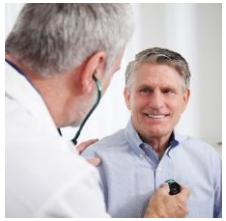
European Federation of Pharmaceutical Industries and Associations

EFPIA survey of EU experience on use of Quality expedited access (inc. EU PRIME toolbox) tools






Diane Wilkinson, AZ

Matt Popkin, GSK

Overview

- A look back: what has been achieved for Quality for expedited access?
- How to further enable the use of tools and strategies developed by regulators and industry?
- The EFPIA survey of Quality approaches for expedited access
- A look forward: what next?

Developing Quality tools and experience for expedited access

2016 — 2019 — 2023

EMA FDA workshops	EMA & FDA guidance	EFPIA Quality Papers	COVID Supply	2022 COVID Vaccines Papers
2017 Prior Knowledge	20-21 EMA Toolbox	EFPIA 2017 unmet	ICMRA workshop	Overarching proposals
2018 PRIME/BT	22 FDA MAPP	EFPIA 2020 COVID CMC	EMA Lessons Learned	Lessons learned & Technical
		2022 Pandemic CMC paper		

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REVIEW ARTICLE

Chemistry Manufacturing and Controls Development, Industry Reflections on Manufacture, and Supply of Pandemic Therapies and Vaccines

Matthew E. Popkin[1] · Markus Goese[2] · Diane Wilkinson[3] · Stuart Finnie[4] · Talia Flanagan[5] · Cristiana Campa[6] · Alexandra Clinch[7] · Andrew Teasdale[8] · Andrew Lennard[9] · Graham Cook[10] · Ganapathy Mohan[11] · Matthew D. Osborne[12]

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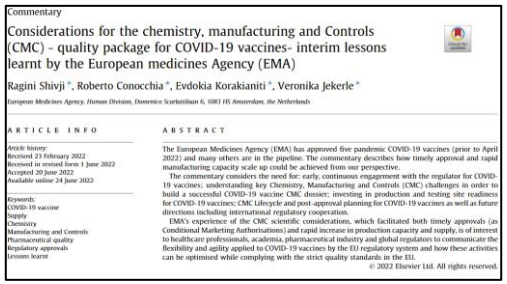
Abstract

This publication provides some industry reflections on experiences from the Chemistry, Manufacturing, and Controls (CMC) development and manufacture and supply of vaccines and therapies in response to the COVID-19 pandemic. It integrates these experiences with the outcomes from the collaborative work between industry and regulators in recent years on innovative science- and risk-based CMC strategies to the development of new, high-quality products for unmet medical needs. The challenges for rapid development are discussed and various approaches to facilitate accelerated development and global supply are collated for consideration. Relevant regulatory aspects are reviewed, including the role of Emergency Use/Conditional Marketing Authorizations, the dialogue between sponsors and agencies to facilitate early decision-making and alignment, and the value of improving reliance/collaborative assessment and increased collaboration between regulatory authorities to reduce differences in global regulatory requirements. Five areas are highlighted for particular consideration in



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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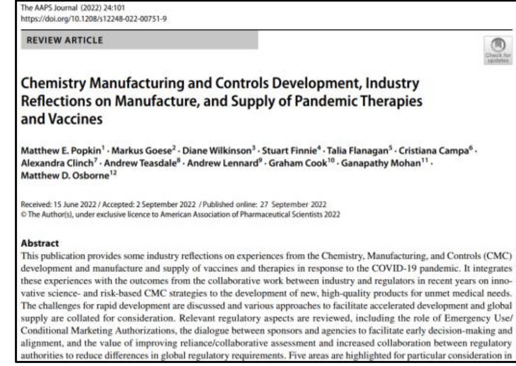
ABSTRACT

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 flexibility and agility applied to COVID-19 vaccines by the EU regulatory system and how these activities can be optimised while complying with the strict quality standards in the EU.

