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# EMA's support to innovation – a status update

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

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# 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

Manufacturing & upscaling

Guidance available

Public acceptance

Compatible with legal framework

Global divergence

Regulators expertise

# Technical & regulatory challenges

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

| | **3D printed bioimplants** | **Gene Editing platform** | **Aseptic automated processing system** |
|---|---|---|---|
| Product description | Cellularised bioimplants by 3D bioprinting (cartilage, stem cells, lipid mediators + growth factors) | In vivo non-viral delivery Gene Editing Platform (CRISPR) | Innovative gloveless robotic isolator technology |
| Questions | • Guidance on biological starting materials + Organ-on-a-Chip model & 3D printing<br>• Classification as medical device/ATMP | • Orphan designation / ATMP classification<br>• GMP & supplier requirements<br>• quality control & characterisation | • GMP requirements (Air Velocity and Flow)<br>• Control strategy |
| Key challenges | • **Classification**<br>• **Tailored scientific advice**<br>• **Guidance limited**<br>• EC Q&A md_mdcg_qa_3d_ppp_covid-19_en_0.pdf (europa.eu) | • **International alignment**<br>• Early engagement on **GMP aspects**<br>• SA on **characterisation + control** | • Early engagement on **GMP aspects**<br>• Translating **platform** approach → **product** (FU on specific SA) |

# 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

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20 November 2018
EMA/49324O/2018
Human Medicines Research and Development Support Division

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

26 November 2018, European Medicines Agency, London

**Purpose**

The European Medicines Agency (EMA) and the US FDA launched the PRIME and Breakthrough Therapy schemes to strengthen their support for the development of medicines that address unmet medical needs with the aim to help patients to benefit from these therapies as early as possible. Experience to date has shown that Applicants face challenges to complete quality and manufacturing development and data requirements during accelerated development. In order to address/overcome these challenges EU and US FDA Regulators wish to support Applicants with guidance and risk-based flexibility regarding their pharmaceutical development programme including, e.g. product characterisation, specification setting, validation and stability testing as well as early identification of quality issues / attributes that are critical to the clinical use of the medicinal product. The aim of this workshop, which constitutes a joint collaboration between EU regulators comprising BWP, QWP and IWG, and international partners including US FDA, is to discuss between Regulators and Industry these quality challenges and possible scientific and regulatory approaches which could be used to facilitate development and preparation of robust quality data packages, to enable timely access to medicines for patients whilst providing assurance that patient safety and product quality are not compromised.

These general discussions will be further elaborated through a number of specific industry case studies (covering chemical molecules, biologicals and ATMPs) and a discussion of experiences to date from early access approaches.

The conclusions from the workshop will be captured in a report, which will be published. The development of further follow-up guidance may be considered. The live broadcast can be followed on the link below under Multimedia tab. https://www.ema.europa.eu/events/workshop-stakeholders-support-quality-development-early-access-approaches-ie-prime-breakthrough

**Location**

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

# Deliverables from the workshop

1

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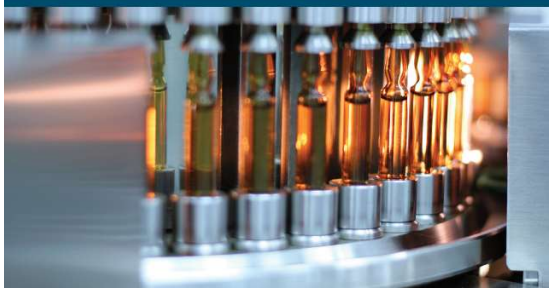
Meeting Report: Workshop with stakeholders on support to quality development in early access approaches (i.e. PRIME, Breakthrough Therapies)



