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SCIENCE MEDICINES HEALTH

Regulatory update from Europe

CASSS CMC Strategy Forum Japan 2023

4-5 December 2023

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Disclaimer

The views expressed in this presentation are those of the speaker and do not necessarily represent those of the EMA and other European Regulatory Agencies.

- ✓ **Global harmonisation and collaboration**
- ✓ PRIME toolbox guidance
- ✓ COVID-19 CMC Learnings
- ✓ BWP priorities

EMA in the global environment

All Divisions/Departments are concerned and the exchange of information with international regulatory authorities is **part of EMA's daily work**.

International collaboration is **key** to:

- **Facilitate alignment** of regulatory approaches between international authorities
- **Speed up patient access** to new and/or affordable medicines
- **Avoid duplication** of work
- **Release scarce resources** for more critical areas
- **Support regulators** outside the EU who may lack resources and/or specific competence

Mechanisms for international collaboration

Bilateral relations

Argentina, Australia, Brazil, Canada, Chile, China, Colombia, Dominican Republic, Israel, Japan, New Zealand, Peru, Republic of Korea, Saudi Arabia, Singapore, South Africa, Switzerland, Taiwan, United Kingdom, United States of America, EDQM, WHO

International Liaison Officers

Confidentiality Arrangements (CA)

Ad Hoc CA

Mutual Recognition Agreements (MRA)

Multilateral relations

ICH harmonisation for better health

OPEN

PIC/S

IPA project

ICMRA

EU-M4all

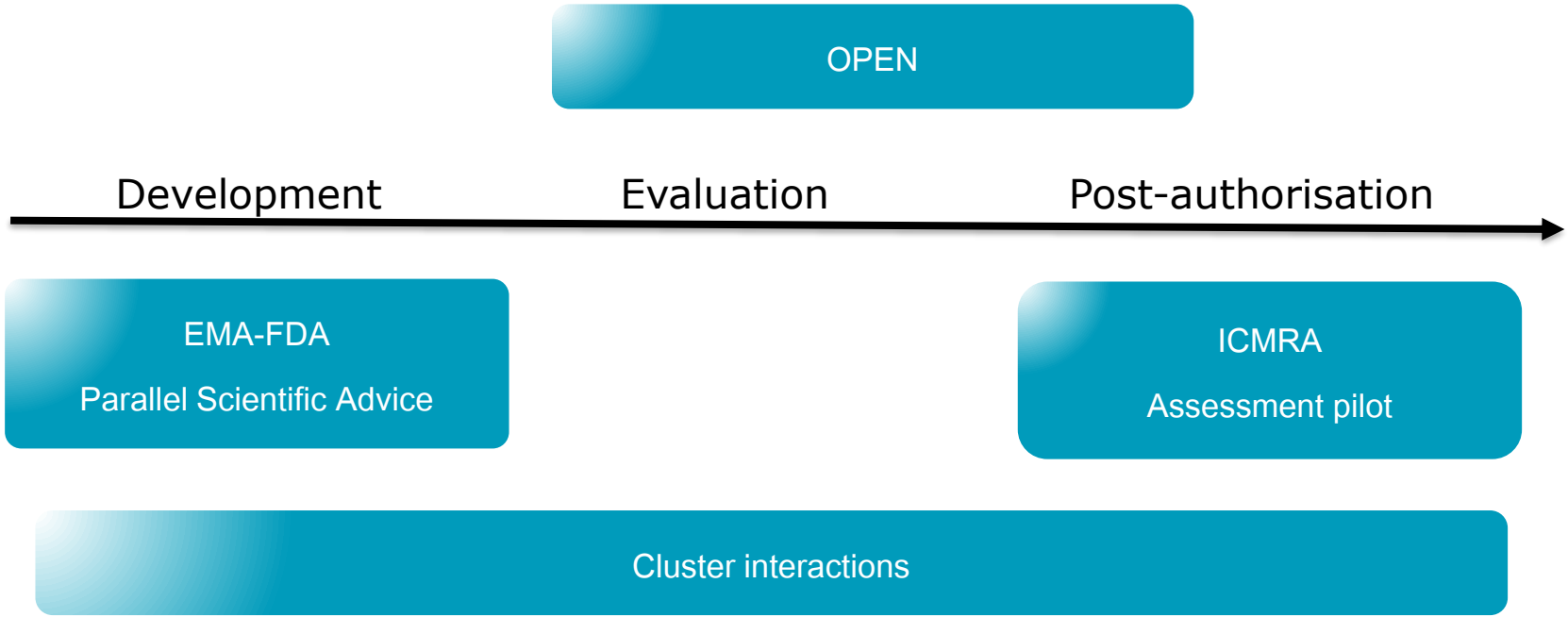
IPRP International Pharmaceutical Regulators Programme

SRA CRP

AMA project

VICH International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

Opportunities for collaborative assessment



Opening our **P**rocedures at **E**MA to **N**on-EU authorities

OPEN is **an international collaboration framework** of near-concurrent review among international regulators.

