Translating innovation in pharmaceutical manufacturing and technologies for the benefit of patients – an EU perspective

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Content

- Innovation trends
- Current challenges (technical/regulatory)
- Regulatory and scientific tools
- What is EMA doing to support innovation
Innovation Trends (2025 – 2030)

- **Gene therapy** and **genome editing** (i.e. *in vivo* gene editing)
- **Microbiome products**
- **Digital health**
- **Vaccines** using novel technologies (mRNA vaccines, viral vectors, nano-delivery systems)
- **Nanomaterials** / innovate materials for targeted / modified release formulations,
- **Novel manufacturing approaches** (i.e. small portable manufacturing sites, decentralised manufacturing (e.g. cell processing ATMPs), 3D printing, end-to end CM)
- Automation, **artificial intelligence/big data** approaches (‘Pharma 4.0’)
- **Individualised therapies** (i.e. platform approaches (e.g. oligonucleotides, genome editing, gene therapy) for rare & ultrarare diseases (1-100 patients))
Support to innovation is a key priority for EMA

- Translation of innovation benefits the patient and public health
- Unmet public health challenges can only be addressed through continuous innovation
- Efficiency and productivity (manufacturing/lifecycle management/licensure)
- Public trust
- Reliability and resilience in the supply chain
- Environmental footprint
Technical and regulatory challenges
Challenges

- Manufacturing & upscaling
- Proof of concept
- Public acceptance
- Clinical risk of the unknown
- Link to academia
- Compatible with legal framework
- Regulatory acceptance
- Business case
- Regulators expertise
Regulatory and scientific tools
EMA/FDA workshop on quality support to PRIME & Breakthrough + toolbox guidance

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Process validation considerations

- Validation at target scale (+ process understanding studies post-approval)
- Concurrent validation, i.e. validation protocol & executing it concurrently with commercialisation of validation batches (EU GMP Annex 15)
- Continuous process verification (ICH Q8)
- Prior knowledge
- Decoupling drug substance and drug product process validation activities
- Defer submission of certain process validation data to post-marketing (+mechanism)
- Filing a more comprehensive control strategy & easing it post-approval (life-cycle planning)
Control strategy – EMA toolbox guidance

- **Impurities** ICHQ3A/B and ICH Q6 presents a challenge (platform knowledge, qualification of impurities possible?)
- **Pharmaceutical quality system** (e.g. handling of out of trend/out of specification results)
- **Prior knowledge**
- **Statistical process controls** or trending to set specifications
- **Front-loading** of control strategy activities (CMC development plan)
Stability – EMA toolbox guidance

- **ICH Q5C**: real time/ real condition data required for Biological/Biotech products
- **Accelerated stability models**
- **Platform knowledge** (e.g. similar products (MABs, synthetic peptides/oligonucleotides, AAV vectors))
- **Stability protocols**
Comparability – EMA toolbox guidance

- **Risk-based approach (RBA)** → extent of comparability exercise, limitation of process changes, clinical comparability
- **Multistep approach** → evaluate impact of each change
- **Analytical methods**: → measuring CQAs, sensitivity versus assay variability, setting of appropriate acceptance criteria
- **Functional assays** → matrix of biological activity, phenotype, proliferation, assay variability
- **Small-scale data / platform data / prior knowledge**
- **Comparability protocols**
  - *Launch from clinical site to shift comparability studies to post-authorisation*
  - **Split batch manufacturing** to deal with Donor/Patient variability (ATMP)
  - Comparability with **surrogate material** (e.g. healthy donors) (ATMP)
### Flexibilities used in COVID vaccines/therapeutics

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<th>Pre-requisite</th>
<th>Scientific tools used</th>
<th>Regulatory tools used</th>
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|               | 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) |

- **Knowledge and dialogue**
- **Validation, comparability, stability, excipients**
- **PACMPs, SOB and Recs**
What is EMA doing to support innovation?

- Early dialogue
- Regulatory science
- Legislation
- Scientific advice
- Guidance
- Global alignment
Contributing to Regulatory Science

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

…‘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. It will also take into account the weaknesses exposed by the coronavirus pandemic and take appropriate actions to strengthen the system’…
Support to Global convergence and alignment

- Flexibility in CMC/Quality data packages for early access approaches
  - Alignment with FDA on flexibility (2018 workshop + toolbox guidance)
  - Joint positions on control strategy, validation, stability & GMP aspects

- Close communication channels with FDA: innovative manufacturing, ATMPs, COVID

- Relations with international regulators on specific topics (COVID-19, nitrosamines, ATMPs ...)

- MRA on GMP inspections (reliance & worksharing)

- ICMRA – mutual reliance and lessons learnt from COVID-19

- IPRP on gene therapy, biosimilars, nanomedicines
Existing opportunities for dialogue with EMA on CMC innovation

- **EMA Innovation Task Force (ITF) meetings**

- **EU innovation network**
  Innovation in medicines | European Medicines Agency (europa.eu)

- **Scientific Advice/Protocol Assistance**

- **QWP/BWP Interested parties (IP) meetings**

- **Global convergence through ICMRA**

- **Collaboration with academia**
  Academia | European Medicines Agency (europa.eu)
We want to hear from you!

Survey until 11 Feb 2022:
https://ec.europa.eu/eusurvey/runner/EMA-QIGsurvey

Pharmaceutical industry

On this page, you will find information on the Agency’s activities that are most relevant to pharmaceutical industry, including news, and events. You can contribute to the Agency’s work by responding to public consultations. Learn more about how the pharmaceutical industry is actively involved in the work of the Agency.

Featured information

Survey on Quality Innovation Group priorities:
Help EMA identify the priorities and necessary expertise for a new, multi-disciplinary Quality Innovation Group to support innovation in the field of chemistry, manufacturing and controls in EU. It will offer developers and academics a platform to discuss new methods, materials and approaches with EMA, including manufacturing processes, analytical technologies, control strategies and other novel technologies. Complete the survey by 11 February 2022.

Change in pre-submission interaction format
To optimise pre-submission interactions with applicants for human medicines, EMA has simplified the process by requesting fewer documents and committing to respond initially in writing within three weeks. Applicants can request a follow-up meeting if required, and EMA may recommend one in complex cases. The aim is to focus pre-submission interactions on topics that require in-depth discussion. EMA has updated its pre-submission guidance to reflect this change. Applicants may still opt to use the previous pre-submission meeting process until January 2022 and should discuss options with their EMA Product lead.

Conclusion

- Pharmaceutical manufacturing and innovation in the spotlight
- Flexibility and risk-based thinking in the context of public health
- Openness for change (by the legislator)

- Global convergence
- Early involvement
- Shared responsibility

Please share your projects & challenges with us so that we can work jointly on solutions
Thank you for your attention

Further information

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EU guidelines

- **Draft toolbox guidance on scientific elements and regulatory tools to support quality data packages for PRIME:** support flexibility in CMC based on risk considerations

- **Guideline on quality documentation for medicinal products when used with a medical device:** final, entry into force: Jan 2022

- **Guideline on quality, non-clinical and clinical aspects of MP containing genetically modified cells:** final June 2021, includes genome editing

- **CHMP Guideline on real-time release testing,** Scope for Bio / Chemicals, applicable to CM or discrete unit operations (e.g. specifications, release tests)

- **CHMP Guideline on process validation** for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission (i.e. continued process verification)

- **CHMP Guideline on process validation for finished products - information and data to be provided in regulatory submissions** chemical & biological medicinal products