EU update on regulatory developments

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Niklas Ekman, Ph.D.
Senior Researcher and Quality assessor for biological medicinal products
Finnish Medicine Agency (FIMEA), Helsinki, Finland
Vice-chair of the Biosimilar Working Party (BMWP), EMA
Alternate of the Biologics Working Party (BWP), EMA
Outline

1. International cooperation at EMA
2. EMA’s efforts to enable timely access
3. Biosimilars in EU – an update
4. EMA relocation

Disclaimer: The views expressed are those of the presenter and should not be understood or quoted as being made on behalf of the European Medicines Agency or its scientific Committees
The four pillars of the EU Medicines Agencies Network Strategy to 2020

1. Contributing to human health
   ▪ Availability, timely access, innovation support, regulatory capability and transparency

2. Contributing to animal health and human health in relation to veterinary medicines

3. Optimizing the operation of the network
   ▪ Scientific and regulatory capacity, operational excellence, effective communication, strengthen links with other authorities and with stakeholders

4. Contributing to the global regulatory environment

http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000292.jsp&mid=WC0b01ac05800293a4
EMA and International Regulatory Cooperation

**Bilateral**
- Confidentiality arrangements
- Mutual recognition agreements (GMP)
- Other types agreements, e.g. specific mechanisms with China, India, Russia, Israel

**Multilateral**
- WHO engagement
- Strategic forums, e.g. ICMRA
- Work-sharing, e.g. IGDRP
- Convergence and harmonisation forums, e.g. ICH, IPRF, PIC/S
- Ad hoc workshops with non-EU regulators

EMA's international cooperation activities aim to:

• Ensure the **quality of medicines** and the integrity and security of the supply chain;
• Ensure the **integrity of data** used to support clinical trials and manufacturing;
• Encourage a **global approach** to authorisation and supervision of medicines;
• Promote **effective use of global regulatory resources** by avoiding unnecessary duplication of efforts;
• Streamline **public communication** on common topics
International Cooperation at EMA

- Activities with FDA, PMDA, Health Canada, TGA, SwissMedic and WHO part of the daily work
  - New countries and regions emerging as important players, especially China, India, Brazil, Africa
- For around 85% of the medicines sold in the EU, at least one manufacturing step takes place outside the Union
- International agreements are the basis for the international cooperation, allowing not only sharing of information but also addressing common challenges
- Growing interactions through multilateral ‘Clusters’
Multilateral Clusters

- Participants: EMA, FDA, Health Canada, PMDA, and TGA in different combinations
- Regular meetings by telephone (1-2 hours)
- Facilitate timely information exchange
  - Increasingly focus on early development strategies or early safety signals
  - Share draft guidelines
- Follow-up meetings on specific topics in more depth
- Joint workshops or upcoming meetings of interest

Cluster topics:
- Advanced-therapy medicinal products
- Biosimilars
- Blood products
- Non-clinical oncology
- Oncology-haematology medicinal products
- Orphan medicinal products
- Paediatric medicinal products
- Patient engagement
- Pharmacogenomics
- Pharmacometrics / Modelling and simulation
- Pharmacovigilance
- Rare diseases
- Vaccines
- Veterinary medicinal products
Bilateral mutual recognition agreements (MRA)

For INDUSTRY:
- Avoid duplication of inspections from different Authorities.
- Waive of import testing of products imported.
- Encourage greater international harmonisation.

For AUTHORITIES:
- Encourage greater international harmonisation.
- Better use of resources.
- Focus on sites of higher risk.

- Manufacturing authorisations.
- Inspection outcomes.
- Manufacturers’ certification of the conformity of each batch to its specifications (without re-control at import)
EU/US MRA: Timelines and milestones

Signature

1st July 2017: EU assessment of FDA (human)

1st November 2017
• Entry into force
• FDA recognized by EU
• 8 EU MSs recognized*

15th July 2019
• All EU MS evaluated
• Batch testing
• Decision on Vets

15th July 2022
- Broaden scope (products)

*) Austria, Croatia, France, Italy, Malta, Spain, Sweden and the UK
## EU/US MRA: Product coverage

**Marketed finished pharmaceuticals for human use:**
- Medical gases
- Radiopharmaceuticals / radioactive biological products
- Herbal products
- Homeopathic products

**Marketed biological products for human use:**
- Therapeutic biotechnology - derived biological products
- Allergenic products

**Intermediates**
Active pharmaceutical ingredients IMPs

**Veterinary products:**
- Veterinary Pharmaceuticals
- Pre-mixes for the preparation of vet medicated feeds

**Vaccines for human use**
Plasma derived pharmaceuticals

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15th July 2022

15th July 2019
EMA’s efforts to enable timely access
EMA initiatives to promote innovation

