EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

How to Leverage Pharmaceutical Development and Manufacturing Data for Marketing Authorisations - EMA's Perspective

2022 CASSS- CMC strategy forum, 17-19 October 2022

SESSION: Efficiency Toolbox: Development and Lifecycle Management

Veronika Jekerle, Head of Pharmaceutical Quality, Human Medicines, EMA

Content

- Problem statement
- EMA toolbox guidance & prior knowledge
- Applications to COVID-19 vaccines
- Lifecycle considerations
- EMA’s global responsibility

Problem statement: accelerated access

- **Development & approval timelines compressed** (e.g. commercial manufacturing, validation, stability, control strategy)
- **Innovation & complexity** (e.g. product characterisation, potency, comparability)
- **Global development** (e.g. comparability, manufacturing & supply, batch release)

- **Same legal requirements** for pharmaceutical quality, safety and efficacy as other medicines in the EU

(**Annex I of Dir. 2001/83/EC**, *Chemical, pharmaceutical and biological information for medicinal products*)

EMA toolbox guidance & prior knowledge

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/493240/2018
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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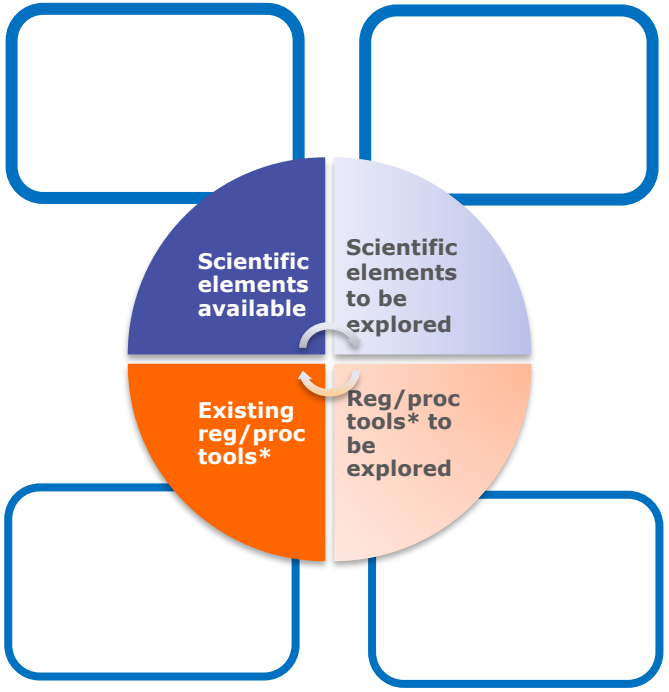
An agency of the European Union

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

Agenda: joint EMA-FDA workshop on quality support to PRIME & Breakthrough

- Problem statement & aims
- **Process validation**
- **Control strategy**
- **GMP compliance**
- Afternoon parallel sessions

  Biological *(PV & CS,* ***comparability, stability****)*
  Chemical *(CS, stability)*
- **Regulatory tools**
- Conclusions



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

*within the existing regulatory framework

Deliverables from the workshop

1

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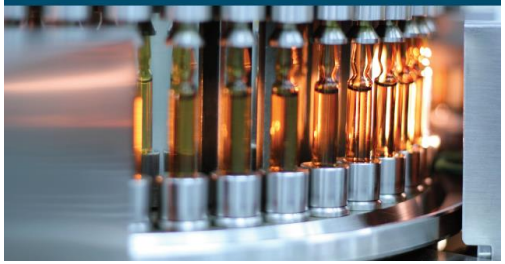
Meeting Report: Workshop with stakeholders on support to quality development in early access approaches (i.e. PRIME, Breakthrough Therapies)



