Between Biosimilars and PRIME: EMA’s report on regulatory trends and priorities for biopharmaceutical products

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EMA mission and priorities

Biologics Working Party (BWP) and trends

Biosimilars

Quality development under accelerated timelines

Regulatory convergence and/or harmonization
EMA mission & priorities
EMA in the EU

Who do we work for?

- Over 500 million people living in the European Union
- 28 member states
- 27% of global sales of medicines
- 24 official languages
Who we are

- 4000 Scientific experts from right across Europe
- 7 Scientific committees
- 1000 marketing authorisations recommended
- 1995 EMA established to evaluate medicines for use in the EU
- 28 Working parties
- ~890 Staff members
EMA’s priorities  (multiannual work programme)

**Theme 1: Contributing to human health**

<table>
<thead>
<tr>
<th>Objective 1: Focus on key public health priorities, including the availability of medicines and antimicrobial resistance</th>
<th>Main areas of work: antimicrobial resistance, needs of specific populations, supply issues and availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective 2: Ensure timely access to new, beneficial and safe medicines for patients</td>
<td>Main areas of work: early access to medicines</td>
</tr>
<tr>
<td>Objective 3: Support patient-focused innovation and contribute to a vibrant life science sector in Europe</td>
<td>Main areas of work: clinical trial regulation, supporting innovation</td>
</tr>
<tr>
<td>Objective 4: Strengthen regulatory capability and transparency</td>
<td>Main areas of work: regulatory capability, transparency</td>
</tr>
</tbody>
</table>

**Theme 2: veterinary medicines**

**Theme 3: Optimising the operation of the network**

**Theme 4: Contributing to the global regulatory environment**
Quality interphase with work program (2018-2020)

1. Public health emergencies: health-threat activities (e.g. Ebola, Zika etc.) (Actionplan and Lessons-learned)

2. Availability of medicines: Minimise risk & impact of shortages (manufacturing problems & quality defects) (Robustness of data packages, Actionplan & coordination across the network)

3. Early access to Medicines: regulatory and scientific support for priority medicines (PRIME) (2018 BWP/QWP workshop)

4. Innovation: translating innovation into medicinal products (Guidance, ITF, stakeholder interaction)

5. Public health: contribute to European and international initiatives on antimicrobial resistance (e.g. Bacteriophages workshop)

6. Regulatory network: Capacity building, training, information sharing

7. Product supply chain/data integrity: control / monitoring of manufacturing & supply chain (information-sharing between regulators, MRA on GMP)

Brexit preparedness

Guidance for Companies
- EC/EMA Q&A
- Guidance to marketing authorisation holders
- EMA procedural guidance
- Guidance on nationally authorised products
  (http://www.hma.eu/535.html)

Regulatory preparedness

Business continuity plan

Relocation to Amsterdam
http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_001893.jsp&mid=WC0b01ac0580cb2e5c

United Kingdom’s withdrawal from the European Union (‘Brexit’)

On 29 March 2017, the United Kingdom (UK) notified the European Council of its intention to withdraw from the European Union (EU), a process known as ‘Brexit’. The European Medicines Agency (EMA) is making preparations to ensure that it can continue to deliver on its mission and protect public and animal health after the UK leaves the EU on 30 March 2019, the date currently set by the timeframe provided in Article 50 of the Treaty on European Union.

One of the consequences of Brexit is that EMA will relocate to Amsterdam, the Netherlands, where it has to take up its operations on 30 March 2019 at the latest.

The Agency continues its operations in accordance with the timelines set by its rules and regulations.

EMA is working on the scenario that the UK will become a third country as of 30 March 2019. As a consequence, the UK will no longer be able to engage as (co-)rapporteur for new marketing authorisation applications for which the centralised procedure would finish after 30 March 2019. This is without prejudice to the outcome of the withdrawal negotiations.

No Member State has previously decided to leave the EU, so there is no precedent for this situation.

