5 and G0

Further justification in relation to the biological activity.
INFLIXIMAB BIOSIMILAR
Inflectra / Remsima

Non – Clinical biosimilarity studies
- In vitro differences (Quality) justified
- no difference in PK in rats between as well as in relation to general toxicity

Clinical biosimilarity studies
- In two clinical trials, similar pharmacokinetics, efficacy, safety, and immunogenicity profiles
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<th>Medicine Name</th>
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Biosimilar product review

- 36 MAAs submitted
  - 29 MAAs reviewed
    - 1 Negative
      - Interferon alfa
    - 21 Positive
    - 7 Withdrawn
      - Insulin (6)
      - Epoetin (1)
    - 19 Valid MAs
      - Somatropin (1)
      - Epoetin (5)
      - Filgrastim (8)
      - Infliximab (2)
      - Follitropin (2)
      - Insulin glargine (1)
  - 7 MAAs under review
    - Etanercept (1)
    - Insulin (1)
    - Enoxaparin sodium (2)
    - Infliximab (1)
    - Pegfilgrastim (1)
    - Rituximab (1)
Better monitoring of biological medicines

New chapter in guidelines on good pharmacovigilance practices

The European Medicines Agency (EMA) has adopted a new chapter to its guidelines on good pharmacovigilance practices (EU-GVP), entitled “Product- or population-specific considerations II: Biological medicinal products”. Good pharmacovigilance practices are a set of measures designed to ensure the robustness of the system of safety monitoring. The new chapter provides guidance on how to better monitor and manage the safety of biological medicines to optimise the safe and effective use of these products in Europe.

Guidelines on good pharmacovigilance practices (GVP)
Introductory cover note, last updated with considerations P.II on biological medicinal products finalised post-public consultation

Guideline on good pharmacovigilance practices (GVP)
Product- or Population-Specific Considerations II: Biological medicinal products
Content – 3 parts

• A - specific issues and challenges associated with PV for biologicals
• B - addressing these challenges when developing and implementing PV
• C - guidance on operation of the EU network: roles and responsibilities of stakeholders

The challenges addressed are:
immunogenicity
manufacturing variability
stability/cold chain
product traceability
EU initiatives to promote early access

**PRIME**
Major public health interest, unmet medical need.
Dedicated and reinforced support.
Enable accelerated assessment.
Better use of existing regulatory & procedural tools.

**Accelerated assessment**
Major public health interest, unmet medical need.
Reduce assessment time to 150 days.

**Adaptive pathways**
Scientific concept of development and data generation.
Iterative development with use of real-life data.
Engagement with other healthcare-decision makers.

**Conditional MA**
Unmet medical need, seriously debilitating or life-threatening disease, a rare disease or use in emergency situations.
Early approval of a medicine on the basis of less complete clinical data.

**Compassionate use**
chronically, seriously debilitating/life threatening diseases, no satisfactory treatment EU authorised; undergoing centralised MAAs or clinical trials; Mandatory/optional scope of centralised procedure. CHMP opinion can only be requested via member states

Modified from slide of Peter Richardson
Reinforce scientific and regulatory advice
- Foster early interaction with dedicated rapporteur
- Multidisciplinary expertise
- Parallel scientific advice with HTAs
- Applicants will be advised on milestones

Optimise development
- Focus on efficient development
- Robust data generation
- Guidance on development plan and regulatory strategy

Enable accelerated assessment
- Facilitated by knowledge gained throughout development and scientific advice
- Intensive guidance will lead to better informed development plans

www.ema.europa.eu
Medicine’s Adaptive Pathways to Patients (MAPP)

Adaptive pathways

Treatments in high medical need areas where collection of data via traditional routes is difficult and where large clinical trials would unnecessarily expose patients who are unlikely to benefit from the medicine
Adaptive Pathway is based on 3 principles

- **Iterative development**
  - Expansion of target population or progressive reduction of uncertainty

- **Progressive gathering evidence through real-life data**

- **Early involvement of patients and health-technology-assessment bodies in discussions on a medicine’s development.**

- Optimises use of regulatory tools and flexibility

- The evidence generated addresses not only the needs of regulators, but of HTA bodies as well

- No change to the *principles* of the benefit vs risk approach

- Acceptance of uncertainty balanced by continued evidence generation
Supporting training and capacity building

• Online European training platform
• New training initiative endorsed by the HMA and EMA
• Mission: Ensure that good scientific and regulatory practices are spread across the network along with harmonised training standards, through the provision of high quality and relevant training materials identified and shared through by the EU NTC platform.

www.hma.eu/otsg.html
http://euntc.eudra.org/
NTC Aims

• Harmonization of assessment

• Fostering science based assessment, inspection, pharmacovigilance, decision making

• Professional development for staff of national regulatory agencies and EMA and, possibly, others involved in development of medicines regulation

• Online European training platform
This presentation has been a joint development by Portugal and Austria

Thank you for your attention!