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

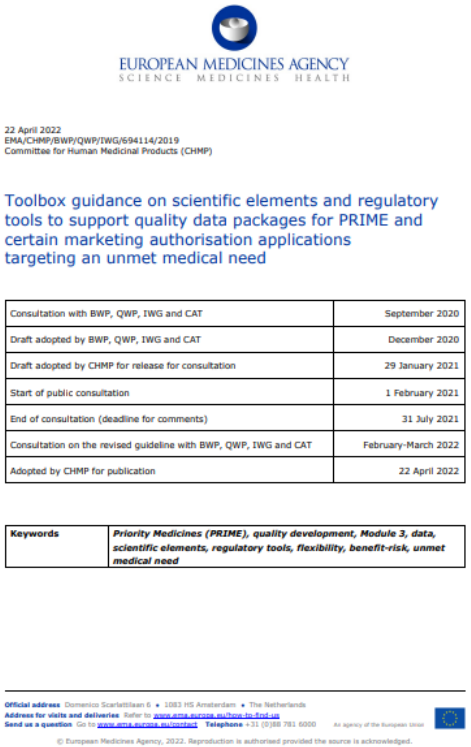
Joint EMA-FDA discussion on PRIME/BT

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

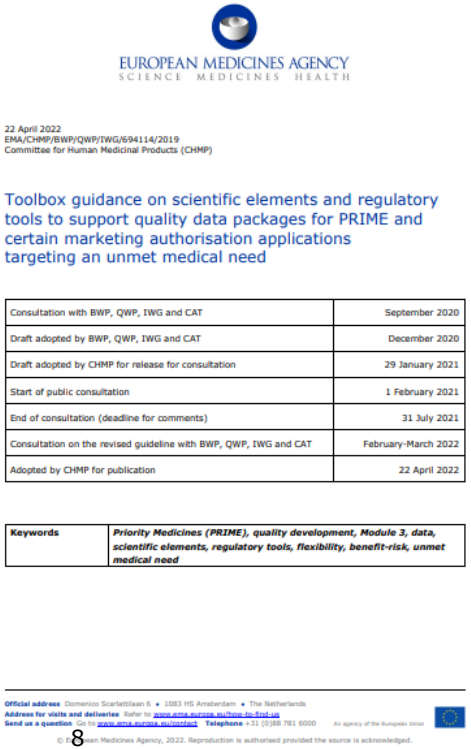
Consultation with BWP, QWP, IWG and CAT	September 2020
Draft adopted by BWP, QWP, IWG and CAT	December 2020
Draft adopted by CHMP for release for consultation	29 January 2021
Start of public consultation	1 February 2021
End of consultation (deadline for comments)	31 July 2021
Consultation on the revised 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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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). 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: **1** continuation/completion of data requirements of flexibility applied during initial MAA; **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)

EMA CMC toolbox guidance (cont.)

- General
- Process validation
- Control Strategy
- GMP
- Stability
- Comparability
- Regulatory tools

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

Stability

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

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

Regulatory tools

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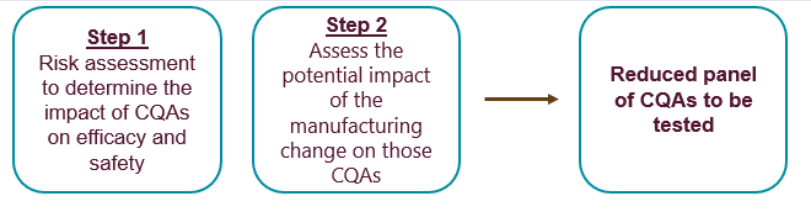
- **Risk-based approach (RBA)**, supported by prior knowledge



- **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

- **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.

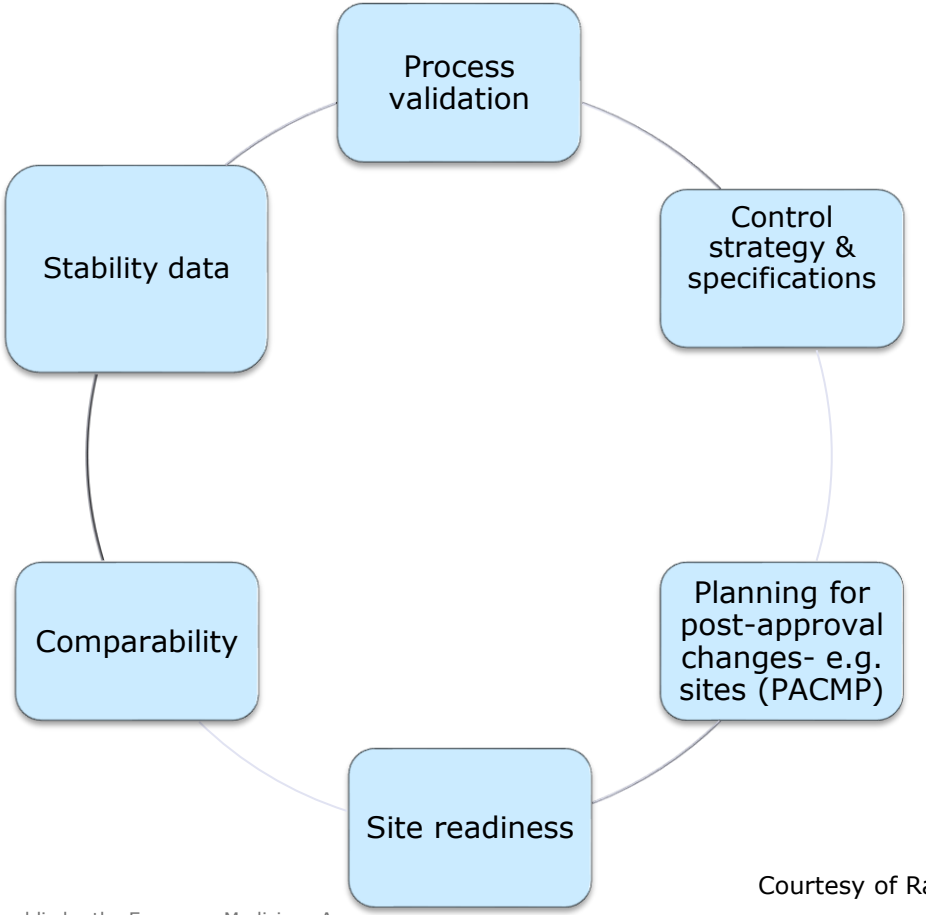
https://www.ema.europa.eu/en/documents/report/meeting-report-joint-biologics-working-party/quality-working-party-workshop-stakeholders-relation-prior-knowledge-its-use-regulatory-applications_en.pdf