Initiatives primarily targeting the risk of development failure:
- ITF (Innovation Task Force)
- Scientific advice, Protocol assistance, Qualification/certification procedures
- Support to SMEs/Academia
- Guidelines

Initiatives primarily targeting the time to access:
- PRIME (Priority Medicines)
- Adaptive Pathways
- Conditional Marketing Authorisation
- Accelerated Assessment
- Compassionate Use
- Interactions with HTA bodies
Launched in March 2016 with the goal to foster the development of medicines with major public health interest

- Aims to bring promising **treatments to patients earlier**, without compromising high evaluation standards and patient safety
- Focuses on medicines that address an **unmet medical need**
- Fosters **early scientific and regulatory support** from EMA and the Rapporteur team to facilitate robust data collection and high quality marketing authorisation applications
- Enable **accelerated assessment** as well as **patient and HTA input**
Overview of PRIME scheme

- Early identification of therapeutic innovation in unmet medical needs
- Iterative Scientific advice
  - Enhanced regulatory guidance
  - Incremental knowledge gain
    - Proactive dialogue
    - Promote use of existing tools
- MAA review under accelerated assessment.

Nonclinical → Phase I → Exploratory → Confirmatory → Evaluation → Post-authorisation

- SA 1☆ (SAWP)
- Eligibility (CHMP)
- SA 2☆ (SAWP)
- SA n☆ (SAWP)
- Accelerated Assessment confirmation (CHMP)
- Parallel advice with HTAs ☆
- Early CHMP Rapporteur appointment

- Full MA
- Exceptional
- Conditional

☆ Patient expert input

SMEs
Academia
Any
sponsor

Lääkealan turvallisuus- ja kehittämiskeskus | 4 Dec 2017 | CMC JPN 2017; niklas.ekman@fimea.fi
PRIME eligibility recommendations (Oct 2017)

137 requests
Around 23% granted
>60% biological substances
>50% Advanced therapies
Adaptive pathways – the concept

- Progressive (or staggered) approval of a medicines that are likely to offer help for a patient population with an unmet medical need
- Initial authorisation in a **restricted patient population** with severe disease where benefit-risk balance may be favorable.

- Repetitive phases of evidence gathering and licensing adaptations
- Stakeholders, such as HTA bodies involved early in the development process
Some concerns raised by stakeholders*

• How will real world data be used and defined?
• Will standards be relaxed?
• How will companies be made to comply with data requirements once their products are on the market?
• Will restricted medicines be restricted in practice?
• How will high unmet medical needs be defined?

Is the Adaptive Pathways lowering the standards?

No!

- Standards for regulatory decision remain the same
- Benefit-Risk must be positive for treatment-eligible population
- Access versus evidence conundrum is acknowledged in the legislation

→ Regulation (EC) No 507/2006, Article 4, conditional MA;
(d) where, “the benefit to public health of the immediate availability on the market [...] outweighs the risk inherent in the fact that additional data are still required”
Adaptive Pathways - Next steps

To make the process sustainable and to utilize a well-established framework, future submissions are treated as parallel HTA/ Scientific advice requests, granting an additional pre-submission meeting:

- Established framework for patient participation
- More sustainable HTA input
- Two additional pre-submission meetings for SMEs
- Other stakeholders (payers, FDA, WHO) may be invited where relevant
PRIME and adaptive pathways – CMC considerations

Less time is available for development and optimization of the manufacturing process, but more upfront discussions should result in less issues identified at late stage of development/MAA.

Quality challenges include:

• Analytical development (characterisation methods/potency)
• Control strategy (e.g. identify CQAs, CPPs), process experience (# Lots)
• Manufacturing process development (e.g. upscale), process validation and comparability
• Stability
PRIME and adaptive pathways – CMC considerations

Some tools and possibilities:

• Utilisation of prior knowledge/ platform knowledge
• Ongoing and/or concurrent process validation
• Post Approval Change Management Protocols (PACMPs)
• Continues manufacture
• Product launch from pilot scale
Biosimilars in EU – an update
Regulatory convergence - biosimilars

• The EU is the global leader in the area of biosimilars; other Competent Authorities benefit from this experience
  - Liaison with international partners (e.g. via International Pharmaceutical Regulators Forum –IPRF BWG, also Biosimilar Cluster)

• EU supports further development / implementation of WHO Similar BiotherapeuticProducts (SBP) guidelines

• EU and international assessor training in November 2016

• Joint EMA-EDQM seminar on biosimilars in February 2017
  - Attended by over 200 participants from 37 countries around the world

• BMWP-Interested parties meeting in September 2017
EU Biosimilar product overview (Oct 2017)