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

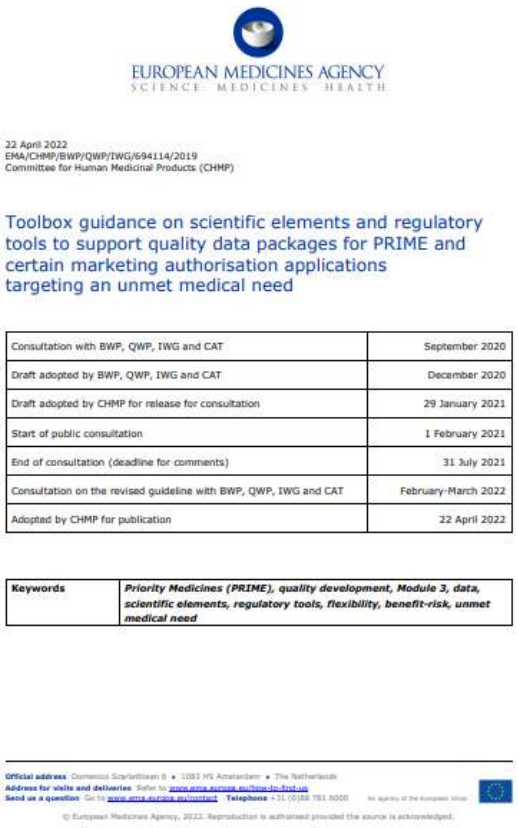
## Joint EMA-FDA discussion on PRIME/BT

**4 joint FDA-EMA Q&As**

- Control strategy
- Process validation
- Stability models
- GMP aspects (launch from former clinical site)

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

# EMA toolbox guidance



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22 April 2022
EMA/CHMP/BWP/QWP/IWG/694114/2019
Committee for Human Medicinal Products (CHMP)

Toolbox guidance on scientific elements and regulatory tools to support quality data packages for PRIME and certain marketing authorisation applications targeting an unmet medical need

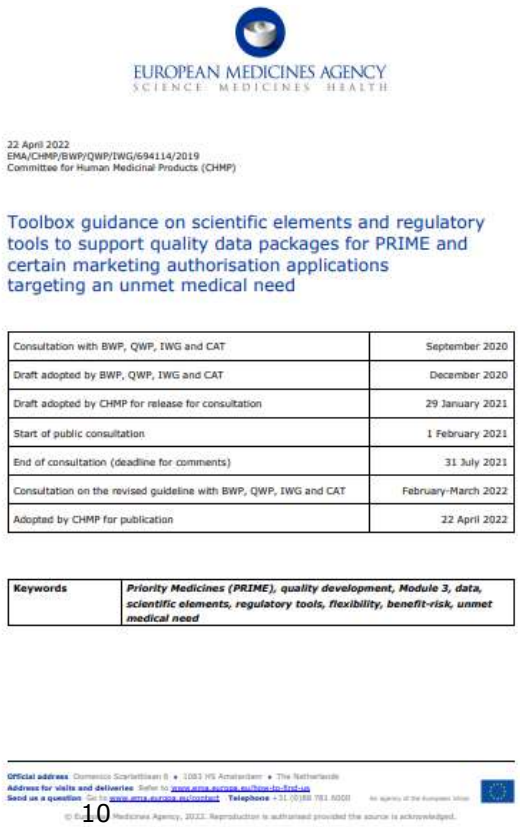
| | |
|---|---|
| Consultation with BWP, QWP, IWG and CAT | September 2020 |
| Draft adopted by BWP, QWP, IWG and CAT | December 2020 |
| Draft adopted by CHMP for release for consultation | 29 January 2021 |
| Start of public consultation | 1 February 2021 |
| End of consultation (deadline for comments) | 31 July 2021 |
| Consultation on the revised guideline with BWP, QWP, IWG and CAT | February-March 2022 |
| Adopted by CHMP for publication | 22 April 2022 |

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

- 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.

https://www.ema.europa.eu/en/documents/scientific-guideline/toolbox-guidance-scientific-elements-regulatory-tools-support-quality-data-packages-prime-certain_en.pdf

# EMA toolbox guidance



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

- 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.

# Toolbox: public consultation Feb – July 2021

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| Stakeholder comments | Agency response |
|---|---|
| Scope beyond PRIME (title should be changed) | Unmet medical need & when justified (→ title adjusted) |
| Pandemic experience should be considered | pandemic experience was considered if within scope (scientific considerations for quality data packages / regulatory tools).<br>GMP flexibilities outside of scope of guidance & specific to COVID |
| Regulatory tools beyond the ones in the GL (e.g. rolling reviews etc.) | Novel regulatory tools to be agree within EU regulatory framework + subsequently referenced in the toolbox (not the other way around) |
| Dedicated section on lifecycle management | Considered premature - important future topic:<br>**1** continuation/completion of data requirements of flexibility applied during initial MAA;<br>**2** new flexibilities afforded in the context of variations |
| ICH Q12 + ICH Q14 tools to be added | tools to be elaborated within ICH process and cross-referred when ready/if relevant |
| further guidance (e.g. models) | guidance should be developed at source and reference in the toolbox (not other way around) |

