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

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An agency of the European Union



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

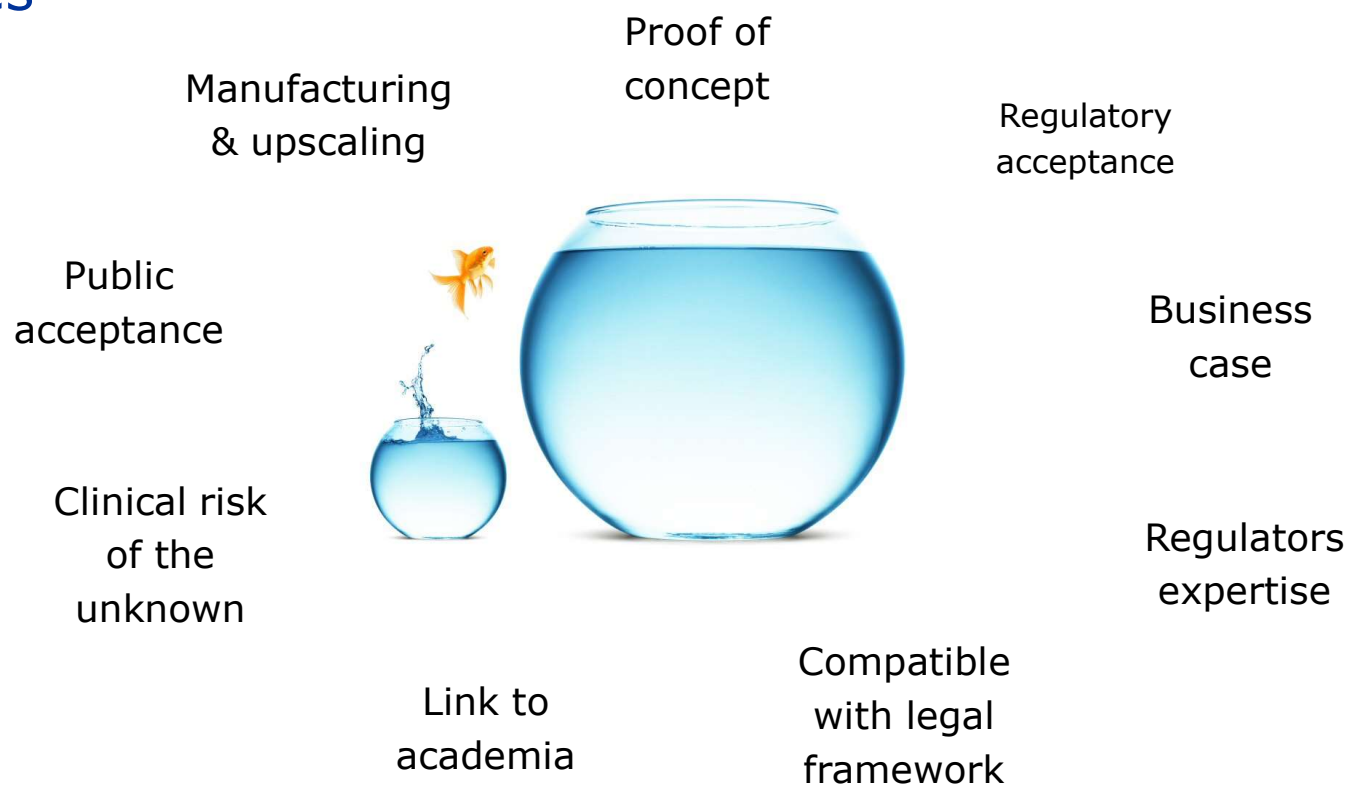
- Translation of innovation benefits the patient and public health
- Unmet public health challenges can only be addressed through continuous innovation
- Efficiency and productivity
(manufacturing/lifecycle management/licensure)
- Public trust
- Reliability and resilience in the supply chain
- Environmental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



