EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA perspectives on international convergence and collaboration for CMC submissions

CASSS CMC strategy forum – Latin America

Presented by Evangelos Kotzagiorgis on 7 November 2023
Pharmaceutical Quality Senior Specialist, H-QS-QUA, European Medicines Agency

Welcome to the community for

Pharmaceutical Quality (H-QS-QUA)

The Quality Office works for patients of today and tomorrow, to ensure medicinal products of consistent and acceptable quality are made available, that meet safety and efficacy expectations across their lifecycle.

Overview

Provides scientific specialist input, oversight and management of the quality aspects of human medicines (chemicals, biologicals, ATMPs) throughout their lifecycle (i.e. scientific advice, marketing authorisation and post-authorisation procedures), ensuring consistent outputs of high quality, in the context of the benefit-risk assessment. Supports innovation in the development of medicines and novel technologies, and advances regulatory science in the EU network.

Coordinates, supports, leads and interacts with other EMA functions, Committees and Working Parties on quality matters, including in crisis situations. Collaborates and leads on international projects, including ICH guidelines, on the quality of medicines.

What does H-QS-QUA do?

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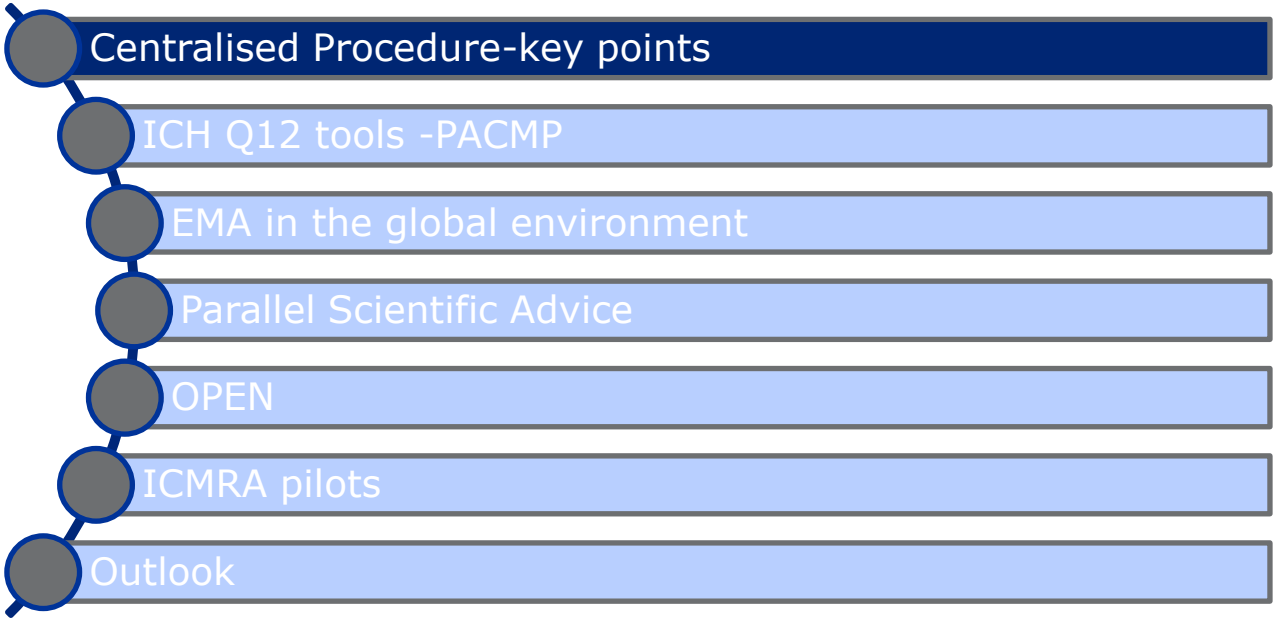
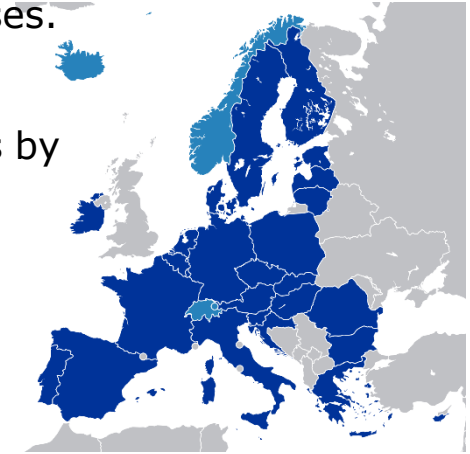
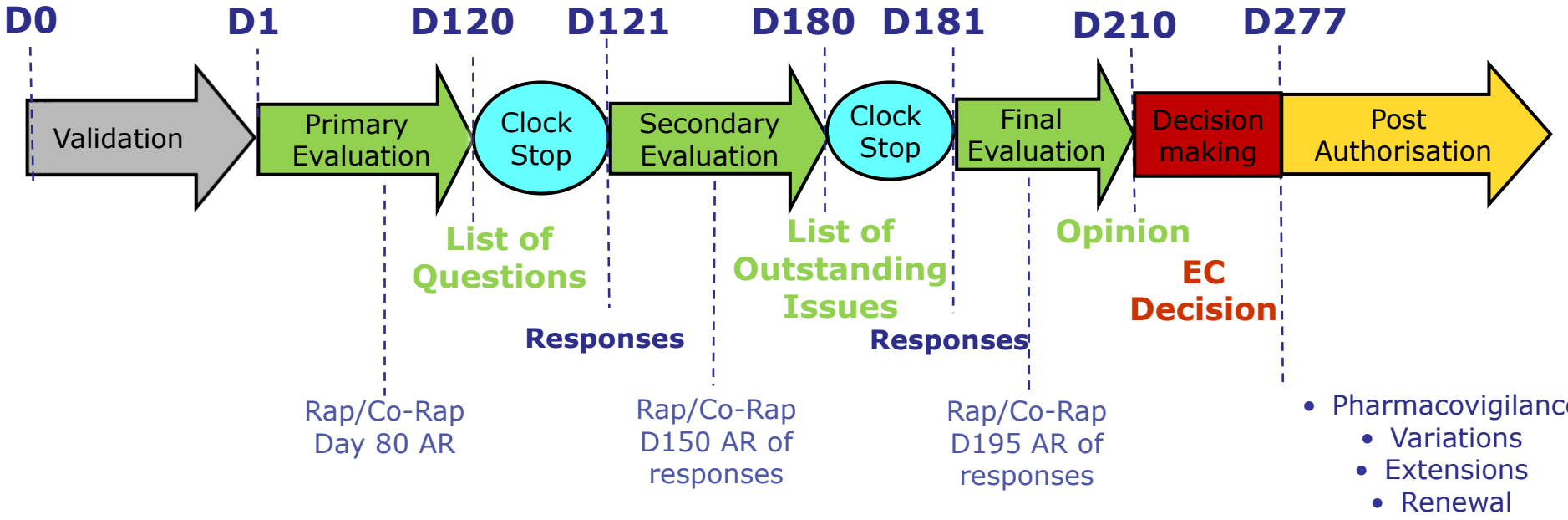