# General

- **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.**

# Process Validation

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- **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


- **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

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- **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

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22 March 2018
EMA/CHMP/BWP/187162/2018
Human Medicines Research and Development Support Division

Meeting Report:
Joint BWP/QWP workshop with stakeholders in relation to prior knowledge and its use in regulatory applications
23 November 2017, European Medicines Agency, London

**Introduction**

Prior knowledge has always been an important tool in designing both manufacturing processes and control strategies for medicinal products. In recent years, it has gained more focus in EU guidelines (e.g. process validation for biotech drug substances[1]; process validation for finished products[2]), and has been a regular topic of conversation at various conferences, symposia and meetings.

At the BWP meeting with interested parties in July 2016 a workshop on the use of prior knowledge was proposed and subsequently included in the BWP workplan 2017[3]. The BWP, in cooperation with the QWP, formed an organising committee of BWP & QWP members and industry representatives nominated by the interested parties to the BWP & QWP.

Making use of prior knowledge in regulatory application dossiers, to support manufacturing and control strategies, could be justifiable in certain circumstances. For prior knowledge to be used in this way, a good understanding among regulators and industry regarding the expectations of how prior knowledge should be documented in regulatory application dossiers is essential. The aim of the workshop was therefore to address what prior knowledge entails and how it can be used to support product development, manufacturing and control strategies. These general discussions were further elaborated through a number of specific industry case studies and a discussion of experiences to date of accelerated access schemes.

https://www.ema.europa.eu/en/documents/report/meeting-report-joint-biologics-working-party/quality-working-party-workshop-stakeholders-relation-prior-knowledge-its-use-regulatory-applications_en.pdf

# Flexibilities used in COVID vaccines/therapeutics

| Pre-requisite | Scientific tools used | Regulatory tools used |
|---|---|---|
| • Development data from non-commercial sites<br>• Platform data<br>• Strategy agreed in rapid scientific advices<br>• Close dialogue<br>• Comparability to clinical development batches shown | • **Protocol** to complete process validation & comparability post-approval<br>• **Concurrent validation** of commercial manufacturing process<br>• **Extrapolation** of stability data (comparability, accelerated conditions + supportive stability data)<br>• **2-tiered comparability** of AS / FP (1: comparison of release and IPC results; 2: additional characterisation test results post-approval)<br>• 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*<br>• **Annex II conditions**<br>• **Recommendations**<br>• Post-Approval Change Management Protocols (**PACMPs**) Exceptional change management process (**ECMP**)* to transfer analytical methods to already approved QC sites<br>• **Derogations** (batch release testing in EU) |
| Knowledge and dialogue | Validation, comparability, stability, excipients | PACMPs, SOB and Recs |



