Recent trends in Biopharmaceuticals in the EU: EMA perspective

CASSS CMC Strategy Forum Europe 2012
Prague, 6th May 2013
EU - New / Revised Legislation

EC Pharmaceutical Package:

• Patient access to information
• Pharmacovigilance
• Falsified medicines

Also of note:

• Variations regulation
• Clinical trials regulation
• Medical devices regulation

Not a major impact on quality guidance
EMA Activities on Quality of Biologicals

The CHMP Biologics Working Party is responsible in:

- Quality aspects of biological medicinal products
- CHMP guidance documents
  - Biosimilars
  - Validation of manufacturing processes
  - Viral safety
  - Pandemic influenza
  - Application of 3Rs
- EU Regulatory activities
  - Variation classification guideline
- International cooperation
Content

- **Biosimilars: update and revision of guidance**
- Variation regulation
- **BWP guidelines: Viral safety, Validation, Vaccines, ATMPs, 3Rs**
Evolution of Biosimilars in the EU

**Legislation**
- Directive 2001/83/EC
- Directive 2004/27/EC
- Directive 2003/63/EC

**Overarching guideline**
- Quality guideline
  - Non-clinical/Clinical guideline

**Guidance**
- Revision of overarching guidelines

**Product evaluation**
- First biosimilars authorised – Omnitrope and Valtropin
- First biosimilar epoetins authorised
- First biosimilar filgrastims authorised
- First biosimilar mAbs under evaluation
Biosimilar medicinal products
Legislation

Annex I of Directive 2001/83/EC

- General principles in a guideline
- Type/amount of data on a case by case basis
- Requirements considering specific characteristic of each individual medicinal product
Biosimilar product experience in EU

Marketing Authorisation

27 MAAs submitted

22 MAAs reviewed

14 Positive

7 Withdrawn

12 Valid MAs

1 Negative

12 Valid MAs

2 Withdrawn

5 MAAs under review

Follitropin alfa (2)
Infliximab (2)
Filgrastim (1)

Epoetin (5)
Filgrastim (1)

Somatropin (1)
Epoetin (1)
Insulin (6)

Interferon alfa
Biosimilar product experience in EU
Scientific advice

Scientific Advice for Biosimilar Monoclonal Antibodies in comparison to other classes
(Data until December 2012)

Source: EMA Scientific Advice database
Guidelines for biosimilars

Overarching Guidelines:

- **Overarching Guideline (CHMP/437/04)**
  - “Guideline on Similar Biological Medicinal Products”
  - Draft GL ~May 2013

- **Overarching non-clinical/clinical Guideline**
  - Draft GL ~May 2013

- **Overarching Quality Guideline**
  - Final GL ~Dec 2013

Class-specific Guidelines: non-clinical/clinical aspects

- **Insulin**
  - 2006
  - 2006
  - 30 Jun 2013

- **Somatropin**
  - 2006

- **G-CSF**
  - 2006

- **Epoetin**
  - 2006 Rev 2010

- **IFN-α**
  - 2009

- **LMWH**
  - 2009 Rev 2013

- **mAbs**
  - 2009

- **IFN-β**
  - 2012

- **Follitropin alfa**
  - 2013

Implementation

- 1 Sep 2013
Main changes:

- Definition of biosimilar and scope of biologicals covered
- Improved efficacy and safety
- Authorisation based on a PK comparative study (minimal clinical data)
- Choice of reference medicinal product: Authorised in the EEA
- Comparability exercise:
  - Single reference product throughout the development programme
  - Non-EEA authorised comparator in certain clinical studies and in vivo non-clinical studies
    - Authorised by regulatory authority with similar scientific/regulatory standards
    - Representativeness of the reference medicinal product
Quality guideline - revision

Main changes:

- Quality target product profile (QTPP)
- Evolution of quality profile through life-cycles
- Comparability at the level of the finished product
- Amino acid expected to be the same as for the reference product
- Section on immunochemical properties to cover additional testing expected for monoclonal antibodies
- Different expression system
Summary of comments

- Clarification requested on how to apply QTTP concept
- Terminology: Comparability vs. Biosimilarity
- Clarification requested on appropriate use of publicly available standards, particularly Ph. Eur. standards
- Global development – further details requested
- CTD requirements (location for Q comparability exercise)
- Further clarity requested on use of different/novel expression system
- Further clarity requested regarding acceptable differences
EC Market access to biosimilars

- Sep 2010 project launch
- Review availability of biosimilars in EU markets
- Define the necessary conditions for patient access
  - Current experience with access and uptake of biosimilars
  - Effects and consequences from the uptake of biosimilars
  - How to promote uptake of biosimilars
- Deliverables -> 22\textsuperscript{th} April
  - Consensus doc: “What you need to know about Biosimilars”
  - Information on reimbursement in EEA countries
  - Study on “biosimilar market access” prepared by IMS
  - Survey conducted by EGA to identify good practices, obstacles related to biosimilar uptake

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Variations Regulation

Regulation (EC) No 1234/2008
- in force since Jan 2010
- medicinal products authorised via centralized (CP), mutual recognition (MRP) and decentralized