Centralised procedure – key elements

- **One single MA application** to EMA
- Compulsory for most innovative medicines, including rare diseases.
- **One assessment** procedure
  (scientific committee's opinion) based on individual assessments by Member States
- Common decision making process (one European Commission decision)
- **One MA valid in all EU member states <u>and</u> EEA**
- Transparent evaluation



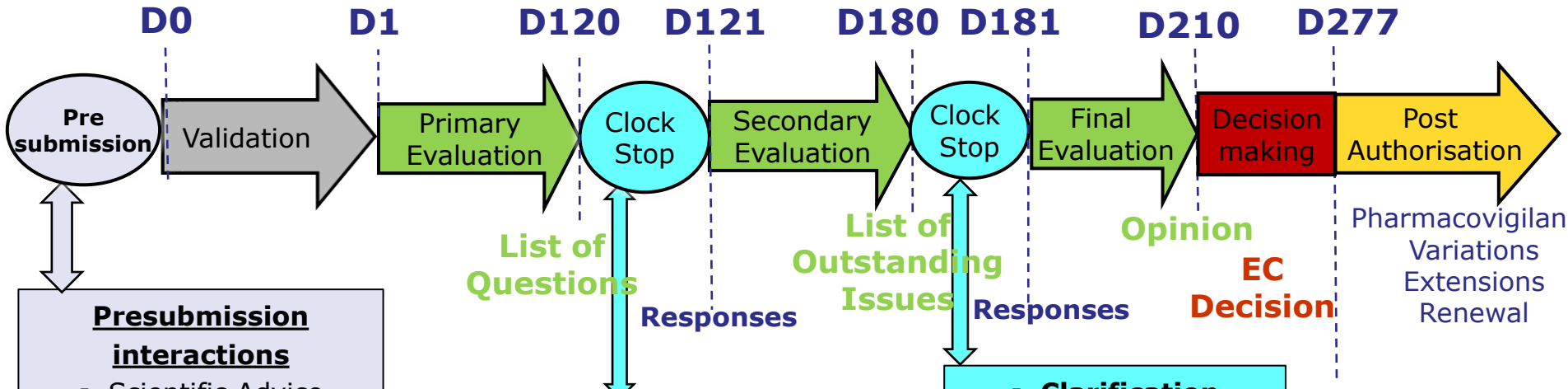
CP - Overview of assessment process



Potential additional steps

- **GMP, GLP, GCP Inspections**
- **Consultation** of Scientific Advisory Group (**SAG**) or ***ad hoc*** expert group, other **committees** or **WP**

CP - Overview of assessment process



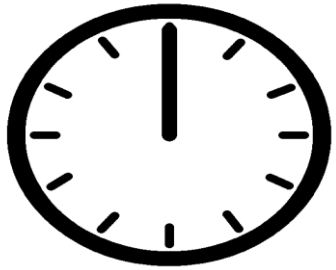
Presubmission interactions

- Scientific Advice (meeting with Applicant)
- Presubmission meeting +EMA=procedural +Rapporteurs= content
- EMA Product team

- **Clarification meeting** +EMA+Rapporteurs = Regulatory expectations & response strategy
- **EMA Product team**

- **Clarification meeting** +EMA+Rapporteurs = Regulatory expectations & response strategy
- **EMA Product team**
- **Oral explanation**

CP - Timelines

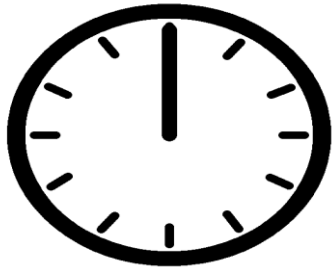


- Assessment according to **published timetables**
- **'Active time'** – time from procedure start to Opinion, excluding clock allowed to prepare written responses or oral explanation)

MAA: Standard maximum active time is **210 days**

- **Time allowed** for preparation of responses can be extended:
  - Up to 6 months after List of Questions
  - Up to 2 months after List of Outstanding Issues
- **Accelerated assessment: max 150 days (specific timetables)**

CP - Timelines



- Assessment according to **published timetables**
- **'Active time'** – time from procedure start to Opinion, excluding clock allowed to prepare written responses or oral explanation)

PAC:

Type IAs 30 days

Type IBs 30 days (+30D 1 x Request for supplementary information (RfSI))

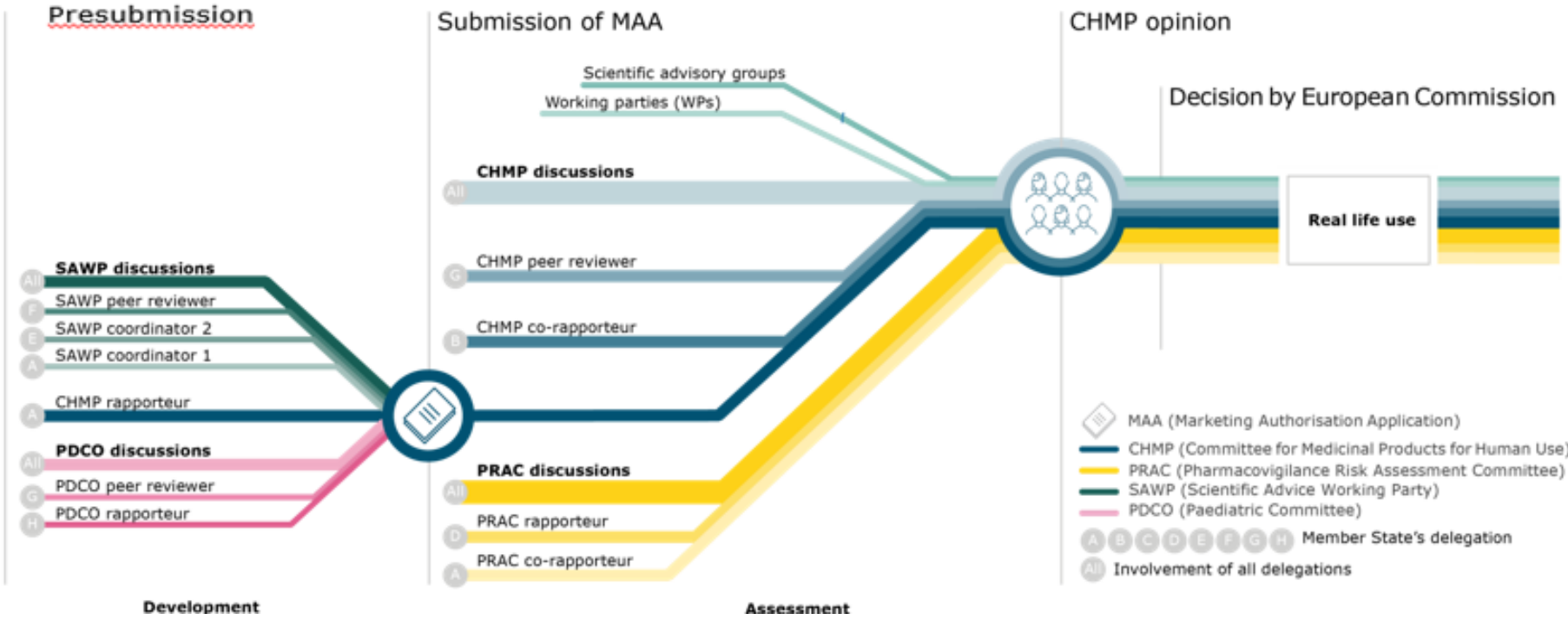
Type IIs 60 days (+60/30D N x RfSI)