* COVID scope only

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

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


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

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

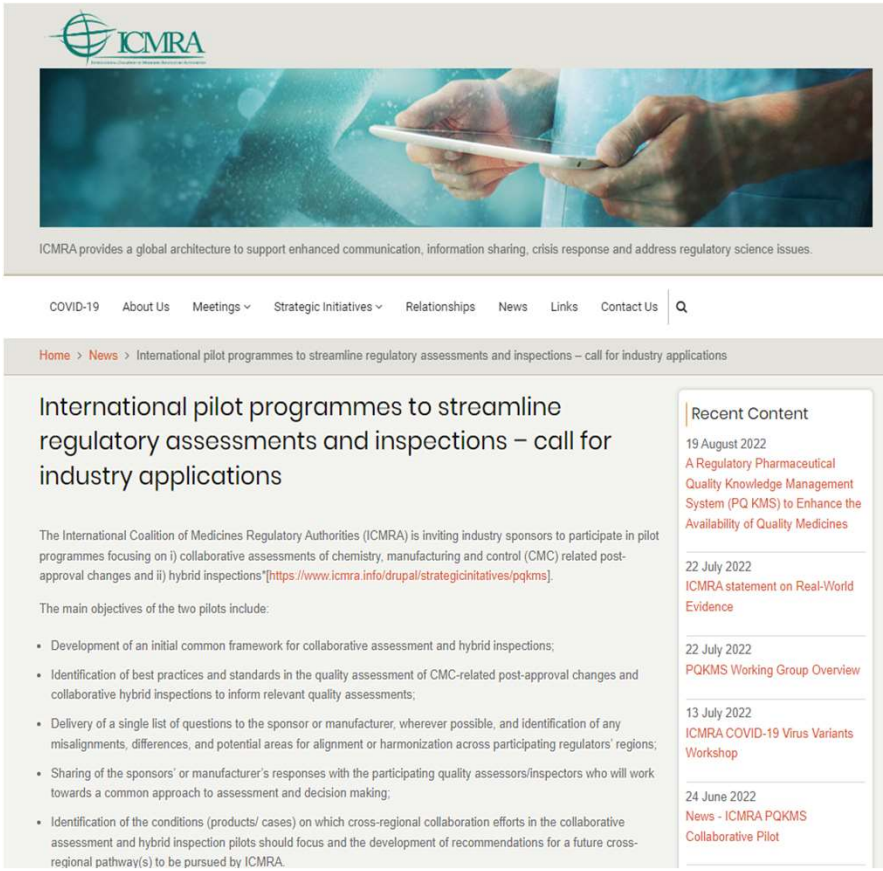
**ICMRA pilots**

- 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

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- 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

EMRN

Predictable reg framework
Incentivise EU innovation

Training, guidance

Support

International regulatory convergence

Assessment support

Quality domain: **BWP/QWP/IWG** liaison

**QIG**
Core + ad hoc experts
→ translate innovation into patient benefits

Academic expertise
Research projects

Support from development throughout lifecycle

Point of entry to EMRN
Informed open discussions

Links

EU Innovation network, ITF, National IOs

# Quality Innovation Group

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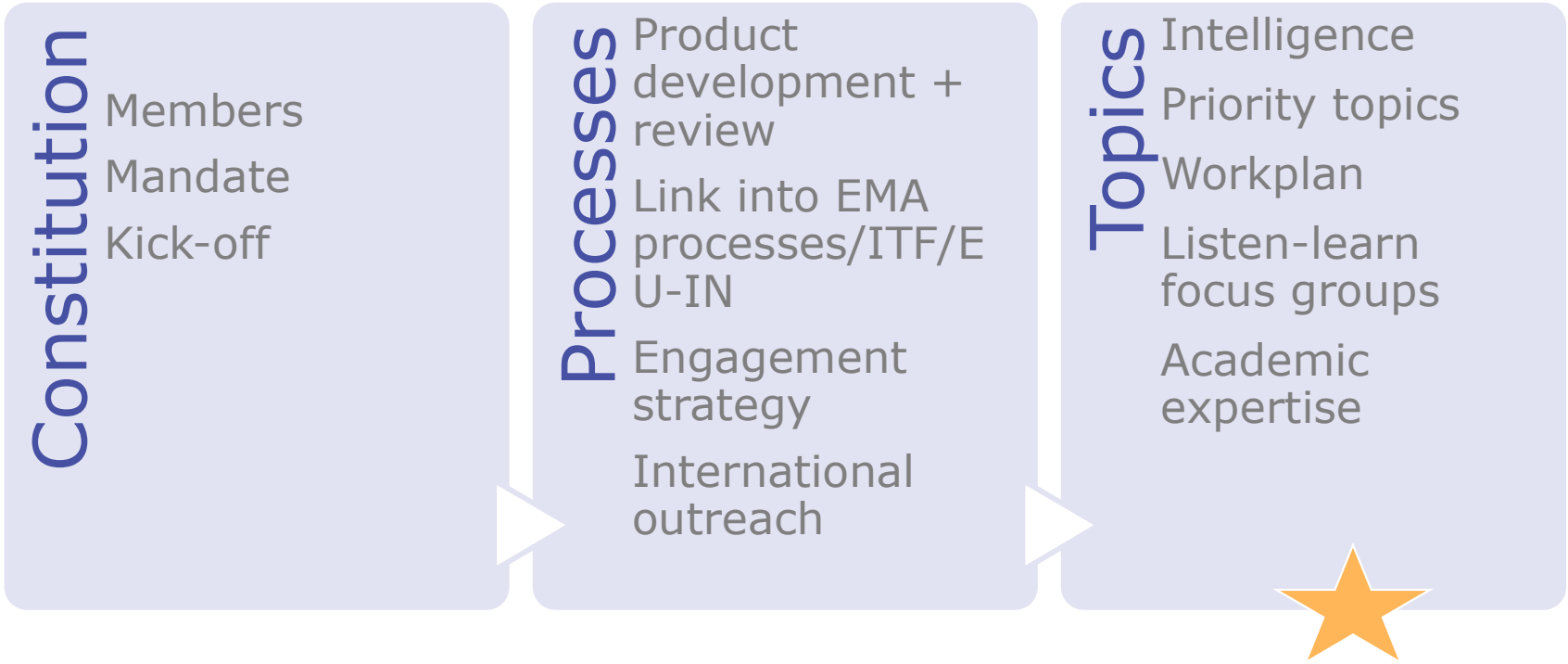
## What is happening right now?