In this section
- Brexit-related guidance for companies
- Relocation to Amsterdam

Continuity of EMA activities
EMA is essential to the functioning of the single market for medicines in the EU. The Agency’s work is vital to providing EU citizens with affordable, safe and high-quality medicines and to maintain a regulatory environment that fosters innovation and the development of new medicines.

The Agency is taking steps to ensure that it can continue to deliver on its mission and protect public and animal health while it prepares to relocate.

Regulatory preparedness (updated)
In April 2018, the EU27 Member States and EMA completed the redistribution of the UK’s portfolio of over 370 centrally authorised products to rapporteurs and co-rapporteurs from the EU27 plus Iceland and Norway, in preparation for Brexit.

EMA will inform the relevant marketing authorisation holders of the new (co-)rapporteurships by the end of April 2018. EMA will then facilitate knowledge transfer.

Related content
- About us
- Governance documents: Annual reports and work programmes

News and press releases
- Redistribution of UK’s portfolio of centrally authorised products (11/4/2018)
- EMA surveys pharma companies on their preparedness for Brexit (23/1/2018)
- Regulatory guidance for pharmaceutical companies to prepare for UK’s withdrawal from EU (1/12/2017)
- Procedural guidance to help pharma companies prepare for Brexit (28/11/2017)
- EMA to relocate to Amsterdam, the Netherlands (20/11/2017)
- EMA’s Business Continuity Plan for Brexit published (16/10/2017)
- EMA publishes comments on Member States’ hosting bids (3/10/2017)
- Update on EMA relocation preparedness (26/9/2017)
- EMA prepares for Brexit (31/7/2017)
- EMA and heads of national competent authorities discuss consequences of Brexit (28/4/2017)
- Statement on the outcome of the UK referendum (6/7/2016)

External links
- Council of the European Union: Information on Brexit®
- European Council®
Biologics Working Party
Biologics Working Party (BWP)

Standing working party to CHMP (since 1995)

Recommendations to the CHMP on **quality** and **safety matters** in relation to quality for biological / biotech MP

- uniform approach on biotech/biological issues
- avoid/eliminate divergences in assessment & interpretation of guidance
- efficient use of European expertise
Biotechnologically-derived and Biological products

- **Recombinant proteins** (mABs, ABD conjugates, fusion proteins, enzymes etc.)
- TEPs, Cell and gene therapies
- Vaccines (Viral, bacterial, other)
- Blood derived products
- Biologically derived products (urine-derived, plant-, tissue- derived)
- Biosimilars of the above (i.e. Recombinant)
Objectives

**Support to dossier evaluation:** BWP reports with recommendations on quality for approval (Pre-authorisation (100%), Post-authorisation (escalated, <5 %))

**Support to scientific advice requests:** BWP reports with provision of scientific advice on general and product specific

**Guideline** preparation, review and update in conjunction with other WPs (and ICH)

**Scientific opinions** upon request by CHMP on e.g. WHO-related topics, CMDh, Referral or crisis situations (e.g. vaccine shortages, safety issues related to Quality)

**Liaison** with Industry associations, European Institutions (EDQM, ECDC, EC, EFSA etc.), other working parties, GMP inspection services etc.

**Training and communication**

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20% 80% 20%
Product-related trends

- **ITF**
  - Nanotechnology
  - 3D printing
  - Bacteriophages
  - Genome editing

- **Scientific advice**
  - Biosimilars
    - (Recombinant + others)
  - Monoclonals/AbDC
  - AAV vectors
  - Genetically modified cells
  - Biologically derived
    - (e.g. pharmabiotic)
  - Continuous manufacturing

- **MAA**
  - Monoclonals/AbDC
  - Biosimilars
  - ATMPs
  - Vaccines

- **Post-authorisation**
  - PACMPs
  - Site transfers
  - Administration devices
  - Manufacturing changes
  - Control strategy
  - Stability

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Scientific discussions to highlight

- Definition of **starting materials** and thereby start of GMP compliant manufacturing (e.g. cell banks, viral vectors, blood/tissue starting material)

- Use of **prior knowledge** (e.g. related to validation data) subject of scientific advice