EFPIA Survey of EU Experience on Tools 2022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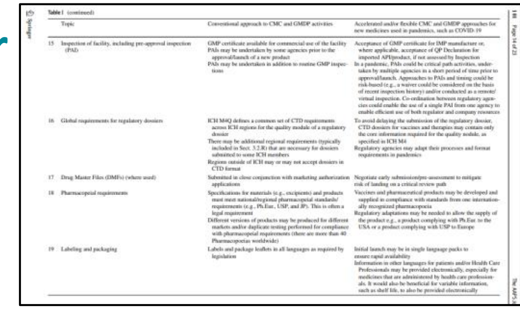
Table 1 (continued)

	Topic	Conventional approach to CMC and GMDP activities	Accelerated and/or flexible CMC and GMDP approaches for new medicines used in pandemics, such as COVID-19
15	Inspection of facility, including pre-approval inspection (PAI)	GMP certificate available for commercial use of the facility PAIs may be undertaken by some agencies prior to the approval/launch of a new product PAIs may be undertaken in addition to routine GMP inspections	Acceptance of GMP certificate for IMP manufacture or, where applicable, acceptance of QP Declaration for imported API/product, if not assessed by Inspection In a pandemic, PAIs could be critical path activities, undertaken by multiple agencies in a short period of time prior to approval/launch. Approaches to PAIs and timing could be risk-based (e.g., a waiver could be considered on the basis of recent inspection history) and/or conducted as a remote/virtual inspection. Co-ordination between regulatory agencies could enable the use of a single PAI from one agency to enable efficient use of both regulator and company resources
16	Global requirements for regulatory dossiers	ICH M4Q defines a common set of CTD requirements across ICH regions for the quality module of a regulatory dossier There may be additional regional requirements (typically included in Sect. 3.2.R) that are necessary for dossiers submitted to some ICH members Regions outside of ICH may or may not accept dossiers in CTD format	To avoid delaying the submission of the regulatory dossier, CTD dossiers for vaccines and therapies may contain only the core information required for the quality module, as specified in ICH M4 Regulatory agencies may adapt their processes and format requirements in pandemics
17	Drug Master Files (DMFs) (where used)	Submitted in close conjunction with marketing authorization applications	Negotiate early submission/pre-assessment to mitigate risk of landing on a critical review path
18	Pharmacopeial requirements	Specifications for materials (e.g., excipients) and products must meet national/regional pharmacopeial standards/requirements (e.g., Ph.Eur., USP, and JP). This is often a legal requirement Different versions of products may be produced for different markets and/or duplicate testing performed for compliance with pharmacopeial requirements (there are more than 40 Pharmacopoeias worldwide)	Vaccines and pharmaceutical products may be developed and supplied in compliance with standards from one internationally recognized pharmacopoeia Regulatory adaptations may be needed to allow the supply of the product e.g., a product complying with Ph.Eur. to the USA or a product complying with USP to Europe
19	Labeling and packaging	Labels and package leaflets in all languages as required by legislation	Initial launch may be in single language packs to ensure rapid availability Information in other languages for patients and/or Health Care Professionals may be provided electronically, especially for medicines that are administered by health care professionals. It would also be beneficial for variable information, such as shelf life, to also be provided electronically

- Scope was products of unmet/critical medical need
- 44 questions, based on AAPS 2022 paper on CMC for pandemics
- Responses based on company understanding and experience
  - Likely not accepted by EMA (red)
  - May be accepted by EMA (amber)
  - Likely to be accepted by EMA (green)
  - X = actual experience
- Identify areas of priority for follow up with regulators
- Potentially repeat annually/ad-hoc – how is regulatory science evolving?

Summary and Example

- 11 company responses
- Typical approach was for companies to hold internal discussion groups
- Company perceptions and (cross)company experience matter
  - Will drive strategy, impact scientific advice requests etc

Example response shown below:

