EU Update on Regulatory Developments

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European Medicines Agency
Overview

- International collaboration
- EMA’s efforts to enable timely access
- Biosimilar update
- Future directions
International collaboration
Global cooperation is a priority

- Changing pharmaceutical environment due to global nature of medicine development and research

- Movement of **clinical trials** outside of EU and US

- Increasing complexity of **supply chains** and **manufacture** of APIs outside of the EU – increasing risks of falsification and concerns over **data integrity**

- Increasing needs for international collaboration, information sharing and work sharing – **reduce/avoid duplication, global strategic vision, adapt to scientific progress**
International collaboration at EMA

- Activities with FDA, PMDA and WHO part of our daily work
- Almost every part of EMA involved in some way
- ~80% of all products going through EMA committees have some discussion at international level
- Growing interactions through multilateral ‘Clusters’
- 8-10 international calls per week
- Host 3-4 international visitors per month
- FDA and PMDA main partners, but other engagements growing
- New countries and regions emerging as important players, especially China, India, Brazil, Africa
EMA global engagement toolbox

Multilateral:

- WHO engagement, AVAREF
- Strategic forums, e.g. ICMRA
- Work-sharing, e.g. IGDRP
- Convergence and harmonisation forums, e.g. ICH, IPRF, PIC/S
- Ad-hoc

Bilateral:*

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

* With European Commission
EU-US Mutual Recognition Agreement (MRA) on GMP

Mutual recognition agreements: introduction

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)
Scope

- Pre-approval inspections
- Post-approval inspections
- Inspect. outside the territory
Products coverage

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

15th July 2019

15th July 2022
Timelines and milestones

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

Signature

1st November 2017
- Entry into force
- 8 EU Member States recognised

15th July 2019
- All EU MS recognised
- Batch testing
- Decision on Vets

15th July 2022
- Broaden scope (products)
Safeguard clause

To ensure the protection of human/animal health

Exceptional cases

Inspection in the territory of the other party

Notification in writing

Right to join the inspection
EMA’s efforts to enable timely access
## EMA initiatives to promote innovation

<table>
<thead>
<tr>
<th>Initiatives primarily targeting the <strong>risk of development failure:</strong></th>
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<tbody>
<tr>
<td>• ITF (Innovation Task Force)</td>
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<td>• Scientific advice, Protocol assistance, Qualification procedures</td>
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<td>• Support to SMEs/Academia</td>
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<td>• Guidelines</td>
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<tr>
<th>Initiatives primarily targeting the <strong>time to access:</strong></th>
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<tbody>
<tr>
<td>• PRIME (Priority Medicines)</td>
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<td>• Adaptive Pathways</td>
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<td>• Conditional Marketing Authorisation</td>
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<td>• Accelerated Assessment</td>
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<td>• Compassionate Use</td>
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<td>• Interactions with HTA bodies</td>
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Requirement for multi-stakeholder engagement is high in all initiatives (no ‘regulator-only’ initiatives)
PRIME scheme - Goal & Scope

To foster the development of medicines with major public health interest.

Reinforce scientific and regulatory advice
- Foster and facilitate early interaction
- Raise awareness of requirements earlier in development

Optimise development for robust data generation
- Focus efficient development
- Promote generation of robust and high quality data

Enable accelerated assessment
- Promote generation of high quality data
- Facilitated by knowledge gained throughout development

Provide platform for patient and HTA input

Building on existing framework; Eligibility according to existing ‘Accelerated Assessment criteria’
Features of the PRIME scheme

Early access tool, supporting patient access to innovative medicines.

- **Written confirmation of PRIME eligibility** and potential for accelerated assessment;
- **Early CHMP Rapporteur appointment** during development;
- **Kick off meeting** with multidisciplinary expertise from EU network;
- **Enhanced scientific advice** at key development milestones/decision points;
- **EMA dedicated contact point**;
- **Fee incentives** for SMEs and academics on Scientific Advice requests.

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

- Full MA
- Exceptional
- Conditional

- SMEs Academia
- Any sponsor
- Patient expert input
PRIME eligibility recommendations adopted by 21 April 2017

- > 90 eligibility requests
  - 20 granted
  - ~ 50% SMEs
  - > 50% Advanced therapies

<table>
<thead>
<tr>
<th>Therapeutic Area</th>
<th>Granted</th>
<th>Denied</th>
<th>Out of scope</th>
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<tbody>
<tr>
<td>Oncology</td>
<td>6</td>
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<tr>
<td>Hematology-haematostaseology</td>
<td>6</td>
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<tr>
<td>Neurology</td>
<td>2</td>
<td></td>
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<tr>
<td>Infectious diseases</td>
<td>2</td>
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<tr>
<td>Cardiovascular diseases</td>
<td>6</td>
<td></td>
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<tr>
<td>Gastroenterology-Hepatology</td>
<td>2</td>
<td></td>
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<tr>
<td>Pneumology-allergology</td>
<td>1</td>
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<tr>
<td>Vaccines</td>
<td>1</td>
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<tr>
<td>Immunology-rheumatology-transplantation</td>
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<tr>
<td>Ophthalmology</td>
<td>3</td>
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<tr>
<td>Endocrinology-Gynaecology-Fertility-Metabolism</td>
<td>1</td>
<td></td>
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<tr>
<td>Dermatology</td>
<td>2</td>
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<tr>
<td>Psychiatry</td>
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<tr>
<td>Diagnostic</td>
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<tr>
<td>Musculo-skeletal system</td>
<td>1</td>
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Out of scope: * This indicates eligibility requests received but not started by EMA as they were deemed outside the scope of the scheme or with a format and content inadequate to support their review. These are not included in the breakdown by type of applicant or by therapeutic area.
Adaptive Pathways – definition

• A **prospectively planned**, adaptive approach to bringing new medicines to patients.