- **PACMP**: Scope, protocol and data package needed for Type 1b variation

- BWP input/scientific advice on **structural similarity** (Orphan similarity)

- Variation of >1 process parameters within the **proven acceptable ranges (PAR)** → demonstration of absence of interactions and capability of control strategy to detect potential negative effects on Q, S&E

- **Specification setting** in the context of clinical qualification
Stakeholder Interactions – Interested parties meeting

**BWP - Interested Parties meetings**
- July 2016
- June 2017
- 20 June 2018

**Participants:** BWP chair, secretariat & members, Stakeholders (Medicines for Europe, Europabio, EFPIA/EBE, APIC, PPTA, Vaccines Europe, IPFA)

**Topics:** Prior knowledge, continuous manufacturing, drug-device combinations, **accelerated access**, extractables & leachables

**New for 2018:** control strategy & specification setting, Guideline applications, accelerated upstream manufacturing (high cell density)
Stakeholder Interactions

Stakeholder workshop
- Prior knowledge (23.11.2017)
- hosted by BWP/QWP
~ 100 participants / 300 remote connections

1. Definition of prior knowledge
2. Development
3. Manufacturing process
4. Control strategy
5. Application to early access approaches
6. Summary & way forward

Stakeholder workshop
- Quality support to early access (26.11.2018)
- Organising Committee: BWP/QWP/IWG
- Chemical, Biologicals, ATMPs
~ 100 participants (Regulators, SME & Big Pharma)

Topics:
• process validation
• control strategy and specification setting
• GMP compliance
• comparability
• starting materials
• stability
• regulatory considerations
Statistical methodology for comparative assessment of quality attributes

Workshop: 3/4 May 2018

BSWP, BMWP, BWP & QWP & FDA

Industry associations

→ comments from public consultation

→ Case studies
Quality documentation for Biological IMPs

Adopted guideline entered into force (26.04.2018)

Vaccines: Guidance *in public consultation*

**Quality aspects included in the product information for vaccines for human use** (public consultation until 31/07/2018)


**Q&A on the Haemagglutination Inhibition (HI) test for qualification of influenza vaccine (inactivated) seed preparations** (public consultation until 31/07/2018)


**Q&A on bovine spongiform encephalopathies (BSE) and vaccines** (public consultation until 31/07/2018)

Biosimilars
Biosimilarity is based on the “totality of evidence”
Topics under discussion - Biosimilarity

• non-clinical and clinical data package needed → outcome of analytical similarity seen (quality level) – residual uncertainty (extrapolation of indication)

• differences at quality level - clinical trials cannot be used to justify substantial differences in quality attributes but confirm biosimilarity already shown at the quality level

• suitability of biosimilar route for different pharmaceutical form (pre-mixed solution in an infusion bag vs. solution for injection (vial))

• Suitability of biosimilar route (recombinant proteins versus products extracted from biological sources, vaccine etc.)
Quality challenges - Biosimilars

**Marketing authorisation applications of mAbs 1997-2017**

*(random selection)*

24 Innovators (cancer/autoimmune/other indication)

12 Biosimilars

4 AB-drug conjugates

→ Major objections at D120 (areas)

→ Major objections at D180 (areas)

→ Approval outcome

PDA 10th monoclonal Abs, Berlin, 26-27 Sep 2017 – ‘BWP lessons learned’ by V Jekerle
## Marketing authorisation application – Biosimilars (mABs)

<table>
<thead>
<tr>
<th>12 products total</th>
<th>Active substance</th>
<th>Finished products</th>
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</thead>
<tbody>
<tr>
<td>Major objections at Day 120</td>
<td>7 products</td>
<td>Control strategy (1x)</td>
</tr>
<tr>
<td></td>
<td>1 MO (6x) 2 MO (1x)</td>
<td></td>
</tr>
<tr>
<td>Major objections at Day 180</td>
<td>4 products (2 in progress)</td>
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</tr>
<tr>
<td></td>
<td>1 MO (4x)</td>
<td></td>
</tr>
<tr>
<td>Other concerns at D 120</td>
<td>All products 36 – 78 OCs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 – 34 OCs</td>
<td></td>
</tr>
<tr>
<td>Other concerns at D 180</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome approval</td>
<td>Yes (7) Ongoing (5)</td>
<td></td>
</tr>
</tbody>
</table>

