EMA & Biosimilar update: Trends from marketing authorisation applications, scientific advice procedures and policies

Presented by: Peter Richardson
Head of Quality Office
Specialised Scientific Disciplines Department, EMA

EMA - 20th Anniversary

Agency Reorganisation
- Review & Reconnect
- Implementation

New Building:
30 Churchill Place
Human medicines

▶ R&D Support
▶ Evaluation
▶ Procedures
▶ Inspections & Pharmacovigilance

**4 Main Divisions**

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**Evaluation Div.**

**Two Departments**

6 / 3 Offices

▶ Therapeutic Area Offices: (EPL) + Labelling Stds.

▶ Quality Office,

Biostatistics,

Non-clinical and clinical p’cology
Primary EMA staff in the context of handling evaluation procedures

**Procedure Manager (PM)**
- Applicant’s primary contact during the course of all evaluation procedures
- Provision of regulatory procedural guidance
- Ensures adherence to procedural guidelines and timelines
- Regulatory scientific support in simpler procedures
- Maintains process performance metrics

**EMA Product Lead (EPL)**
- Leads the EMA product team
- Accountable for overall product knowledge
- Provides clinical and regulatory science input
- Supports consolidation of a committee position
- Facilitates cross-committee discussions
- Reference for the defined products/disease area

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Evolution of Biosimilars in the EU

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

**Guidance**
- Overarching guideline
- Quality guideline Non-clinical/Clinical guideline
- Product-class specific guidelines

**Revision**

**Product Authorisations**
- somatropin
- epoetin
- filgrastim
- infliximab & follitropin
- insulin glargine

*amending Directive 2001/83/EC
Biosimilar product review

32 MAAs submitted

29 MAAs reviewed

3 MAAs under review

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7 Withdrawn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)

2 Withdrawn
Filgrastim (1)
Somatropin (1)

Etanercept (1)
Insulin (1)
Enoxaparin sodium (1)

Business Pipeline

Forecast and business intelligence
businesspipeline@ema.europa.eu

- BP dialogue with companies - 50+ companies actively participating in the BP activity
- Internal discussion - Contributions to the EMA planning and reporting cycle
- Business intelligence - 20/25 BP meetings per year
- Forecast - increase in biosimilar MAAs in 2015
Guidelines for biosimilars

General Guidelines:

Overarching Guideline (CHMP/437/04 Rev. 1)
“Guideline on Similar Biological Medicinal Products”

Non-clinical/clinical Guideline  Quality Guideline

Class-specific Guidelines: non-clinical/clinical aspects:

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Quality – the foundation of biosimilars:
highly structured development

Quality
• Define Target Profile
• State of art analytical tools
• Structured development: QbD
• Critical Quality Attributes – systematically Controlled
• Non-critical attributes – greater tolerance
How to evaluate biosimilarity at the quality level

**mAb case study – Quality Profile**

<table>
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<tr>
<th>Quality attribute</th>
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<th>Min/Max ranges</th>
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<tr>
<td>HGD activity</td>
<td>Reference</td>
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**Quality**
- **QbD – Risk Analysis**
- **Determine CQAs**
- **Control Operating Ranges for CQAs**
- **Non-Critical attributes – less stringent control**

**Outcome**
- **Biosimilar: high level of control and similarity to originator product**

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**Insulin guideline**

*Revision finalised in March 2015*

- Intermediate-, long-acting insulin preparations and insulin analogues now included
- Risk-based approach for non-clinical *in vivo* studies
- More detailed guidance on the design of the insulin clamp study
- Expectations regarding the safety study & prerequisites for waiving the safety study
  - Biosimilarity convincingly concluded from physico-chemical & functional characterisation and from PK and PD profiles
  - Impurity profile and nature of excipients of low risk / concern
  - Scientific justification always required
First biosimilar insulin approved

- Robust quality and non-clinical

- PK/PD clamp studies provided pivotal evidence of similar efficacy

- Two clinical studies (HBA1c) in patients with type 1 and 2 diabetes
  - Provided supportive evidence in relation to efficacy
  - Provided the required safety and immunogenicity data

Scientific advice for biosimilars

Around 75% of scientific advice requests are for monoclonal antibodies
Trends from scientific advice procedures

- Explore use of statistical methodology for comparative assessment of quality attributes
- Global development – increasing use of non-EU comparator
- Variety of clinical approaches proposed to demonstrate biosimilarity

Statistical methodology for quality comparability

20 May 2012
Committee for Medicinal Products for Human Use (CHMP)

Concept paper on the need for a reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development

Agreed by Biostatistics Working Party: March 2013
Adoption by CHMP for release for consultation: 30 May 2013
Start of public consultation: 28 June 2013
End of consultation (deadline for comments): 30 September 2013

Comments should be provided using this template. The completed comments form should be sent to biostatistics@ema.europa.eu.