- Type IIs 90 days (+60/30D, N x RfSI) (extension of indication)
- Type IIs 30 days (+60/30D, N x RfSI) (e.g. urgent safety issues)

post-authorisation procedural advice for users of the centralised procedure

Robustness by Design

Scientific Advice and Scientific Assessment in EMA



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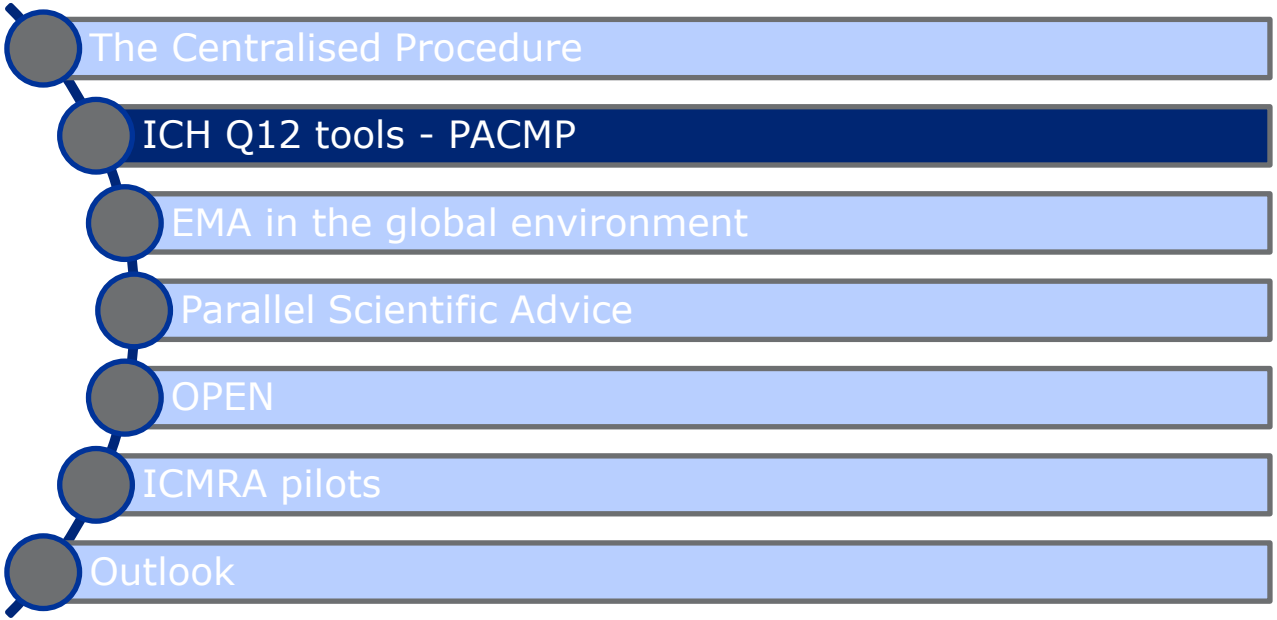
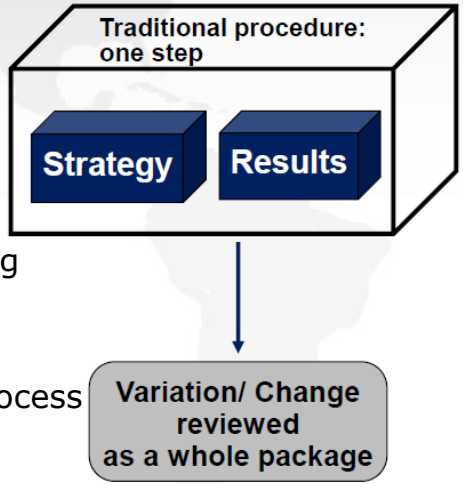


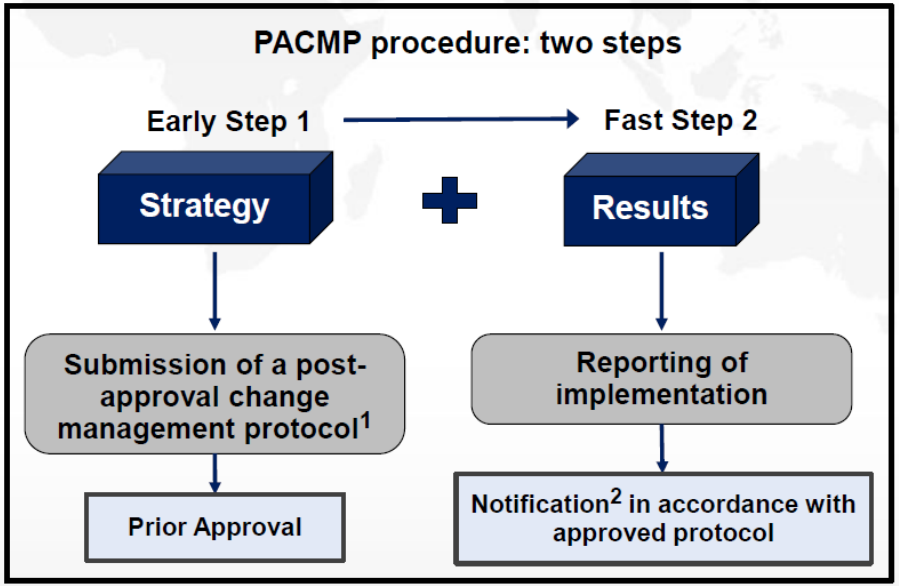
ICH Q12 Module 4

ICH Q12 Module 4

- Addition of new manufacturing site(s)
- Scale up of manufacturing process
- Change in formulation
- Change of raw material suppliers
- Change of packaging components/suppliers
- Change in analytical methods
- PACMPs can cover single or multiple changes, to a single product or to multiple products



Traditional Change procedure compared to PACMP approach



1: PACMP may be submitted with the original MAA or subsequently as a standalone submission