### Findings:
- mAbs: very good track record for approval (both Innovators & Biosimilars)
- GMP major objections!
- Innovators: control strategy including specifications, potency and stability & shelf life
- Biosimilars: fewer MOs but attention to analytical biosimilarity & comparability
- Antibody drug conjugates: own issues on the control strategy of the components and the manufacturing process
Examples of recent EMA initiatives on biosimilars

- Pilot project on tailored scientific advice for biosimilars to support stepwise development
- Improvement of the information in the European Public Assessment Report (EPAR)
- Product identifiability for pharmacovigilance
- Communication plan (e.g. guide for healthcare professionals, webpage updates)
Quality development under accelerated timelines
PRIME eligibility criteria

‘a major therapeutic advantage over existing treatments, or benefit patients without treatment options’

medicine to show its potential to benefit patients with unmet medical needs based on early clinical data
PRIME eligibility and designation

32 PRIME designated products in total
10/32 from SMEs

- 4 monoclonal antibodies
- 1 ABD conjugate
- 2 fusion proteins
- 2 enzymes

### Topic areas of scientific advice requests

**PRIME**

<table>
<thead>
<tr>
<th>Product</th>
<th>Areas</th>
<th>Raw materials</th>
<th>Orphan similarity</th>
<th>Cell banks</th>
<th><strong>Starting materials</strong></th>
<th>Vector</th>
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<td>2</td>
<td>5</td>
<td>1</td>
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</table>

<table>
<thead>
<tr>
<th>Process</th>
<th>Areas</th>
<th>Process development</th>
<th>Comparability</th>
<th>Change management</th>
<th>Validation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># Q</td>
<td>4</td>
<td>13</td>
<td>2</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Control</th>
<th>Areas</th>
<th>Potency assay</th>
<th><strong>Analytical control strategy</strong></th>
<th>Specifications</th>
<th>Adventitious agents</th>
<th><strong>Stability</strong></th>
<th>Product-rel. impurities</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># Q</td>
<td>4</td>
<td>6</td>
<td>7</td>
<td>2</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>

Critical areas

Number of question > 5

Prior knowledge workshop 23 November 2017 by V Jekerle
BWP’s current thinking - use of prior knowledge

Expected quality package

Control strategy + Prior knowledge

Module 3 data

X months

development and assessment

accelerated access

PACMP/commitments

conventional approval

post-authorisation

E.g. 9 months

Prior knowledge workshop
23 November 2017 by V Jekerle
Prior knowledge during accelerated assessment

- **made available for assessment** in order to facilitate a consistent review across regulators

- Its **relevance and justification** for use should be agreed with Regulators (SA) for better plannability

- Its **way of documentation** should be agreed

- dynamic and evolving amount of data should be made available over regulatory submission (incl. regulatory tools → recommendations, PACMPs)
Regulatory convergence and/or harmonization
EMA involvement in international activities

- WHO

- IPRP (e.g. gene/cell therapy, biosimilars, nanotechnology)

- Training
  - Workshop/training participation of international partners
  - EU Network training (HMA: http://www.hma.eu/otsg.html)
  - International awareness sessions (Sep 2017 /Mar 2018)

Regulatory convergence & harmonization

- ICH (e.g. ICH Q12)

- Cluster telephone conferences (product-specific, e.g. Biosimilars, ATMPs, Vaccines)

Some further examples:

**FDA:** EU-US GMP MRA, Biosimilars, PRIME and accelerated access, statistical approaches for the comparison of quality attributes, continuous manufacturing, PAT team

**Japan:** statistical approaches for the comparison of quality attributes, continuous manufacturing, ICH

**Globally:** WHO, International regulators, African countries

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2017/06/event_detail_001480.jsp&mid=WC0b01ac058004d5c3
Acknowledgements:

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Further information

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