67 MAAs submitted

55 MAAs post-review

12 Withdrawn (pre-approval)
- Insulin (6)
- Epoetin (1)
- Pegfilgrastim (4)
- Trastuzumab (1)

41 Positive opinions

36 Valid MAs

- Somatropin (1)
- Epoetin (5)
- Filgrastim (5)
- Infliximab (3)
- Follitropin alfa (2)
- Etanercept (2)

- Insulin glargine (2)
- Enoxaparin (1)
- Teriparatide (2)
- Rituximab (6)
- Adalimumab (3)
- Insulin lispro (1)

12 MAAs under review

- Adalimumab (2)
- Bevacizumab (2)
- Infliximab (1)
- Insulin glargine (1)
- Pegfilgrastim (3)
- Trastuzumab (3)

2 Withdrawn (post-approval)
- Filgrastim (2)
- Somatropin (1)

2 Awaiting EC decision
- Adalimumab (1)
- Trastuzumab (1)

- Insulin (6)
- Epoetin (1)
- Pegfilgrastim (4)
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12 MAAs under review

- Adalimumab (2)
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2 Awaiting EC decision
- Adalimumab (1)
- Trastuzumab (1)
Product traceability in EudraVigilance (1/3)

• **Aim of study:** to assess level of precise identification of biologicals in ADR reports received from European clinical practice

• All cases received as spontaneous adverse drug reaction (ADR) between 1 Jan 2011 - 30 Jun 2016, and in which at least one of the suspected or concomitant medicinal products involves a biological for which:

  • **A biosimilar has been approved** in the EEA (epoetin alfa, etanercept, filgrastim, follitropin alfa, infliximab, insulin glargine, somatropin); or

  • **A related product has been approved** in the EEA (human normal immunoglobulin, interferon beta-1a, octocog alfa)
Product traceability in EudraVigilance (2/3)

Results show **robust levels of overall product identification** for classes of biologicals for which biosimilars are approved.

<table>
<thead>
<tr>
<th>Product</th>
<th>Total, n</th>
<th>Identifiable product, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>etanercept</td>
<td>19,716</td>
<td>19,012 96.4%</td>
</tr>
<tr>
<td>infliximab</td>
<td>12,045</td>
<td>11,342 94.2%</td>
</tr>
<tr>
<td>insulin glargine</td>
<td>2,446</td>
<td>2,364 96.6%</td>
</tr>
<tr>
<td>filgrastim</td>
<td>1,043</td>
<td>934 89.5%</td>
</tr>
<tr>
<td>epoetin alfa</td>
<td>1,084</td>
<td>1,045 96.4%</td>
</tr>
<tr>
<td>somatropin</td>
<td>1,047</td>
<td>1,006 96.1%</td>
</tr>
<tr>
<td>follitropin alfa</td>
<td>448</td>
<td>442 98.7%</td>
</tr>
</tbody>
</table>

95.5% overall

Courtesy of Ana Hidalgo-Simon, EMA
Product traceability in EudraVigilance (3/3)

- Even more robust levels of product identification for classes of biologicals for which related biologicals are approved

<table>
<thead>
<tr>
<th>Product</th>
<th>Total , n</th>
<th>Identifiable product , n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>human normal IG</td>
<td>9,130</td>
<td>9,070 99.3%</td>
</tr>
<tr>
<td>interferon beta-1a</td>
<td>4,573</td>
<td>4,562 99.8%</td>
</tr>
<tr>
<td>octocog alfa</td>
<td>1,059</td>
<td>1,055 99.6%</td>
</tr>
</tbody>
</table>

- Overall batch traceability of 20.5% for suspected biologicals
- Final results + peer-reviewed article will soon be published

Courtesy of Ana Hidalgo-Simon, EMA
Statistical approaches for similarity assessment


4 Dec 2017  CMC JPN 2017; niklas.ekman@fimea.fi
Reflection paper on the use of statistical methodology for quality comparability (EMA/CHMP/138502/2017)

• Triggered by the constantly increasing number of questions raised during SA/MAA procedures
• Provides thinking on how statistical tools could be applied – does not give a final solution
• Main aim is to establish a framework and a common language to facilitate future discussions among stakeholders
• A public workshop will be held at the end of the 12-month public consultation phase
A few thoughts from a quality assessor’s point of view

• Understand data and data generating process (random sampling?), the sources of variability (e.g. between and within batches) and the assumptions that has to be made - Be aware of the limitations!

• There are no ‘right’ or ‘wrong’ statistical methods; equivalence testing is a well-understood approach from a statistical point of view, but is not always practical for assessment of analytical similarity

• Independently of the approach taken, the statistical method itself cannot define what is sufficiently similar
EMA relocation

Who is going and where?
Amsterdam!

Starting from 30 March 2019 (at the latest)
Thank you for your attention!

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The pictures used in the presentation were obtained from www.freepik.com and from the Dutch bid for EMA