Technical and regulatory challenges



Challenges



Regulatory and scientific tools



EMA/FDA workshop on quality support to PRIME & Breakthrough + toolbox guidance



Published
31st July
2019



1 2 February 2021
2 EMA/CHMP/BWP/QWP/IWG/694114/2019
3 Committee for Human Medicinal Products (CHMP)

4 Draft toolbox guidance on scientific elements and
5 regulatory tools to support quality data packages for
6 PRIME marketing authorisation applications
7

Consultation with BWP, QWP, IWG and CAT	September 2020
Draft adopted by BWP, QWP, IWG and CAT	December 2020
Draft adopted by CHMP for release for consultation	29 January 2021
Start of public consultation	2 February 2021
End of consultation (deadline for comments)	31 July 2021

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11 Comments should be provided using this [template](#). The completed comments form should be sent to
12 QWP@ema.europa.eu

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Keywords *Priority Medicines (PRIME), quality development, Module 3, data, scientific elements, regulatory tools, flexibility, benefit-risk*

<https://www.ema.europa.eu/en/events/stakeholder-workshop-support-quality-development-early-access-approaches-such-prime-breakthrough>

Classified as internal/staff & contractors by the European Medicines Agency

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**

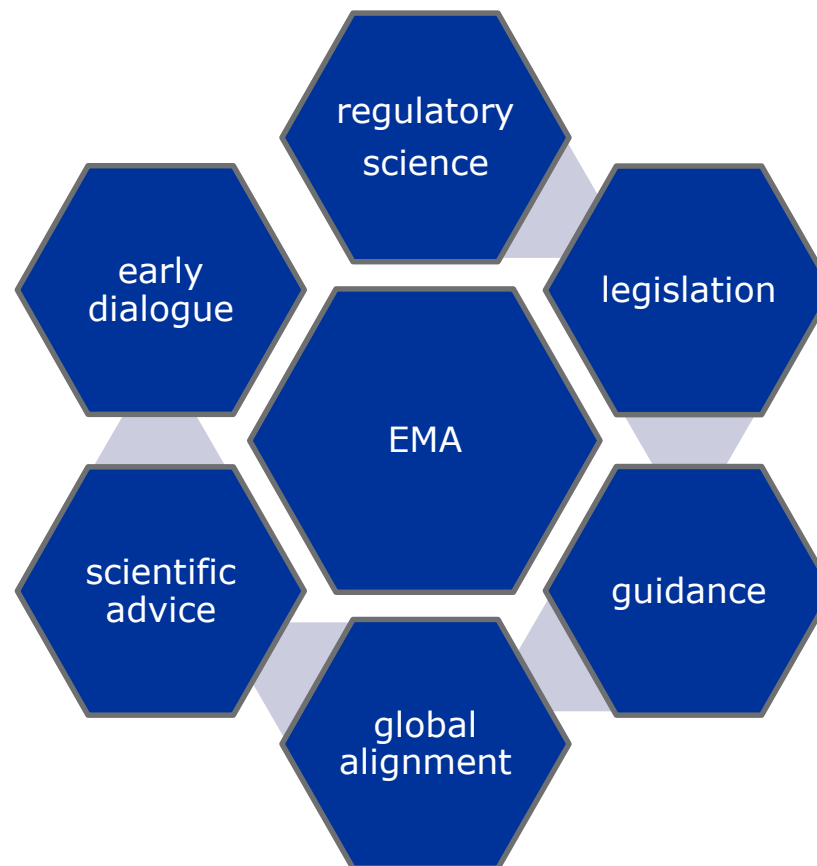
Comparability – EMA toolbox guidance

- ❖ **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

Pre-requisite	Scientific tools used	Regulatory tools used
<ul style="list-style-type: none"> • Development data from non-commercial sites • Platform data • Strategy agreed in rapid scientific advices • Close dialogue • Comparability to clinical development batches shown 	<ul style="list-style-type: none"> • 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) 	<ul style="list-style-type: none"> • Specific Obligations (completing validation/comparability/novel excipient datasets) <i>with interim timepoints</i> • 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?