2: Approval by the regulatory authority may be required prior to implementation

Source: https://www.ich.org/page/quality-guidelines

ICH Q12 Module 4

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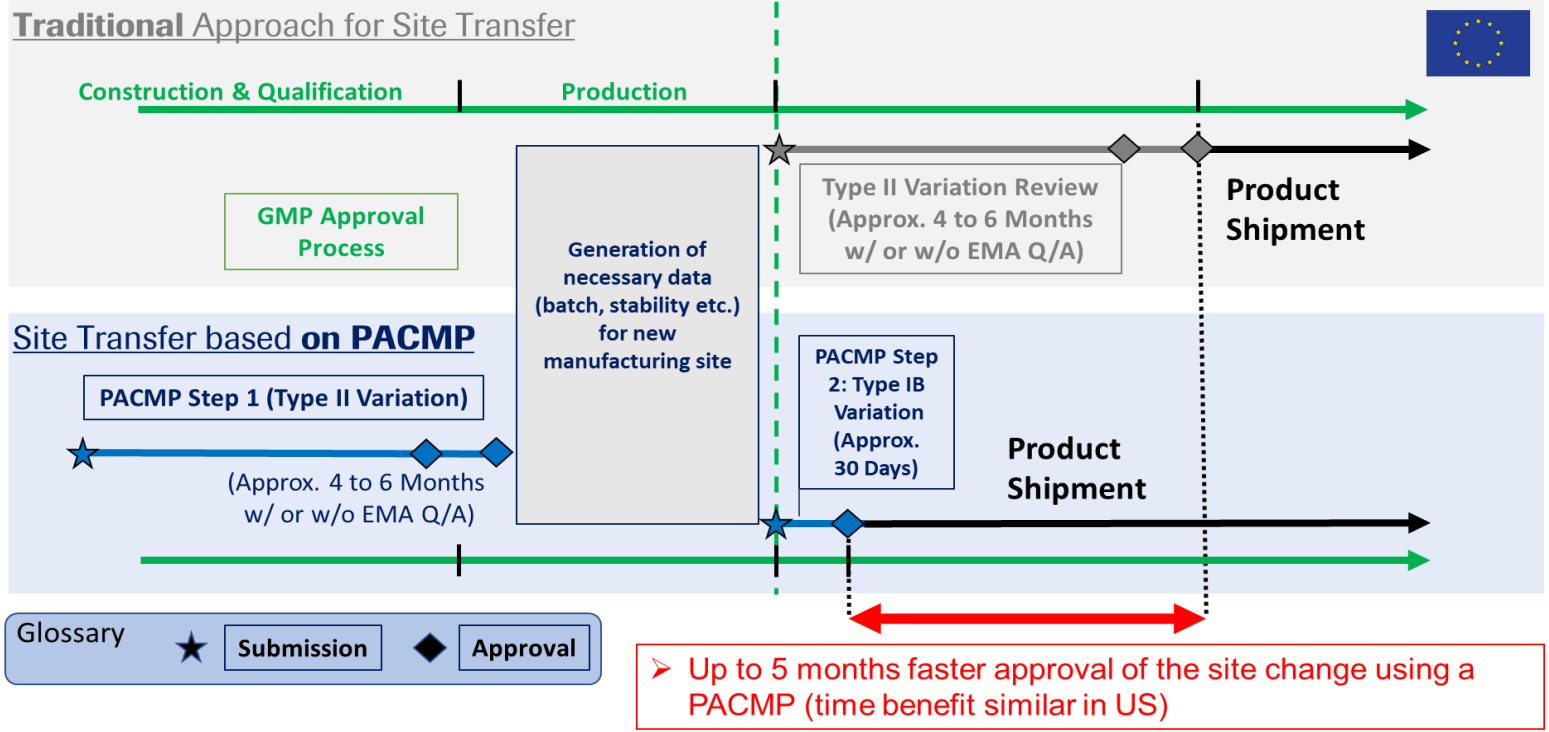
Example - Manufacturing site transfer: Timelines PACMP Approach vs. "Traditional" Approach* (based on EU/EMA case)



*Note: approval timelines for type II variation in this scheme include positive CHMP opinion and Commission Decision

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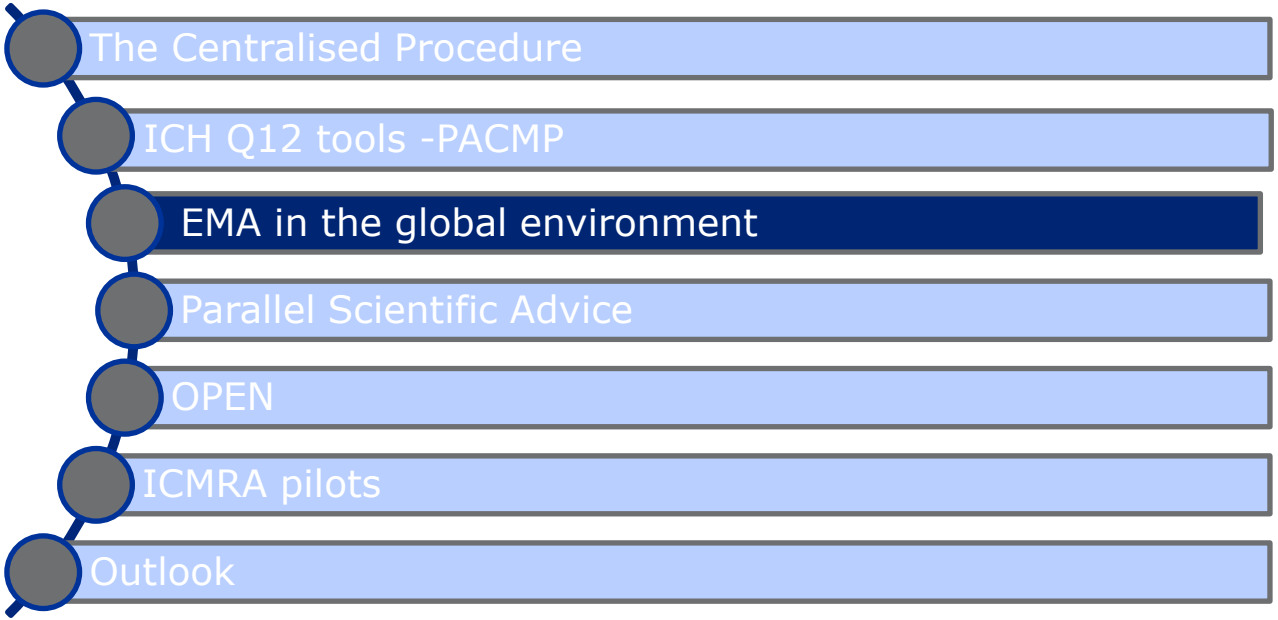


EMA in the global environment

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 compete

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)

