EMA’s support to innovation – a status update

11th meeting of the CMC Strategy Forum Japan - 5-6 December 2022

Veronika Jekerle, Head of Pharmaceutical Quality, Human Medicines, EMA
Content

- Innovation trends and challenges
- What EMA does to support innovation
- Where do we focus: EMA’s survey on Innovation
- Quality Innovation group
Innovation trends and challenges
Support to innovation is a key priority for EMA

- Benefits patient and public health
- Can address unmet medicinal needs & public health challenges
- Efficiency and productivity (manufacturing/lifecycle management/licensure)
- Reliability and resilience in the supply chain
- Environmental footprint
Challenges

- Proof of concept
- Guidance available
- Manufacturing & upscaling
- Public acceptance
- Global divergence
- Regulators expertise
- Compatible with legal framework
### Technical & regulatory challenges

Examples from EMA’s Innovation Task Force (ITF) meetings (2021)

<table>
<thead>
<tr>
<th></th>
<th><strong>3D printed bioimplants</strong></th>
<th><strong>Gene Editing platform</strong></th>
<th><strong>Aseptic automated processing system</strong></th>
</tr>
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<tbody>
<tr>
<td><strong>Product description</strong></td>
<td>Cellularised bioimplants by 3D bioprinting (cartilage, stem cells, lipid mediators + growth factors)</td>
<td>In vivo non-viral delivery Gene Editing Platform (CRISPR)</td>
<td>Innovative gloveless robotic isolator technology</td>
</tr>
</tbody>
</table>
| **Questions**          | • Guidance on biological starting materials + Organ-on-a-Chip model & 3D printing          | • Orphan designation / ATMP classification  
                          |                                                                 | • GMP & supplier requirements  
                          |                                                                 | • quality control & characterisation  
                          |                                                                 | • GMP requirements (Air Velocity and Flow)  
                          |                                                                 | • Control strategy  |
| **Key challenges**     | • **Classification**  
                          |                                                                 | • **International alignment**  
                          |                         | • **Tailored scientific advice**  
                          |                                                                 | • Early engagement on **GMP aspects**  
                          |                         | • **Guidance limited**  
                          |                                                                 | • Translating platform approach → **product**  
                          |                         | • EC Q&A [md_mdmcg_qa_3d_ppp_covid-19_en_0.pdf](europa.eu)  
                          |                                                                 | (FU on specific SA) |
                          |                                                                 | • SA on **characterisation + control**  
                          |                                                                 | |
What EMA does to support innovation
Joint EMA-FDA workshop on quality support to PRIME & Breakthrough

Scope:

- Identify scientific elements/tools within existing guidance to help address the challenges (i.e. EU, US & ICH guidance)
- Identify gaps in the current guidance landscape
- Explore areas of common agreement & areas that would benefit from further harmonisation between EMA/FDA

Deliverables from the workshop

1. Meeting Report: Workshop with stakeholders on support to quality development in early access approaches (i.e. PRIME, Breakthrough Therapies)

2. EU toolbox guidance

   In addition, the organizing committee proposes to develop a ‘Toolbox guidance’ for PRIME products, which shall summarise the identified scientific elements/regulatory tools that are already available in the EU to address some of the challenges faced during the development of products under PRIME and generation of robust quality packages for MAA review. This toolbox will include scientific elements/regulatory tools applicable to small molecules, Biologicals/Biotechnological products and ATMPs.

3. Joint EMA-FDA discussion on PRIME/BT

   4 joint FDA-EMA Q&As
   - Control strategy
   - Process validation
   - Stability models
   - GMP aspects (launch from former clinical site)

To summarise the identified scientific elements/regulatory tools already available in the EU to address some of the challenges faced and generation of robust quality packages.

Applicable to small molecules, Biologicals/Biotechnological products and ATMPs

Living document – to be updated as experience evolves.

EMA toolbox guidance

- Primary scope: PRIME designated medicines
- but... it is also recognized that some of the tools may be considered, on a case by case basis, and subject to prior agreement with EMA, for certain products intended for early access that address an unmet medical need, but where PRIME status may not have been requested by the applicant.
<table>
<thead>
<tr>
<th>Stakeholder comments</th>
<th>Agency response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scope beyond PRIME (title should be changed)</td>
<td>Unmet medical need &amp; when justified (→ title adjusted)</td>
</tr>
<tr>
<td>Pandemic experience should be considered</td>
<td>pandemic experience was considered if within scope (scientific considerations for quality data packages / regulatory tools). GMP flexibilities outside of scope of guidance &amp; specific to COVID</td>
</tr>
<tr>
<td>Regulatory tools beyond the ones in the GL (e.g. rolling reviews etc.)</td>
<td>Novel regulatory tools to be agree within EU regulatory framework + subsequently referenced in the toolbox (not the other way around)</td>
</tr>
<tr>
<td>Dedicated section on lifecycle management</td>
<td>Considered premature - important future topic: 1 continuation/completion of data requirements of flexibility applied during initial MAA; 2 new flexibilities afforded in the context of variations</td>
</tr>
<tr>
<td>ICH Q12 + ICH Q14 tools to be added</td>
<td>tools to be elaborated within ICH process and cross-referred when ready/if relevant</td>
</tr>
<tr>
<td>further guidance (e.g. models)</td>
<td>guidance should be developed at source and reference in the toolbox (not other way around)</td>
</tr>
</tbody>
</table>
• **Unmet medical need**-> **flexibility** for data submission for **timely patient access (PRIME)**.