Contributing to Regulatory Science



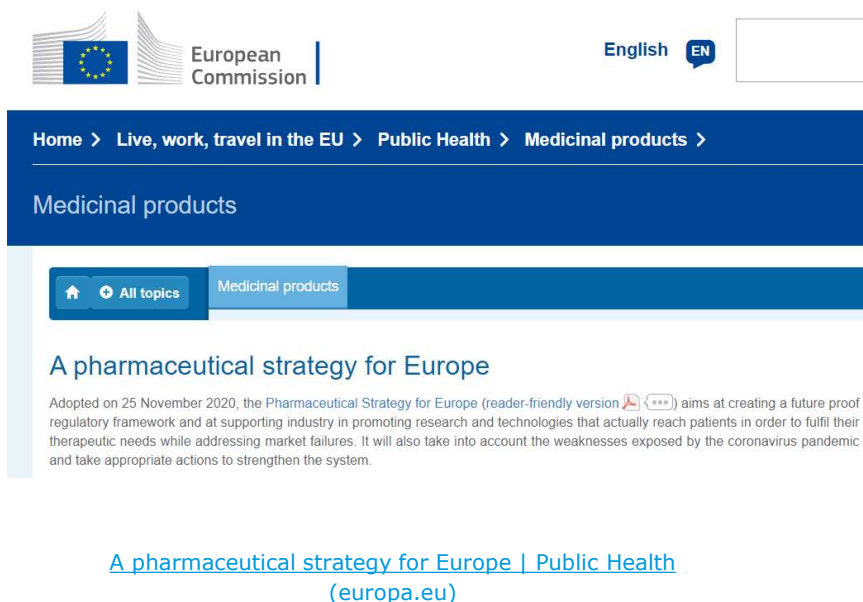
Goal 1: Catalysing the integration of science and technology in medicines' development

- 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**

https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ema-regulatory-science-2025-strategic-reflection_en.pdf

Contributing to the review of legislation

European Commission



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A pharmaceutical strategy for Europe

Adopted on 25 November 2020, the Pharmaceutical Strategy for Europe (reader-friendly version  ) 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.

[A pharmaceutical strategy for Europe | Public Health \(europa.eu\)](#)

*... '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



ICMRA Statement on Pre-Requisites for Regulatory Flexibility in Pharmaceutical Manufacturing Change Management

Since early 2020, medicines regulators and the pharmaceutical industry have worked together as part of ICMRA to advance innovation in development of new therapeutics and vaccines to address urgent, unprecedented global needs caused by the COVID-19 pandemic. The scientific achievements of the past year have been remarkable, and effective vaccines and therapeutics have been authorised in many parts of the world. All efforts are now focusing on ensuring that these medicines are produced and made available on an unprecedented global scale. Therefore, it is important for ICMRA and industry

Recent content

- COVID-19
- ICMRA Statement on Pre-Requisites for Regulatory Flexibility in Pharmaceutical Manufacturing Change Management
- ICMRA workshop on enabling manufacturing

Existing opportunities for dialogue with EMA on CMC innovation

EMA Innovation Task Force (ITF) meetings

[https://www.ema.europa.eu/en/human-regulatory/research-development/innovation-medicines#ema's-innovation-task-force-\(itf\)-section](https://www.ema.europa.eu/en/human-regulatory/research-development/innovation-medicines#ema's-innovation-task-force-(itf)-section)

EU innovation network

[Innovation in medicines | European Medicines Agency \(europa.eu\)](#)

Scientific Advice/Protocol Assistance

<https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance>

QWP/BWP Interested parties (IP) meetings

Global convergence through ICMRA

Collaboration with academia

[Academia | European Medicines Agency \(europa.eu\)](#)

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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](#).

Survey until 11 Feb 2022:

<https://ec.europa.eu/eusurvey/runner/EMA-QIGsurvey>

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.

<https://www.ema.europa.eu/en/pharmaceutical-industry>

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)
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- 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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Send a question via our website www.ema.europa.eu/contact

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