Clusters

Multilateral relations

ICH harmonisation for better health

OPEN

PIC/S

IPA project

ICMRA

EU-M4all

IPRP International Pharmaceutical Regulators Programme

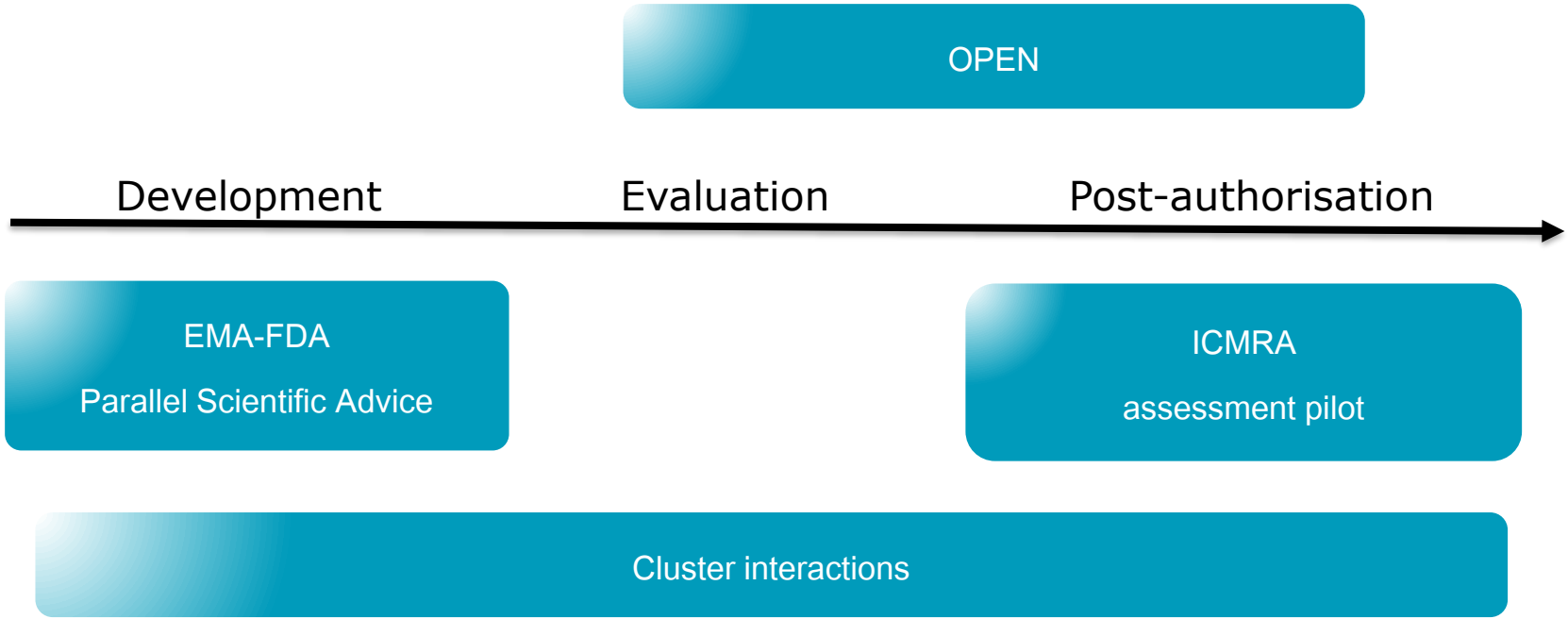
SRA CRP

AMA project

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

IPA: Instrument for Pre-accession Assistance
AMA: African Medicines Agency

Opportunities for collaborative assessment



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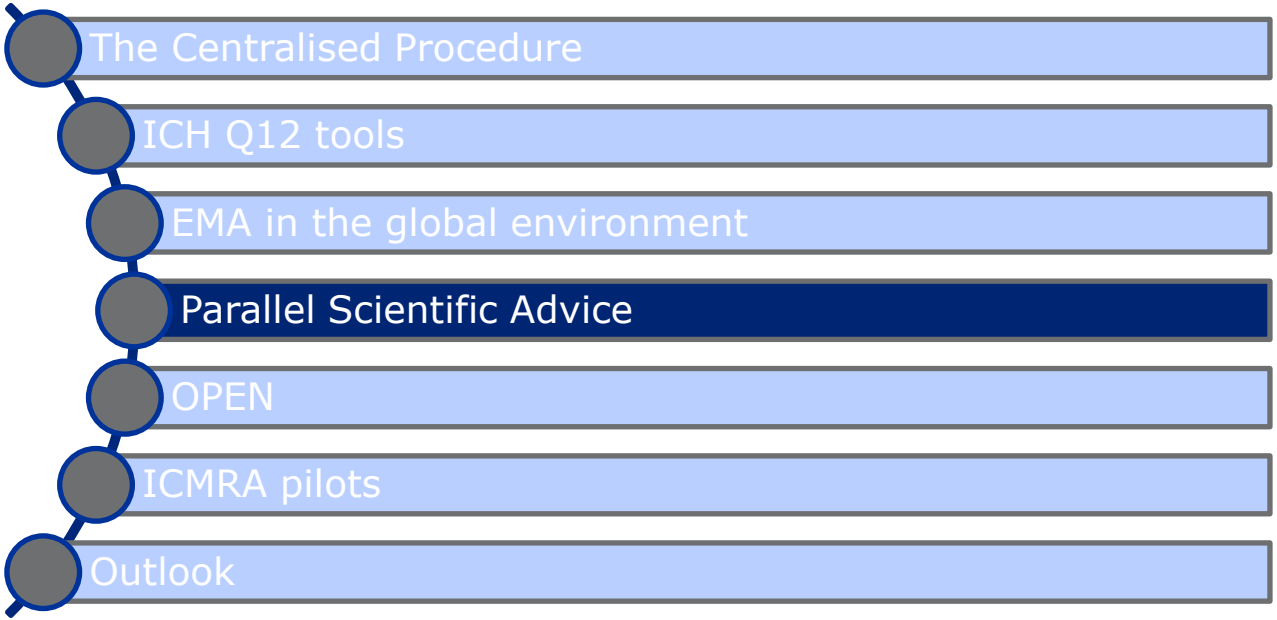


What is EMA-FDA parallel scientific advice (PSA)?

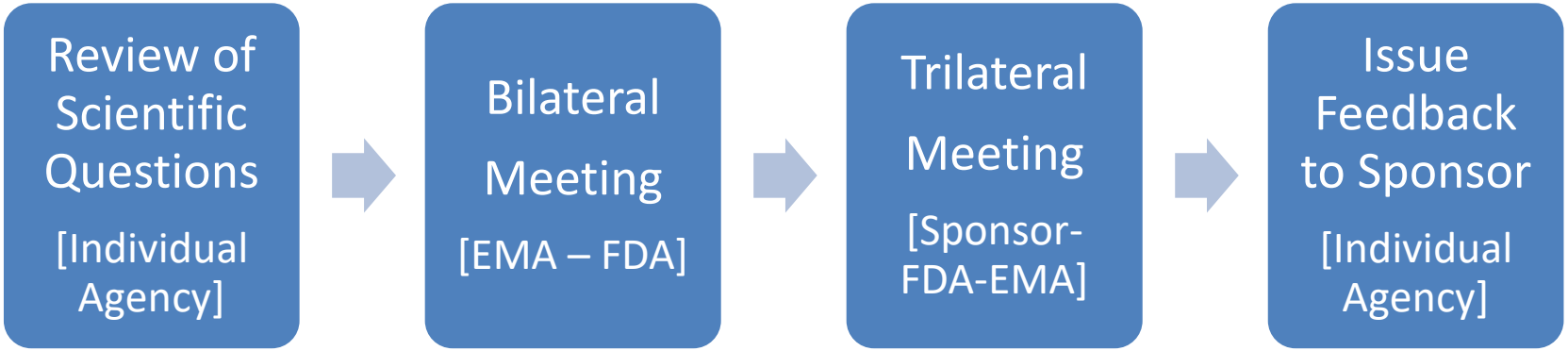
A mechanism where EMA and FDA concurrently exchange their views on scientific issues with the sponsor