Quality Innovation Group | European Medicines Agency (europa.eu)

# ITF and QIG

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## Innovation Task Force (ITF)

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

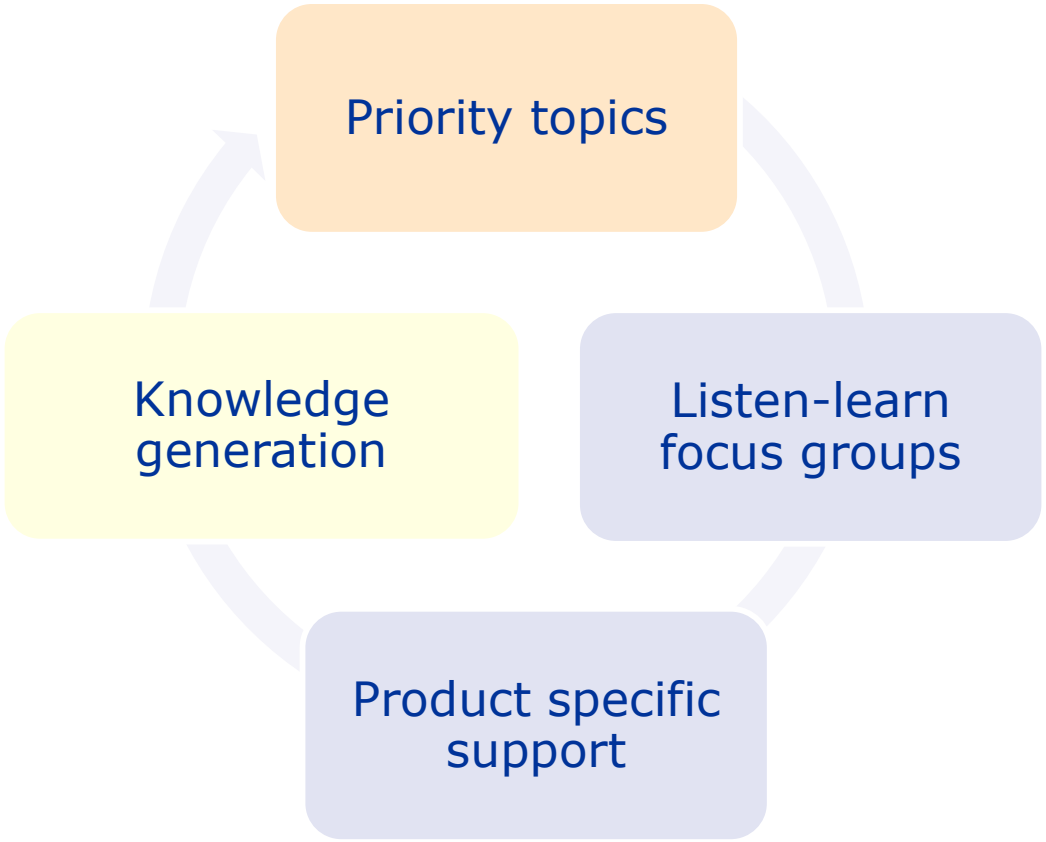
- Early landing platform
- One off, follow-up usually not planned
- Multidisciplinary, scope goes beyond manufacturing/CMC
- Covers products/technologies with an innovative component
- Industry and Regulators (EMA/network)

## 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:




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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# Any questions?

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