OPEN Pilot (December 2020 – May 2023)

Goal: Sharing scientific expertise to tackle common challenges on COVID-19 vaccines and therapeutics

Approach: Participating non-EU experts invited to **attend and contribute** to **ETF and CHMP evaluation**

OPEN experts follow **similar requirements** as the EU experts *(e.g., confidentiality, absence of conflict of interests).*

OPEN regulators

EMA, Health Canada, Swissmedic, TGA, MHLW/PMDA, WHO

All participating under the terms of their Confidentiality Arrangement with the EU.

OPEN products

All the COVID-19 vaccines and therapeutics evaluated since the launch of the pilot.

Implementation:

- **EMA conducted a full review** of applications but shared and discussed assessments in real-time with OPEN experts
- OPEN experts **participated actively** in Emergency Task Force (ETF) and CHMP meetings
- OPEN experts **exchanged comments and reviews** with EMA product leads and assessment teams.
- All Regulators kept full scientific and regulatory **independence.**

Scope for extension of OPEN

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Expand to identified areas

1. **Antimicrobial resistance** (AMR) *global threat where progress requires a collective effort for human and veterinary products*
2. Priority medicines designated under the **PRIME scheme (temporarily not including ATMPs products)** and products which **address high unmet need** (e.g. RSV, Alzheimer, ALS)
3. Medicinal products responding to health threats or **public health emergencies**

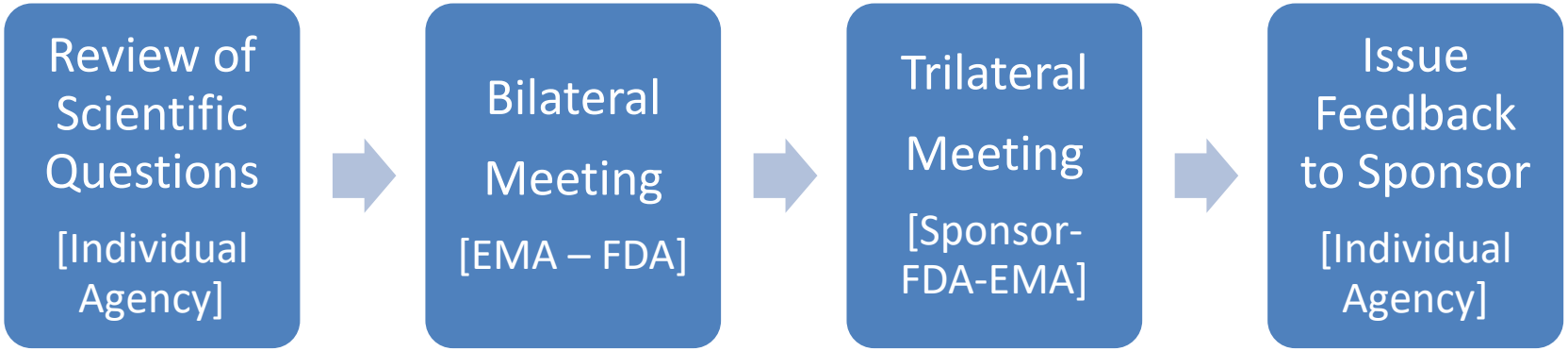
Consolidate the pilot's operation

- Engaged with all OPEN partners to:
  - **Define terms of reference that promote RECIPROCITY and more active** participation
  - Increase the initiative **visibility** with more **systematic and coordinated communication** by all OPEN participants