- Opportunity for engagement with both regulatory agencies
- Avoid duplication of work
- Targeted to innovative products, lacking or diverging regulatory guidance or products for challenging populations
- '*Both agencies will strive to provide PSA responses that are convergent' (PSA General Principles)*
- Common approach where feasible or better understanding of the reasons for potentially remaining divergences

PSA General Principles

Conducted under Confidentiality Commitments

PSA - Overview of collaboration



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

PSA General Principles

More information/contact

- Email: emainternational@ema.europa.eu
- Email: US-FDA-EUR@fda.hhs.gov

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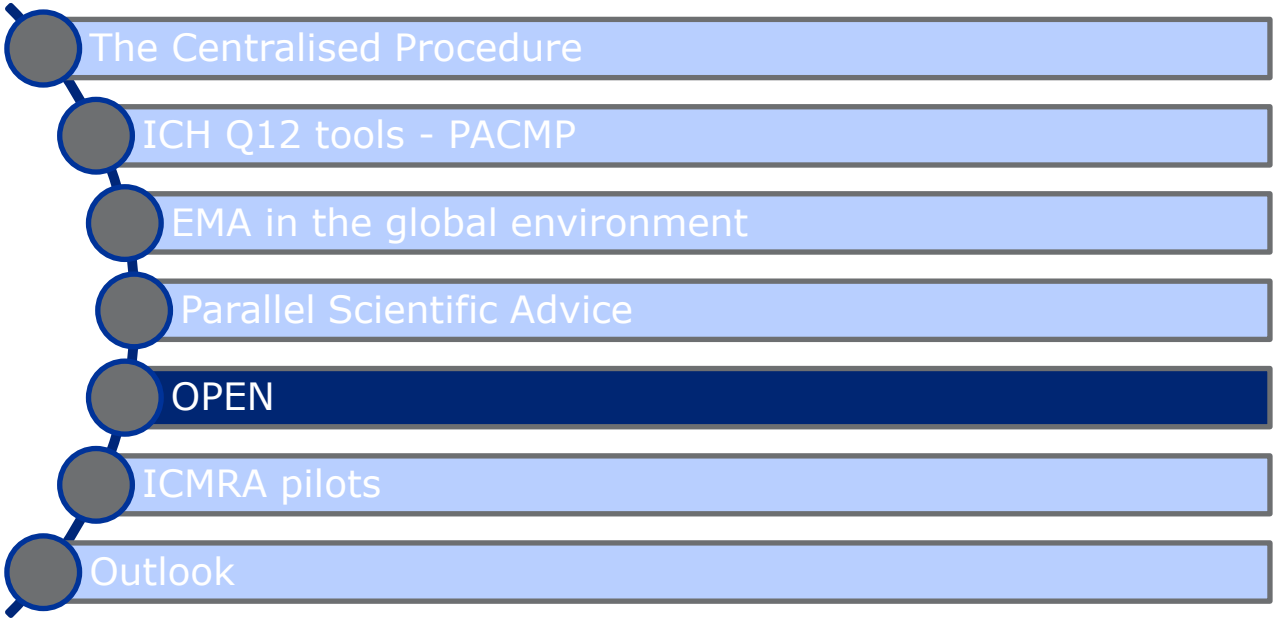

Opening our **P**rocedures at **E**MA to **N**on-EU authorities

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

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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OPEN regulators







Expand to identified areas

1. **Antimicrobial resistance** (AMR) *global threat where progress requires a collective effort for human and vet 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 of the initiative **visibility** with more **systematic and coordinated communication** by all OPEN participants

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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

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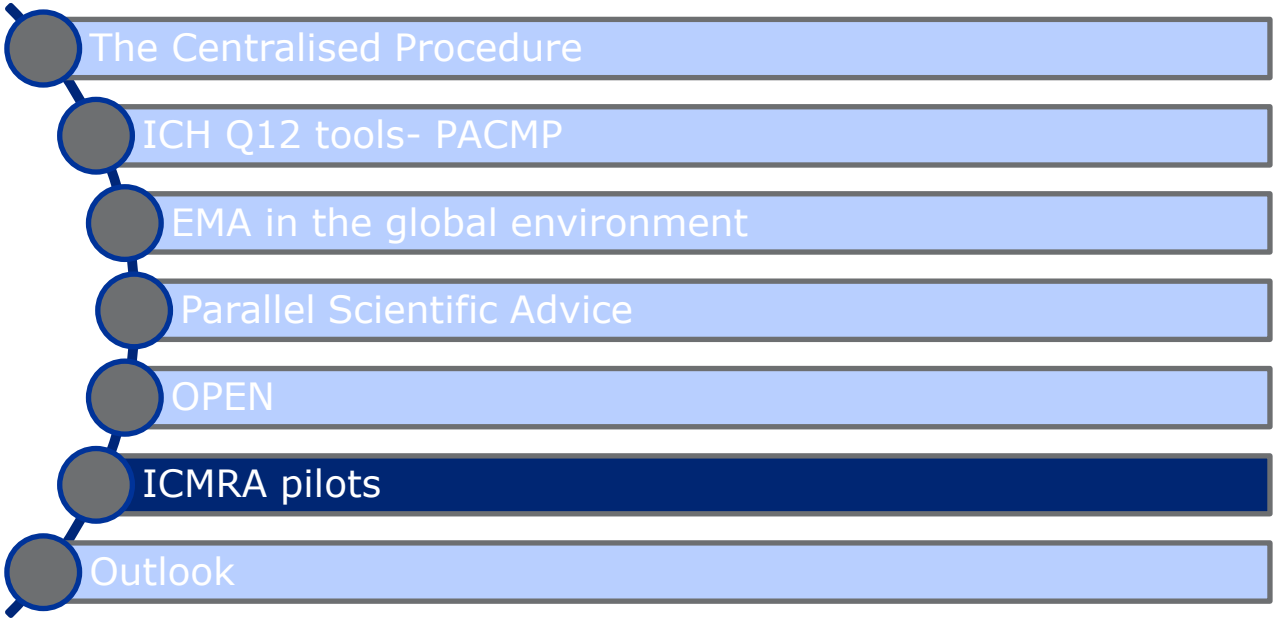
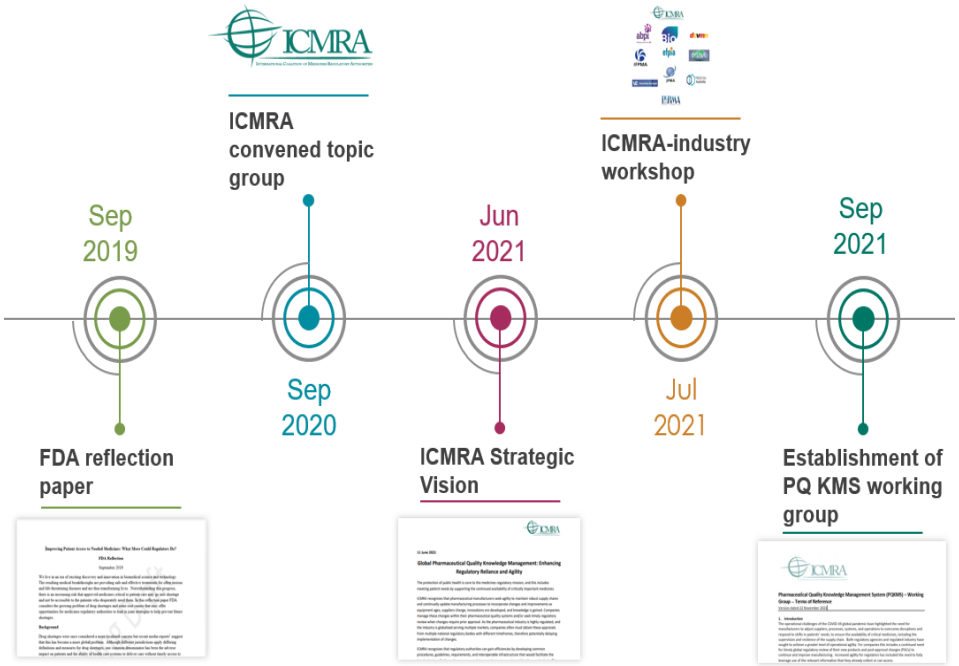