Comparability for significant changes to biological drug	**B**	**Comparability can be justified on the basis of risk-based analytical evaluation of CQAs, without the need for clinical evaluation**	X	x	X (using prior knowledge to set range)	X					
Comparability for significant changes to biological drug	**B**	Generally, PACMPs are accepted as a tool to enable changes to the manufacturing process and address comparability, (e.g. Predictable data requirements and lower reporting categories)	X	x	X	X	X	Although would be good NOT to have to use PACMPs for every change for accelerated programs		X	X
Comparability for significant changes to biological drug	**B**	**Comparability can be justified on the basis of analytically demonstrated control of CQAs (e.g. based on meeting the release specification), without the need for demonstrating process consistency (e.g through additional characterisation data or the need to have significant batch data/alignment with historical trends etc)**		for new MAA/ or variation?	X (needs clarification- Lilly doesn't usually include consistency in comp - separate activities but wring complete PPQ for	X					
PACMP comparability for significant changes to biological drug	**B**	PACMPs are accepted as a tool to enable changes to the manufacturing sites and address comparability (e.g. predictable data requirements and simpler reporting categories)	X	x	X	X	X	Yes, but too much emphasis on PACMPs		X	
PACMP Comparability for change to manufacturing site	**A**	PACMPs are accepted as a tool to enable changes to the manufacturing scale and address comparability (e.g. predictable data requirements and simpler reporting categories)	X	x	X			Yes, but too much emphasis on PACMPs			X

Conclusions and Proposals (1)

- **There has been considerable progress in developing a stable and predictable Quality framework to expediate access for products of unmet medical need – EMA and FDA have been world leading**
- **Of greatest impact have been the growing acceptance of alternative evidence and approaches, particularly regarding stability, use of prior knowledge and comparability for biological products**
- **Areas of ongoing focus (biologics focused):**
  - Acceptance of **streamlined approaches for PPQ**
  - **Comparability** -use of modelling and clinical impact based assessment and use of alternative manufacturing processes to support acceleration of access.
  - **Control Strategy:** concerns about ability to adapt an initial "constrained" control strategy
    - **Specifications:** setting impurity acceptance criteria based on clinical relevance, not limited batch data
    - **Use of non-clonal cell lines – more recent examples of acceptance of this approach**
    - **GMP and Supply**: need to enable market supply from GMP IMP sites – raise at IWP?

Conclusions and Proposals (2)

- **Continue to collaborate, to further address areas where CMC principles for expedited access can be further developed**
  - e.g. Clinical comparability, flexible development of control strategies, GMP approaches for early access to UMN medicines.
- ***"EFPIA's view is that during the COVID19 pandemic, the greatest value in securing supplies of critical medicines was provided by regulatory flexibilities granted by the EMA for ongoing manufacture and supply…"***
  - EFPIA feedback to Commission on 2022 HERA workplan
  - Subsequent positive impact on some other Agencies
- **Alternative Quality approaches and expedited pathways are essential to addressing drug shortages and their causes.**
  - 2022 FDA MAPP Quality for Expediated Access " *the approaches described in this MAPP may also be considered [to] address drug shortages….*"
- **Need to keep focused on the lessons of COVID**

Conclusions and proposals (3)

Enhance and enable "alternative approaches" via updates to EMA PRIME/UMN Quality Toolbox and EU regulations

- E.g., revision/simplification (future proofing) of 2001/83, especially Annex I (future Annex II)
  - *"Module 3 marketing authorisation dossier data requirements must be in line with scientific guidelines and technical requirements according to the EU legislation (Annex I of Dir. 2001/83/EC)*
  - *A commercial manufacturing authorisation issued under Article 40 of Directive 2001/83 confirming that the IMP manufacturer is authorised to manufacture products to be marketed will be required at the time of the opinion to the MAA"*
- Expand the scope to "expedited access", addressing drug shortages and their causes

Build "alternative approaches" into ICH and other global guidance

EMA toolbox is already having a positive impact on worldwide acceptance of 'alternative approaches' and use of regulatory tools. Need to continue to build on this:

- Update to ICHQ1/5c stability has started and ICHQ6 specifications update hoped to start soon
- Complete the modernisation of ICH quality guidance (e.g. the ICHQ5 series, updates to ICH Q8-10 PTC, ICHQ3…);
- Continue dialogue (e.g. at ICMRA) regarding streamlined data requirements.

Recommendations:

- **Continue the very effective Industry and Regulatory collaboration to ensure key medicines are brought to patients as soon as they safely can be, via further development of the Toolbox**

- **Shared with EMA BWP Sept. 2023, for consideration of areas for EMA 2024 draft work plan and beyond.**

- **Publication of specific examples of application and its acceptance of use of EMA Toolbox,**
  - which may assist in building confidence in the application of such data by Assessment Agencies and use by companies.

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