Expected benefits for industry and global health

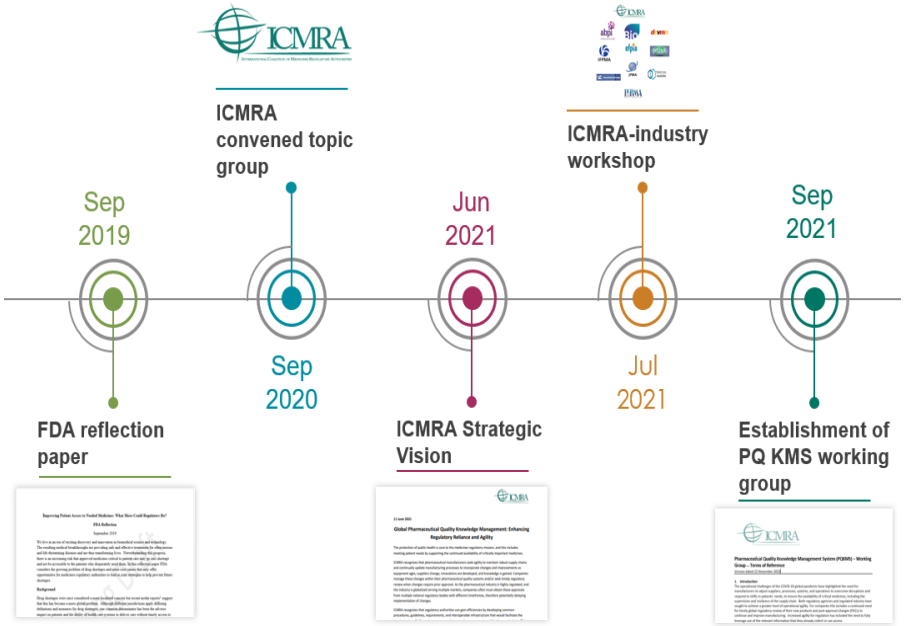
- Alignment of dossiers to improve regulatory convergence within OPEN partner countries
- Potential faster overall global approval through leveraging existing or ongoing assessments and expertise beyond the EU regulatory network (e.g. fewer questions for industry)
- Potential to align also the post-approval lifecycle management for major changes and/or also using reliance mechanism
- Promoting capacity optimisation and convergence of assessment standards
- Possibility to engage with EMA in a discussion to harmonise global standards of submissions

EMA-FDA parallel scientific advice - Overview of collaboration



Overall process aligned with CHMP Scientific Advice (SA) procedure (70-day timeline) and timeline for Type B Meeting at FDA

The **ICMRA** Pharmaceutical Quality Knowledge Management System (PQKMS) project



ICMRA
ICH harmonisation for better health
PIC/S
IPRP International Pharmaceutical Regulators Programme


Version Dated: 21 July 2022

A Regulatory Pharmaceutical Quality Knowledge Management System (PQ KMS) to Enhance the Availability of Quality Medicines

ICMRA-ICH-PIC/S-IPRP Joint Reflection Paper

Background and Rationale

Changes to pharmaceutical manufacturing processes, technological innovations, and altered supply chains are just some examples of the many issues requiring operational agility that affect the availability of medicines required to meet patient needs. Whether pursuing continuing improvement in manufacturing a novel therapeutic based on post approval experience, or routine updates to operations, equipment, suppliers, and other post approval changes (PACs) later in a product life cycle, manufacturers are expected to proactively manage pharmaceutical quality using existing frameworks outlined in the internationally harmonized guidelines. Specifically, this includes ICH Q10 Pharmaceutical Quality System[1], building on the guidance in ICH Q8 Pharmaceutical Development[2], while applying the principles in ICH Q9 Quality Risk Management[3], and utilizing the enablers and tools outlined in the ICH Q12 guideline on Lifecycle Management[4].

While companies manage these PACs within their pharmaceutical quality systems (PQS), the current operating environment requires prior approval by the regulatory authority of each region and country individually. For a product to be globally available to patients, this can translate to numerous and often duplicative regulatory review processes and time frames. This presents regulatory complexity that can significantly constrain manufacturer agility in addressing

TWO pilot programmes:

- Collaborative Assessment PACMP
- Collaborative Hybrid Inspection

Cluster interactions for biologicals

Biosimilars Est. 2011
3 meetings per year
EMA, FDA, Health Canada, PMDA, Swissmedic