Applications to COVID-19 vaccines

Key CMC issues during COVID-19 vaccines MAA

Enablers:

- Risk-based approach to agreeing flexibilities
- Case by case based on strength of supporting data & product understanding
- Characterisation data and appropriate analytical technology



Courtesy of Ragini Shivji

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

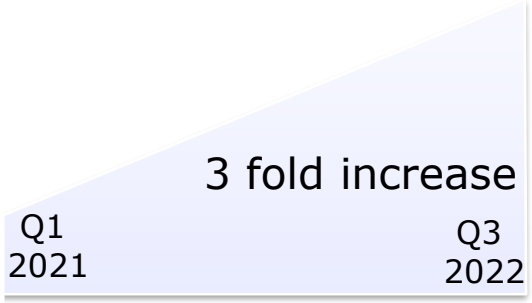
GMP aspects and flexibilities

- **Distant (remote) inspections / extensive interactions & reliance** on inspections from trusted international partners → replaced on-site EU inspections (pandemic travel-restrictions)
- Existing **GMP certificate validity** extended
- Flexibilities to facilitate the QP activities granted
- **Risk-based approaches** to manage distant inspections & postponement (e.g. inspections for biological starting material sites)
- **On-site inspections** were generally required for new sites/activities + sites with major issues (history of EU regulatory non-conformity)
- Early interactions with EDQM (OMCL network) necessary – timely transfer of quality control tests to OMCL (independent verification of quality of each vaccine batch).

➢ GMP expectations for sites and product development remained the same

Lifecycle considerations

Availability, supply & use of COVID-19 vaccines

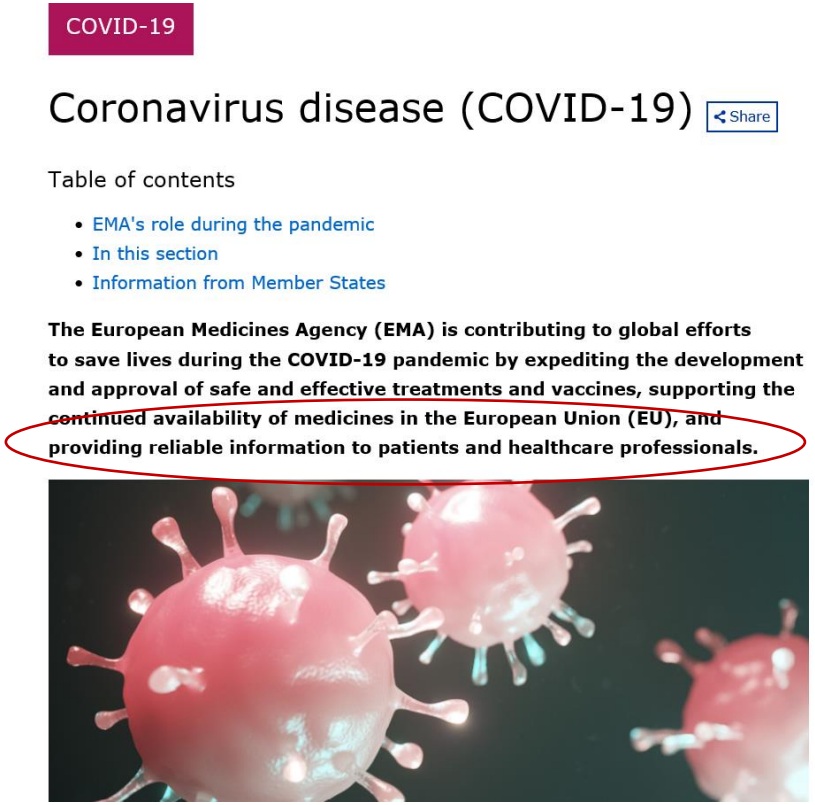


❖ **Manufacturing capacity**: # sites approved

✓ **Regulatory filings**

- Approx. 400 regulatory filings (excluding PAMs)
- Approx. 170 Quality Type II variations

→ updates to product information & labels, approval of additional manufacturing sites, scale up of manufacturing capacity, additional raw material suppliers, new formulations to optimise transport and storage conditions to facilitate supply.