• **Prior knowledge**: relevance; postponement / alternative approach

• ‘**Risk-based approach’**

**Potential risk in context of benefit-risk assessment.**

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**General Process Validation**

• **Concurrent validation** (exceptional circumstances) - **protocol** scope, tests & acceptance criteria;

Need appropriate **process evaluation & control strategy**.

• **Defer** submission (certain data) to the post-authorisation phase.

• Prior Knowledge- non-PV batch data incl at other sites.

• **Decoupling drug substance and drug product process validation activities**
Control strategy

Adapted control strategy to off-set reduced product/process knowledge

- Additional spec. tests
- Additional IPCs, etc
- Higher CPPs, narrower ranges

‘Relax’ strategy once data available (implementation-PACMP?)

Prior knowledge/ manufacturing experience for flexibility but possible less product/ process knowledge

Stability

ICH Q5C: real time/ real condition data for Bio products Accelerated stability data-trend analysis

Stability models (prior knowledge of structurally similar products), fit model?

Extrapolation risks mitigated by sufficient data/prior knowledge

Protocol & post-approval commitments
Comparability

- Risk-based approach (RBA), supported by prior knowledge
  
  **Step 1**
  Risk assessment to determine the impact of CQAs on efficacy and safety
  
  **Step 2**
  Assess the potential impact of the manufacturing change on those CQAs
  
  Reduced panel of CQAs to be tested

- Small-scale data / platform data / prior knowledge informs RBA

- Extent of downstream comparability

- Stressed/accelerated stability data

- Comparability protocols

- Separate assessment of individual changes or part of the process, when justified

Regulatory tools

- **PRIME scheme** (support, frequent interactions, early Rapporteur appointment)

- **Scientific advice** / Pre-submission meetings

- **Accelerated assessment** of MAA/Conditional Marketing Authorisation (CMA)

- **PACMPs**

- **PAMs**
Prior knowledge workshop (2017)

- What is prior knowledge
- How to use it & justify
- Case studies
  - product development,
  - process development & manufacture,
  - control strategy

### Flexibilities used in COVID vaccines/therapeutics

<table>
<thead>
<tr>
<th>Pre-requisite</th>
<th>Scientific tools used</th>
<th>Regulatory tools used</th>
</tr>
</thead>
</table>
| Development data from non-commercial sites | **Protocol** to complete process validation & comparability post-approval  
**Concurrent validation** of commercial manufacturing process  
**Extrapolation** of stability data (comparability, accelerated conditions + supportive stability data)  
**2-tiered comparability** of AS / FP (1: comparison of release and IPC results; 2: additional characterisation test results post-approval)  
Initial batch data + supplier information for excipient from clinical development and risk-based considerations (safety/quality) | **Specific Obligations** (completing validation/comparability/novel excipient datasets) *with interim timepoints*  
**Annex II conditions**  
**Recommendations**  
Post-Approval Change Management Protocols (**PACMPs**)  
Exceptional change management process (**ECMP**) *to transfer analytical methods to already approved QC sites*  
**Derogations** (batch release testing in EU) |
| Platform data | | |
| Strategy agreed in rapid scientific advices | | |
| Close dialogue | | |
| Comparability to clinical development batches shown | | |

**Knowledge and dialogue**  
**Validation, comparability, stability, excipients**  
**PACMPs, SOB and Recs**

* COVID scope only
Commentary

Considerations for the chemistry, manufacturing and Controls (CMC) - quality package for COVID-19 vaccines - interim lessons learnt by the European medicines Agency (EMA)

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ABSTRACT

The European Medicines Agency (EMA) has approved five pandemic COVID-19 vaccines (prior to April 2022) and many others are in the pipeline. The commentary describes how timely approval and rapid manufacturing capacity scale up could be achieved from our perspective.

The commentary considers the need for: early, continuous engagement with the regulator for COVID-19 vaccines; understanding key Chemistry, Manufacturing and Controls (CMC) challenges in order to build a successful COVID-19 vaccine CMC dossier; investing in production and testing site readiness for COVID-19 vaccines; CMC lifecycle and post-approval planning for COVID-19 vaccines as well as future directions including international regulatory cooperation.