Advanced Therapies Est. 2008
5-6 meetings per year
EMA, FDA, Health Canada, PMDA

Vaccines Est. 2005
4 meetings per year
EMA, FDA, Health Canada

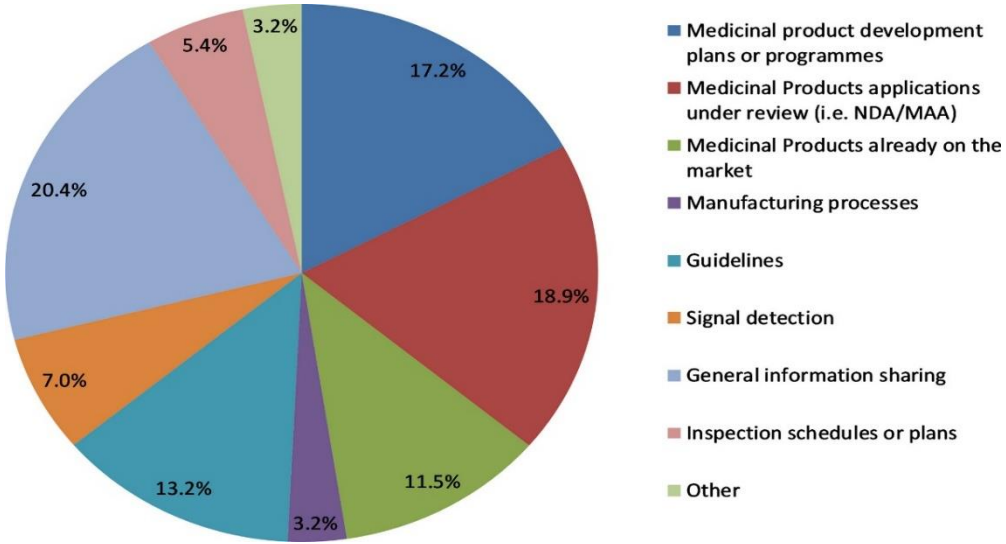
Blood products Est. 2010
3 meetings per year
EMA, FDA, Health Canada

+ ad-hoc product- or issue-related meetings

Cluster interactions

- Regular interactions between core groups of topic experts
- Around 30 different clusters
- Facilitate timely information exchange

Areas of discussion:



Source: "Are the European Medicines Agency, US Food and Drug Administration, and Other International Regulators Talking to Each Other?", Clinical Pharmacology & Therapeutics, Volume: 107, Issue: 3, Pages: 507-513, First published: 26 August 2019, DOI: (10.1002/cpt.1617).

- ✓ Global harmonisation and collaboration
- ✓ **PRIME toolbox guidance**
- ✓ COVID-19 CMC Learnings
- ✓ EMA priorities in biotech area

PRIME (5 years review 2016-2022)

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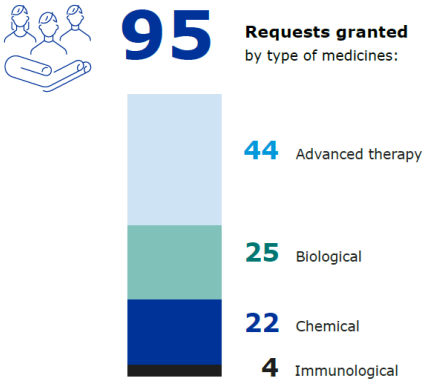
PRIME – PRIORITY MEDICINES

PRIME eligibility



In 2022:
8 medicines with
PRIME designation approved

Beyfortus (nirsevimab), Std MA, AA,
Breyanzi (lisocabtagene maraleucel), Std MA, orphan, Annex II condition (Q)
Carvykti (ciltacabtagene autoleucel), conditional MA
Ebvallo (tabelecleucel), MA under exceptional circumstances
Hemgenix (etranacogene dezaparvovec), conditional MA
Roctavian (valoctocogene roxaparvovec), conditional MA
Tecvayli (teclistamab), conditional MA, AA, orphan
Xenpozyme (olipudase alfa), std MA, AA

EMA PRIME 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***

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- Scope: PRIME and unmet medical need
- scientific elements/regulatory tools available to address challenges in generating robust quality packages
- Applicable to small molecules, Biologicals & ATMPs
- *living document –update as experience evolves*

EMA PRIME toolbox guidance

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- General
- Process validation (incl. concurrent validation)
- Control Strategy
- GMP
- Stability
- Comparability
- Regulatory tools

EMA Toolbox guideline on scientific elements, regulatory tools - PRIME MAs

Joint EMA-FDA workshop on quality support to PRIME & BT - 2018

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PRIME - **support scheme** for timely **development** and **delivery** of medicines to patients without compromising product quality