COVID-19

Coronavirus disease (COVID-19) Share

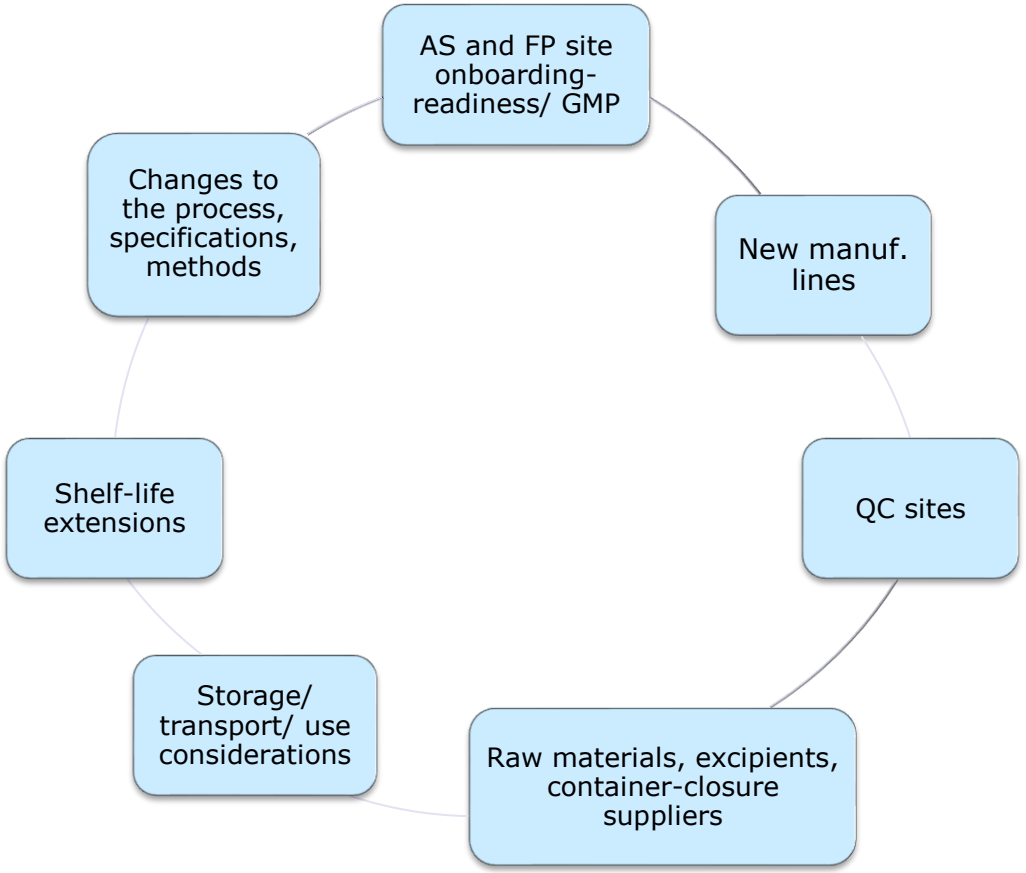
Table of contents

- EMA's role during the pandemic
- In this section
- Information from Member States

The European Medicines Agency (EMA) is contributing to global efforts to save lives during the COVID-19 pandemic by expediting the development and approval of safe and effective treatments and vaccines, supporting the continued availability of medicines in the European Union (EU), and providing reliable information to patients and healthcare professionals.

Key CMC issues during COVID-19 vaccines Post-authorisation

- Regular EMA-MAH interactions (e.g. weekly)
- Prioritisation of public health relevant CMC variations + rapid TTs
- GMP –initial verification prior to submission for site changes
- Regulatory filings: x10 higher than other vaccine MAs
- **Initial planning anticipated in MA → more effective** (rapid/to plan)



Courtesy of Ragini Shivji, updated

Toolbox Learnings from COVID-19 vaccines

Learning

Engagement

- Early & continuous engagement with regulators across lifecycle using the right regulatory tools (resource-intensive)

Learning

CMC dossier

- well-planned timely data packages of good quality & EU format
- understand major CMC issues to build dossier
- understand extent of regulatory flexibilities subject to product/process knowledge & site readiness- 'risk-based' approach
- agreement on key confirmatory data expected to be filed post-approval.