Procedural guideline

Variation classification guideline

Regulation (EC) No 712/2012
- in force since Nov 2012
- extend the scope -> medicinal products authorised at national level
- Changes in decision making process for product involving a CP
  - EC decision only for type II variations favourable & affecting annexes, acc. to Art 2.3.1(a)

Variation to all MAs in EU subject to the same rules

Earlier implementation for most Quality changes for CPs -> as no EC decision needed.
Revision of classification guideline

As part of update to Regulation, review of guideline to consider:

• New Pharmacovigilance legislation;
• Other changes to reflect experience;
• Outcome of Art. 5 recommendations
Revision of Classification guideline

Overview of Quality related changes

• New scopes:
  - As result of Art 5 (e.g. stability protocol)
  - From frequent questions to CA/ Clarification purposes (e.g. novel excipient, WCB storage)
  - Align requirements (e.g. consistency between active and product)
  - In relation to enhanced development (QbD) (e.g. changes to change management protocols)
  - relevant to biological products e.g. design space DP, adventitious Agents Safety, batch control/testing sites
Post approval change management protocols

“Traditional” approach
Evaluation of a proposed variation as a ‘whole’
(Strategy + Results)

Early Step 1:
Submission of a Protocol
MAA / Type II Variation

Quick Step 2:
Implementation of the change
Type IB Variation for biologics
PACMP – EMA Experience

### 30 Protocols received (MAA, type II) on a broad range of changes:

<table>
<thead>
<tr>
<th>Type of Change</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site transfers: active substance / finished product</td>
<td>20</td>
</tr>
<tr>
<td>Changes to manufacturing process</td>
<td>6</td>
</tr>
<tr>
<td>(Virus filtration steps, transfer of QC methods, extension of column lifetime)</td>
<td></td>
</tr>
<tr>
<td>WCB replacement using a new procedure</td>
<td>2</td>
</tr>
<tr>
<td>Increase in batch size</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
</tr>
</tbody>
</table>

- The same protocol can be used several times
- Several changes can be included in the same protocol if they are related
- Step towards a more flexible and risk-based approach for managing changes post approval

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Viral safety activities

• Drafting of guideline on porcine trypsin -> comments by Aug 2013
  – To ensure safety of medical products where trypsin used (cell culture, virus particle activation, protein-cleaving reagent)
  – Limitation of viral inactivation capacity of biological FP (e.g. Live vaccines, cell products).

• Revision of guideline on bovine serum -> publication May 2013
  – If contamination of Bovine diarrhoea virus (BVDV), limit should be below demonstrated inactivation limit.
  – Deletion of limits of anti-BVDV Abs present
Validation of manufacturing processes

• EMA/Industry Workshop 9th April 2013
  - Agreement on terminology
  - Expectation on what to be included in process validation studies
  - Traditional vs. Enhanced approach.

• Drafting of guideline on validation of manufacturing process of biological APIs
  - expected data in MAA
  - Scope: mainly on recombinant proteins
  - process validation: evaluation, verification, continued process verification
  - points to consider in process validation
Vaccines

• Revision of Guidance on Influenza Vaccines Quality Module

  • Scope on influenza vaccines: pre-pandemic, mock up/pandemic and seasonal inactivated vaccines; seasonal LAIV
  • Replaces quality requirements of existing EMA guidance on influenza
  • Provides guidance on development, manufacturing and control for marketing-authorisation applications
  • Updated guidance in the light of experience gained during the recent pandemic
  • Consolidates the current existing guidelines for influenza vaccines
Vaccines

- Revision of Guidance on Influenza Vaccine

  Quality Module, selected features:

- Manufacturing development:
  Information covering multiple strains to build up a knowledge database

- Characterisation:
  Extended characterisation studies for enhanced process and product understanding, to provide information about consistency from one season to another, allow better prediction of impact of process changes
  Besides HA and NA, other relevant antigens to be characterised as far as technically feasible

- Potency:
  Enhance information on quality characteristics such as amount, antigenicity of the relevant influenza antigens and their formulation
  Use of alternative assays (to SRD), which could be applied prior to the availability of SRD reagents, is encouraged
Advanced therapies

- Revision of Quality Guidance on Gene Therapy Medicinal products (Concept paper: Mar 2010)
  - Reflect scientific advances and new regulatory requirements (Reg. 1394/2007)
  - Cover development genetics, production, purification, characterisation, and comparability

- Implementation of the principles of risk based approach.

- Establishment of quality standards of starting materials for ATMPs with EDQM
3Rs initiative

- Replacement, reduction and refinement of animal testing -> Dir 2010/63/EU
- Ad hoc expert group on 3Rs: eliminate repetitious and unnecessary animal testing in EEA.
- Interinstitutional collaborations -> EDQM, ICH
- Revision on animal testing requirements in 5 guidelines by BWP:
  - Development, production, characterisation and specifications for MAbs
  - Potency testing cell based immunotherapy medicinal products
  - Production and control of animal Ig and immunosera for human use
  - Production and quality control of cytokine products
  - Pharmaceutical aspects of combined vaccines.
- Acknowledgement of the need of animal testing in certain instances
- Batch release testing of authorised products?
- Justification/assessment of compliance with Dir 2010/63/EU
- Regulatory acceptance of 3Rs testing requirements
  -> Work in progress.
Thank you

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