• Through **iterative phases of evidence gathering** followed by evaluation and license/reimbursement adaptation.

• To maximise the positive impact of new medicines on public health by **balancing timely access** for patients with the need to provide **adequate information on benefits and harms**.

Why adaptive pathways?

• The concept is not for all medicines: meeting an unmet medical need is a necessary driver

• Enable development of non-conventional ('difficult') products
  ➔ Medicines for rare conditions, ATMPs are difficult to develop
  ➔ Opportunity to reduce (unavoidable) uncertainties fast

• Adaptive pathways offers an opportunity to optimise collection of clinical data needed by decision makers, with a view to facilitate patients access

• Key element: early interactions with various stakeholders to better target patients who may benefit the most from the medicine and to better plan evidence generation
Adaptive Pathways: lowering the standards?

• Standards for regulatory decision remain the same
• Benefit-Risk must be positive for treatment-eligible population
• Access versus evidence conundrum has always been acknowledged:

... 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"

[Regulation (EC) No 507/2006]
Adaptive Pathways - Next steps

To make the process sustainable and utilise 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
CMC considerations for PRIME and adaptive pathways

- Limited CMC data vs risk management
  - CMC a time limiting factor?

- Requires a well thought out plan

- More upfront discussions with Regulators should result in less issues identified at late stage of development / marketing authorisation application

- Options under consideration:
  - Use of prior/platform knowledge to guide development
  - Process validation: concurrent validation protocol
  - New manufacturing site, scale up: opportunity to use PACMPs
  - Specifications: review based on pre-defined criteria, reassessment of control strategy, submission of post-approval variations
  - Shelf life: use of stability models, extrapolation, ... ?
Biosimilar update
Regulatory convergence

- The EU is the global leader in the area of biosimilars and other Competent Authorities benefit from our experience
- EU supports further development / implementation of WHO Similar Biotherapeutic Products (SBP) guidelines
- Liaison with international partners (e.g. via International Pharmaceutical Regulators Forum – IPRF BWG, also Biosimilar Cluster EMA/FDA/HC/PMDA)
- EU and international assessor training in November 2016
- Quality standards (e.g. monograph requirements) increase transparency
  - Joint EMA-EDQM meeting in February 2017
  - **Compliance with a monograph is not sufficient to demonstrate biosimilarity**
- BMWP-Interested parties meeting in September 2017
Biosimilar products overview (April 2017) *

- **61 MAAs submitted**
- **46 MAAs post-review**
- **15 MAAs under review**

**2 Negative (pre-approval)**
- Interferon alfa
- Insulin

**10 Withdrawn (pre-approval)**
- Insulin (6)
- Epoetin (1)
- Pegfilgrastim (3)

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

**28 Valid MAs**
- Somatropin (1)
- Epoetin (5)
- Filgrastim (7)
- Infliximab (3)
- Follitropin alfa (2)
- Etanercept (1)
- Insulin glargine (2)
- Enoxaparin (2)
- Teriparatide (2)
- Rituximab (1)
- Adalimumab (2)

**34 Positive opinions**

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

**2 Negative**
- Interferon alfa
- Insulin

**10 Withdrawn (pre-approval)**
- Insulin (6)
- Epoetin (1)
- Pegfilgrastim (3)

**3 Awaiting EC decision**
- Etanercept (1)
- Rituximab (2)

- **Adalimumab (2)**
- Bevacizumab (2)
- Insulin glargine (1)
- Insulin lispro (1)
- Pegfilgrastim (2)
- Rituximab (3)
- Trastuzumab (4)

* Information on EMA website
Tailored scientific advice pilot

- Pilot launched in February 2017
- Pilot runs for 6 complete procedures
- Intended to support stepwise development of biosimilars
- In-depth advice on development programme based on a review of available quality data (a mature data package is expected to fully benefit from the pilot)
- Contact/further details: ScientificAdvice@ema.europa.eu

Reflection Paper: Statistical methodology for quality comparability

- Triggered by increasing number of examples, e.g. scientific advice requests
- Reflection Paper provides thinking on how to apply statistical tools
- CHMP not setting acceptance ranges for quality attributes
- Adopted by CHMP in March 2017
- Public consultation until March 2018
Information guide on biosimilars for healthcare professionals

Prepared jointly by the European Commission and the European Medicines Agency


To foster:

- General understanding of biological medicines, including complex nature and manufacturing process
- Sound and common understanding of what biosimilars are and how they are developed and approved
- Confidence in the use of biosimilars, as for all medicines approved via EMA in the EU
- Trust in the robustness of the regulatory system for approval of biosimilar medicines in the EU
- Appreciation of the safety and efficacy of biosimilars, as supported by evidence
- Ability of health professionals to adequately respond to patients queries on biosimilars
- Consistency in public health messages on biosimilars across the EU
Future directions
Connecting the dots

- Changing face of our international collaboration with regulators
  - From information sharing to work sharing
  - From bilateral to multilateral cooperation
  - Key question is now how best to collaborate

- Need for continued dialogue and learning by both industry and regulators
  - Support to global development
  - Benefit to the patient

- Strong regulatory science is critical to innovation
  - Supporting new approaches to improve product manufacturing and quality
  - Ensuring regulators readiness to evaluate innovative emerging technologies

- Mapping of international initiatives:
Thank you for your attention

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