EMA’s experience of the CMC scientific considerations, which facilitated both timely approvals (as Conditional Marketing Authorisations) and rapid increase in production capacity and supply, is of interest to healthcare professionals, academia, pharmaceutical industry and global regulators to communicate the
Focussing Regulatory Science on support to innovation

Goal 1: Catalysing the integration of science and technology in medicines’ development

- Facilitate the implementation of novel manufacturing technologies
- Support translation of ATMPs into patient treatments
- Develop understanding of, and regulatory response to, nanotechnology and new materials in pharmaceuticals

Goal 5: Enabling and leveraging research and innovation in regulatory science

Pharmaceutical Strategy for Europe

...'aims at creating a future proof regulatory framework and at supporting industry in promoting research and technologies that actually reach patients in order to fulfil their therapeutic needs while addressing market failures.

- **Access (affordability & unmet medical need)**
- **Competitiveness, innovation, sustainability**
- **Crisis preparedness & response**
- **EU voice**

**Digitalisation & innovation:**
- emerging new manufacturing methods
- master files
- personalised medicines & platform approaches
- Variations & lifecycle management

**Next steps:**
- March 2021 Roadmap
- Consultation activities ongoing
- new pharma legislation expected in 2023 (timeline tbc)

https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe_en#next-steps
Support to Global convergence and alignment

**ICMRA pilots**
- Collaborative assessments (scope: PACMP)
- Hybrid inspections

**Objective:** increase collaboration and convergence of assessment approaches when assessing manufacturing facilities and reviewing PACs and PAC Management Protocols.

- Open call to Industry for both pilots since June 2022
- A number of proposals submitted for the collaborative assessment
- 1st pilot submissions selected and starting soon

- The pilots remain open - encourage new proposals
Where do we focus: EMA’s survey on Innovation
Survey Overview

- Development of vision – overall aims
- Survey of industry, tech. organisations and SMEs for identification of priority topics
  - 38 respondents
  - Novel manufacturing technologies:
    - Continuous manufacturing (CHE and BIO) (13)
    - Digitalization, automation, AI (11)
    - Aseptic micro-filling, sterility assurance related tech (9)
    - Microfluidics (7)
    - Closed automated system technologies (cell and gene therapies) and mRNA platforms (6)
  - Novel analytical technologies
    - Rapid microbiological methods (12)
    - Digitalization/AI/modelling (11)
    - Advanced process controls and multi-attribute methods (10)
Quality Innovation Group
QIG - the Vision

Predictable reg framework
Incentivise EU innovation

QIG
Core + ad hoc experts
\(\rightarrow\) translate innovation into patient benefits

International regulatory convergence

Support

Support from development throughout lifecycle

Assessment support

Training, guidance

Academic expertise
Research projects

Links

Point of entry to EMRN
Informed open discussions

Quality domain: BWP/QWP/IWG liaison

EU Innovation network, ITF, National IOs

EMRN

Classified as public by the European Medicines Agency
Quality Innovation Group

What is happening right now?

**Constitution**
- Members
- Mandate
- Kick-off

**Processes**
- Product development + review
- Link into EMA processes/ITF/EU-IN
- Engagement strategy
- International outreach

**Topics**
- Intelligence
- Priority topics
- Workplan
- Listen-learn focus groups
- Academic expertise

ITF and QIG

Innovation Task Force (ITF)

**Early informal** meetings to support **innovative drug development**

- Early landing platform
- One off, follow-up usually not planned
- Multidisciplinary, scope goes beyond manufacturing/CMC
- Covers products/technologies with an innovative component
- Industry and Regulators (EMA/network)

Quality Innovation Group

**Product-specific** support on **key technology topics**

- Eligibility based on topic priorities & maturity of technology
- Scope on manufacturing/CMC and facility
- Ongoing product-specific interaction across lifecycle
- Industry with Regulators (EMA/network) & Academia
- International outreach
- Scientific guidance development
QIG - what can Industry expect:

Priority topics

Knowledge generation

Listen-learn focus groups

Product specific support

Topics (1st priority)

Advanced manufacturing approaches
- Continuous Manufacturing for Biologicals
- Decentralised manufacture
- Digitalisation/automation
- Other (feedback from Industry)

Deliverable
- Challenges/solutions
- Case studies
- Guidance
- Training material
- Communication material
Key points

• Support to innovation is a **key priority** for EMA & EU regulatory Network

• Innovation in manufacturing & product design is associated with **challenges** → lack of guidance, legal framework, time & resources, divergencies between regions etc.

• **Solutions:** specialised guidance, flexible legislation, international harmonisation on technical requirements, predictability & direct communication channels w. Regulators

• **Quality innovation group:** product specific & ongoing support on key technology; engagement on priority topics with all stakeholders (Reg, Acad, Ind, Internat)

• **Risk-based flexibility** developed before & used during Pandemic continues to play a role

• **International** alignment and mutual reliance are an area of focus
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