Global alignment

Flexibility -when quality data submitted & managed

Risk-based thinking to relate available quality data vs. requirements-context of **benefit/risk assessment**

EMA-FDA Joint Questions and Answers on quality and GMP aspects for PRIME/BT applications*

New

1. Control strategy

- Establishment specs
- Revision specs post-approval
- CS adaptation to offset reduced knowledge
- PPs criticality
- Use prior knowledge
- Analytical method validation

2. Process validation

- PV requirements
- Concurrent PV
- Use prior knowledge
- Decoupling API and FP PV
- PV when launching from an investigational site

3. Stability

- Deviation from ICH
- Real time vs supportive data
- Use prior knowledge
- Modelling

4. GMP

- Launching from investigational process & facility
- GMP inspections
- BIO starting materials
- Inventory from clinical studies for supply

*publication pending

- ✓ Global harmonisation and collaboration
- ✓ PRIME toolbox guidance
- ✓ **COVID-19 CMC Learnings**
- ✓ BWP priorities

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Flexibilities used in COVID vaccines/therapeutics

Pre-requisite	Scientific tools used	Regulatory tools used
• **Development data from non-commercial sites** • **Platform data** • **Strategy agreed in rapid scientific advices** • **Close dialogue** • **Comparability to clinical development batches shown**	• **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

* 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

COVID-19 CMC Learnings

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CMC Learnings

Learning

Regulatory planning for MAA

- COVID-19 vaccine applications were **resource intensive**, requiring well-planned, timely data packages of good quality

Learning

Engagement

- Early & continuous engagement with regulators from development through post-authorisation required using the right regulatory tools.

Learning

Manufacturing readiness

- 'At-risk' investment
- Intensity of regulatory engagement from early stage
- Need for distant inspections, MRA, trusted partners' inspections

Learning

CMC dossier

- Understand major CMC issues to build dossier
- Understand that the extent of regulatory flexibilities subject to product/process knowledge & site readiness- tailored to each product
- Key confirmatory data expected to be filed post-approval

Learning

- **Post-approval planning**
- Should be incorporated during MAA (PACMP, plan GMP)
- **Resource intensive** (prioritisation), requires regular interaction, accelleration when impacted supply

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Use of regulatory flexibility and CMC Toolbox post-COVID?

Scientific tools that can offer flexibility in terms of timepoint for full completion of certain quality data packages, e.g.

- Validation data supporting required changes post-approval
- Shelf-life definition based on stability models and /or supportive knowledge

For example, to mitigate shortages?

- ✓ Global harmonisation and collaboration
- ✓ PRIME toolbox guidance
- ✓ COVID-19 CMC Learnings
- ✓ **BWP priorities**

BWP priorities in 2023: Scientific guidelines

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➢ New guidance/reflection papers:

- Reflection paper on new active substance status of biological active substances
- Concept Paper on the development of a Guideline on the quality aspects of mRNA vaccines
- Q&A on BWP learnings
- Q&A on modelling approaches
- Concept Paper on the development of a Guideline on phage technology
- Guideline on quality, non-clinical and clinical requirements for applications for clinical trials for ATMPs

➢ Under Revision:

- CHMP Position Statement on CJD and plasma-derived and urine-derived medicinal products
- Guideline on Radiopharmaceuticals Based on Monoclonal Antibodies
- ICH: Q13, Q2/Q14, Q3E, M4Q, Q5A, Q1

BWP priorities in 2023: others

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- **European activities:**
  - Support to EDQM
  - Annual meeting with relevant experts on Influenza vaccines
  - Support to Pharma strategy proposals
  - Support revision of pharmaceutical legislation, variation regulation
- **Collaboration with international regulatory authorities outside of Europe**
- **Dialogue and engagement with stakeholders and external parties**
  - Support to workshops: e.g. mRNA workshop, genome editing, biopharmaceutical modelling
  - BWP Interested Parties meetings (6 September 2023)

In summary…

- ✓ **Global harmonisation and collaboration** is a key priority for EMA and the EU regulatory network
- ✓ **PRIME toolbox guidance** has been used effectively to address CMC challenges for products for unmet medical need
- ✓ **COVID-19 CMC learnings** confirm the utility of these scientific and regulatory tools
- ✓ **BWP priorities** include multiple new and revised guidelines, contribution to new EU pharmaceutical legislation, international collaboration and engagement with stakeholders

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