Learning

Post-approval planning

- incorporated during MAA (incl. GMP)
- use right tools: PACMP for effective lifecycle management
- Resource intensive (prioritise key variation – supply-relevant), requires regular interaction

Courtesy of Ragini Shivji, updated

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.

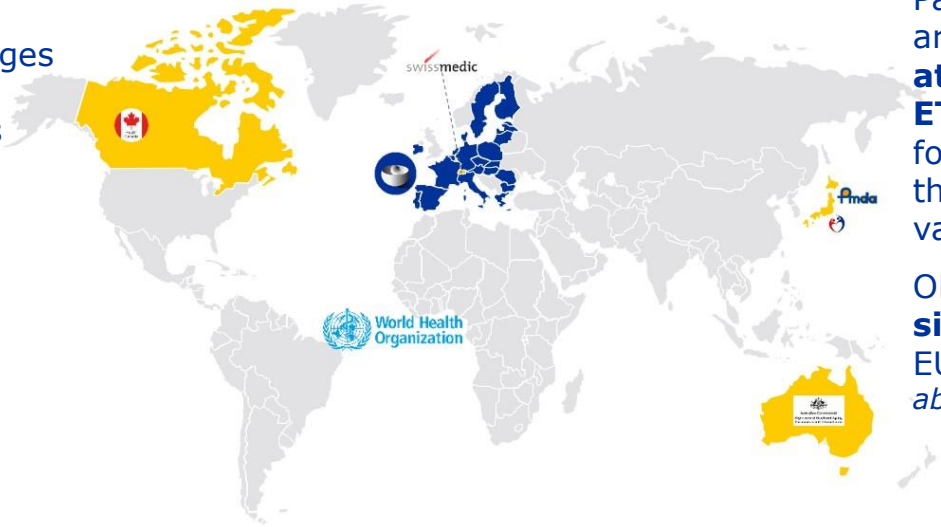
EMA's experience of the CMC scientific considerations, which facilitated both timely approvals (as Conditional Marketing Authorisations) and rapid increase in production capacity and supply, is of interest to healthcare professionals, academia, pharmaceutical industry and global regulators to communicate the

EMA’s global responsibility: reliance on EMA’s opinions OPEN

Opening our Procedures at EMA to Non-EU authorities

OPEN

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



Participating non-EU experts are invited to **attend and contribute** to **ETF and CHMP evaluation** for COVID-19 vaccines and therapeutics (IMA, major variations, inspections).

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

OPEN regulators

TGA
EMA
Health Canada
Swissmedic
MHLW/PMDA
WHO

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

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.

Before the pandemic some non-EU regulators participated as Observers in selected Committees/WP cluster meetings and requested EMA clarifications on questions or assessments.

With OPEN :

- EMA conducted a full review of applications but shared and discussed assessments on COVID-19 vaccines and therapeutics 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.**

OPEN global health impact

Reliance significantly accelerated decisions from national regulatory authorities in **LMICs**.

EMA is regulatory authority of record for the **WHO Emergency Use Listing** (EUL) for the 5 of the 6 vaccines approved in the EU.

The WHO EUL enables LMIC national regulatory authorities to **speed the registration** of COVID-19 vaccines. It is also needed to allow **procurement** by UN agencies and World Bank Group partners.

unicef Gavi The Vaccine Alliance COVAX

EMA assessment → **WHO Emergency Use Listing** → **National registrations in 160 LMICs**

of 5 EU-approved vaccines
(for which EMA is sole or co-NRA)

156 countries for **Comirnaty**
77 countries for **Spikevax**
142 countries for **Vaxzevria**
115 countries for **Jcovden**
34 countries for **Nuvaxovid**

Figures from March 2022

Key points

- **Risk-based flexibility** developed in the context of PRIME was extensively used in the approval of COVID-19 vaccines
- **Scientific tools** e.g. concurrent validation, prior knowledge, stability models, comparability protocols used across many developments
- A **totality of evidence approach** linking the CMC data package to clinical safety & efficacy & public health need
- **Close communication** during development & post-authorisation phase facilitated execution of effective filing/approvals but resource intensive
- **Risk-based approaches & regulatory agility** extended into the lifecycle phase and focussed on public health need/impact
- **International reliance** on EMA's scientific opinions of COVID-19 vaccines (initial approval & lifecycle) involved 160 countries worldwide

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