The ICMRA Pharmaceutical Quality Knowledge Management System (PQKMS) project



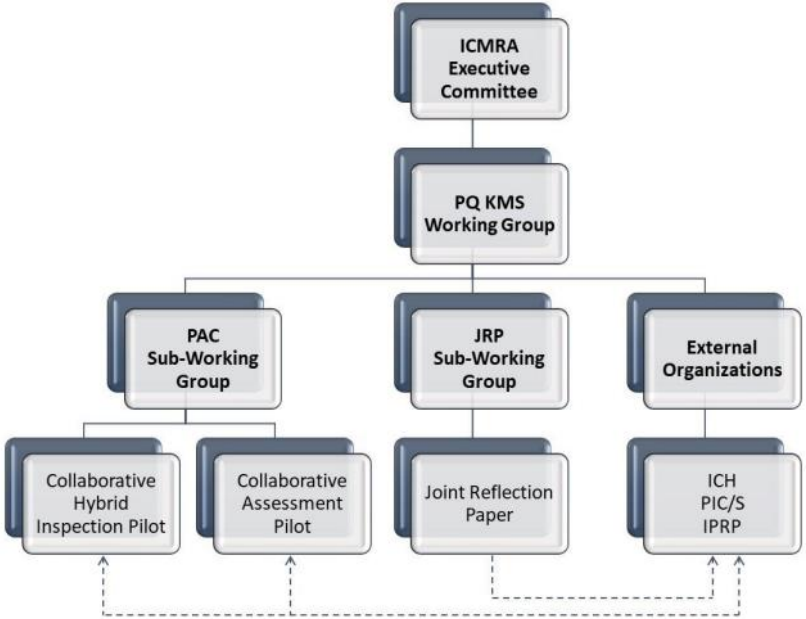
The envisioned capability would provide for:

- Transitioning to harmonized structured and standardized electronic formats using unique facility identifiers to enable rapid analyses of quality information and to support risk-based oversight of manufacturers.
- Sharing of information about manufacturing facilities, among multiple regulators.
- Developing a framework that can support harmonization of data requirements and facilitate management of PACs.
- Enabling more mutual reliance among regulators.

PQKMS working group

Aims

- Enhance **regulatory reliance** and **agility**
- Enhance regulatory **effectiveness** and **efficiency**
- **Harmonise** data submissions, expectations, assessments, and inspections
- Enhance availability of **quality medicines**



Commencement of two **pilot programmes**

Publication of a joint **Reflection Paper**

Aim of the ICMRA Collaborative Assessment Pilot

- Develop a framework, which provides a platform for multiple regulatory agencies to participate in a **collaborative assessment of post-approval CMC changes** including post-approval change management protocols (PACMPs)
- Deliver a **single list of questions** to the applicant wherever possible, however a stated goal of the pilot is to **identify** misalignments, differences, and potential **areas for further convergence** or harmonization across regions → predictability
- Regulators to work towards a **common approach** to the application assessment and decision making.
- Develop **best practices** in the quality assessment of CMC post-approval changes and share learnings to build further collaborations in assessment

Collaborative Assessment Pilot – Status update

- Call to industry is open since June 2022 → 12 proposals submitted
- First pilot (completed): EMA lead– FDA participating authority, Observer: Japan
- Second pilot (completed): FDA lead – EMA participating authority, Observers: Japan, Singapore, Brazil, Canada
- Third pilot (ongoing) FDA lead – EMA, MHRA, Swissmedic participating authority, Observers: Brazil, Canada

Decision to **expand the number of applications** in the pilot

Two more pilots are expected to start in Q4 2023

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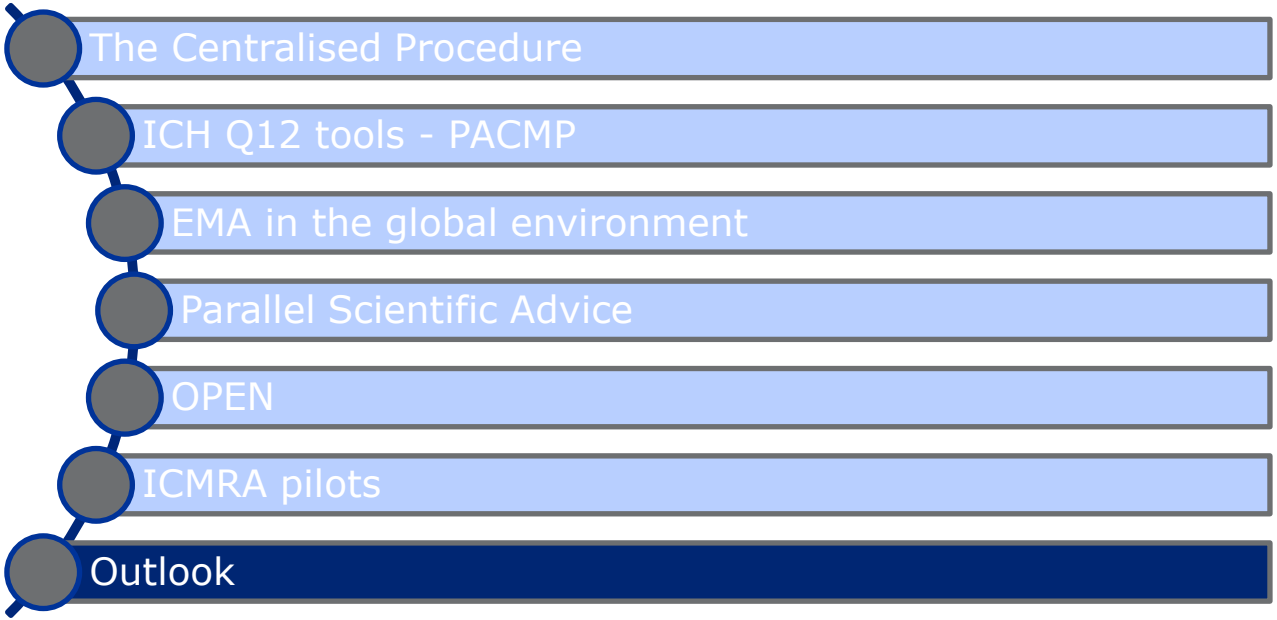