Keywords: statistical methodology; quality attributes; equivalence testing; biosimilar; biological product
Statistical methodology for quality comparability

- Triggered by increasing number of scientific advice requests
- 25% of SA requests in 2014 for biosimilars include discussion on statistical methodology for quality aspects
- Reflection paper to cover both biosimilar developments and comparability evaluation as per ICH Q5E
  - Challenges: Limited number of batches + Diversity of critical quality attributes
  - Discuss limitations of existing methodologies and suggest alternative approaches

Overarching Guideline

“Global Development” option:
(i.e. Reference Product from non-EU area)

- Aim: Facilitate global development
- Reference product must be authorised in the EEA
- Comparability exercise: Non-EEA authorised comparator can be acceptable for certain clinical studies and in-vivo non-clinical studies, provided it is:
  - Authorised by regulatory authority with similar scientific/regulatory standards
  - Representative of the reference medicinal product (to be demonstrated by the applicant – bridging data required)
Scientific Advice on global development

- Global development approach proposed in 75% of the scientific advice requests for biosimilars in 2014

Experience from Scientific Advice requests

- Extrapolation
  - Frequently raised topic
  - More difficult with complex substances (e.g. mAb)
  - Generally: single study acceptable
  - May need additional PK/PD bridging

- Clinical Indication
  - Flexibility in clinical model can be discussed
  - Increased proposals to use oncological indications
Regulatory Convergence

- EU guidelines and experience continue to be important reference for other Competent Authorities
- EU supports further development / implementation of WHO SBP guidelines
- Liaison with international partners (e.g. via International Pharmaceutical Regulators Forum – IPRF BWG, also Biosimilar Cluster EMA/FDA/HC/PMDA)
- Parallel scientific advice/ad hoc discussions with FDA

Biosimilar identification & INN

- EMA uses INNs according to the WHO policy
- Acceptable for biosimilar to use same INN as its reference product (subject to successful demonstration of comparability)
- EMA follows closely the discussions on a WHO Biological Qualifier: uncertain value for EU

http://www.who.int/medicines/services/inn/inn_bio_bq/en/
Pharmacovigilance/prescribing

For all biologicals:
- Brand name and batch number should be included in adverse reaction reporting (Directive 2010/84/EU)
- Brand name prescribing desirable - should be included in cross border medical prescriptions (Directive 2012/52/EU)

- Study showed good product identification for biosimilars (Vermeer et al, Drug Saf 2013;36(8):617-25)
- July 2016 → Implementation of ISO standards: Identification of Medicinal Products (IDMP)

Biosimilars – product information

Information available to the healthcare professional:
- Name and INN included in the labelling
- Biosimilar: Summary of Product Characteristics (SmPC) closely follows the SmPC of the reference product
- Product identified as a biosimilar in the SmPC
- Details regarding the basis for approval (e.g. comparability studies performed) are outlined in the European Public Assessment Report (EPAR), available on the EMA website
Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins

Revision started in March 2014

- Points under discussion
  - More specific guidance for the presentation of immunogenicity data
  - Requirements of data on antibody assays
  - Role of in-vitro and in-vivo non-clinical studies
  - Risk-based approach to immunogenicity
  - Clinical data to study potential consequences of unwanted immune responses
  - Comparative immunogenicity studies
  - Post-licensing immunological studies

- Workshop planned: 4Q 2015

BMWP info session on Biosimilars

EMA Human Scientific Committees’ Working Parties with Patients’ and Consumers’ Organisations (PCWP) and Healthcare Professionals’ Organisations (HCPWP) joint meeting

Conclusions from meeting:

- There is a clear need for education in this area: to resolve misconceptions and increase knowledge / awareness
- Emphasise: All biologicals are subject to thorough evaluation and surveillance
- Further discussion on substitution and interchangeability need to take place at member state level
EMA Website - Biosimilar landing page


Links to:
- Q and A for biosimilars
- Biosimilar guidelines
- BMWP mandate & work plan
- Procedural guidance for biosimilars
- Public assessment reports (EPARs) for biosimilars

Thank you for your attention

Peter Richardson,
Specialised Scientific Disciplines Department, EMA
Head of Quality Office
peter.richardson@ema.europa.eu

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(Quality Office)

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(CHMP & SAWP member)