Outlook

- Strengthening international collaboration an important objective for quality domain including the new Quality Innovation Group (**QIG);** key to building trust
- Resource considerations
- Reliance
- Convergence (e.g. ICH guidelines) important enabler for efficient collaboration/reliance
- Applicants encouraged to make further use of available tools (ICH Q12)
- Early transparent dialogue with Regulators and also throughout lifecycle.

Acknowledgements

Veronika Jekerle- Head of Pharmaceutical Quality Office

Klara Tiitso – Pharmaceutical Quality

Brian Dooley -Pharmaceutical Quality

Radhouane Cherif – International Affairs

Thorsten Vetter – Scientific Advice

Any questions?

Further information

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Back-up

Collaborative Assessment Pilot – observations from first pilot

- Strong commitment of all parties
- Good collaborative spirit, goal oriented
- Informative, constructive discussions
- Procedural flexibility - resource intensive
- Successful in achieving harmonised outcome
- Successful in providing valuable lessons
- Positive uptake by regulators - positive feedback from Industry

decision to **expand the number of applications** in the pilot

EU Registration routes

National Procedure

Mutual Recognition procedure

Decentralised Procedure

1 MA in a MS *No MA in <u>any</u> of MSs*

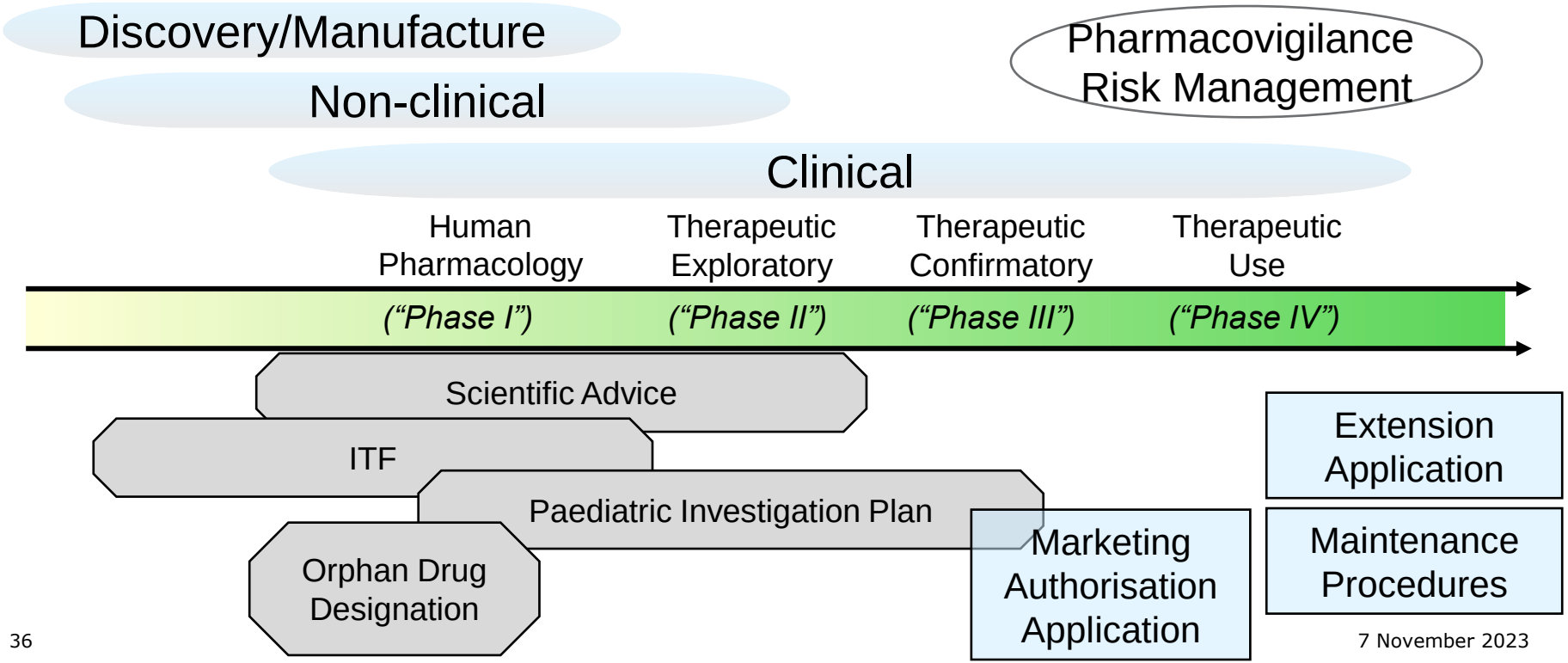
Application to an individual NCA

Authorisation by several MSs, based on main assessment by Reference EU MS

Centralised Procedure (via EMA)

Application to EMA, authorisation by European Commission, valid in all EU MSs

Drug Development Overview



PSA Timeline*

Day	FDA	EMA
Anytime	Sponsor submits informal request for Parallel Scientific Advice to FDA and EMA; Agencies decline, no PSA; Agencies accept, Sponsor begins drafting meeting package according to SAWP procedures	
Day -1 to -45		Meeting Package and Validation Phase; Option for prep meeting with EMA per SAWP procedures
Day 0	FDA receives validated meeting package	EMA validates meeting package
Day 5		EMA procedure begins (SAWP1)
Day 15-25	FDA internal meeting	EMA SAWP internal discussion
Day 30-34	FDA sends Preliminary Comments to EMA	EMA sends List of Issues to FDA
Day 35	Bilateral FDA/EMA meeting (SAWP2)	Bilateral FDA/EMA meeting (SAWP2)
Day 65	Trilateral Sponsor/FDA/EMA meeting (SAWP3)	Trilateral Sponsor/FDA/EMA meeting (SAWP3)
Day 75 to 95	FDA issues final meeting minutes (30 days after trilateral)	EMA issues final advice letter (10 days after trilateral)