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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.

1. Introduction

After the approval of COVID-19 vaccines in the EU [1], we highlight key Chemistry, Manufacturing and Controls (CMC) early learnings for Marketing Authorisation (MA) approval and lifecycle management.

- The EMA is contributing to global efforts during the COVID-19 pandemic by expediting the development and approval of safe, effective vaccines of good quality, supporting their continued availability and providing reliable information to patients/healthcare professionals.
- In this pandemic, there is unprecedented demand for vast quantities of COVID-19 vaccines in accelerated timeframes. The response to this requires an understanding of vaccine authorisation and manufacturing capacity scale-up.
- Here we take stock of EMA's experience from the COVID-19 vaccine submissions and first approvals[1] with focus on pharmaceutical quality, conditions of use, storage and availability.

2. Early, continuous engagement with the regulator

EMA advocates early, continuous engagement by COVID-19 vaccine developers using multiple engagement routes (engagement with EMA's pandemic task force, rapid scientific advice, pre-submission and rolling review interactions).[2].

- Early, frequent engagement, including regarding site-readiness, was critical in the rapid approvals of COVID-19 vaccine Conditional Marketing Authorisations (CMA). In some submissions, the CMC package, manufacturing readiness and supply chain management dramatically lagged behind clinical development. In a pandemic, where positive interim clinical trial read-outs facilitate early approval by CMA, immature CMC packages or late supply chain planning can delay approval and supply. Engagement should occur as soon as a suitable technology has been identified. Planning pandemic vaccine development can also be subject to significant change, hence the importance of ensuring continuous engagement.
- The applicant's familiarity with the European regulatory system and the company size or capacity to understand the EU requirements determined the need for regulatory support. Even with promising clinical data, a certain threshold of CMC data and

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manufacturing readiness is required to commence review. Administrative issues e.g., incorrectly structured documents increase the review time.
- For life-cycle management, regular EMA-company interactions facilitated streamlined, timely approvals of post-approval changes avoiding bottlenecks. Experience shows that early-stage supply planning prepares for the scale-up needed immediately at approval.
- The EU regulatory framework contains a number of regulatory tools to facilitate timely patient access to COVID-19 vaccines.[2] One of the uses of CMA is to respond to public health threats allowing additional data to be provided post-marketing within defined timelines as 'specific obligations'. EMA expedited evaluation by using 'rolling reviews', allowing accelerated assessment of discrete data packages as soon as available. This framework also provides opportunities for international regulators' information exchange and interactions as needed, to support timely CMC and site readiness aspect decisions, in line with pre-existing confidentiality agreements.

Learning: early engagement on CMC (using the appropriate tools) facilitates timely dossier finalisation. CMC dossier maturity should coincide with clinical trial read-outs, to avoid approval delays. Early engagement is needed for site readiness aspects and supply chain planning and both should be undertaken in parallel to dossier development.

3. Understand key CMC challenges in order to build a successful CMC dossier

CMC requirements are not waived to accelerate EU COVID-19 vaccine approvals. The pandemic requires an alternative, flexible approach for data provision in the context of the benefit/ risk judgement.

- The authorised COVID-19 vaccines benefitted from existing CMC flexibilities for PRIME products [3] as the risk from the incomplete data package could be compensated with development data for similar products with a plan to file any remaining data post-approval.
- For the approved COVID-19 vaccines, major objections raised during review included comparability of the commercial product to that used in clinical trials, validation and an appropriate control strategy of the commercial manufacturing process to demonstrate product reproducibility and product stability data. The observed challenges are expected as the required batch data to fine-tune control limits, demonstrate commercial process validation and stability throughout the proposed shelf life are generated in real time. Product-specific flexibilities have been tailored e.g., experienced developers leveraged prior knowledge from similar production platform technologies, or manufacturing experience from clinical/pilot manufacturing site(s) and regulatory agreements were reached to complete certain data sets (i.e., validation, stability) after authorisation. The approach taken for each authorised COVID-19 vaccine is described in the respective, published, European Public Assessment report.[1] The EMA was already prepared for the need to adapt the standard approaches in a pandemic having understood, in developing proposals for PRIME products[3], those CMC flexibilities and the associated supporting provisions and safeguards, which would be required for products on a fast-track development path. EMA regards good product understanding when demonstrated through characterisation data and appropriate analytical technology, a prerequisite to a flexible process validation approach as product quality can then be reliably monitored as part of routine batch release specifications.

Learning: Granted flexibilities are tailored i.e., *vaccine-specific, allowing filing of some data post-approval if justified by alternative supporting data or information. Planning and agreeing these in parallel to dossier development reduces approval time.*

4. Invest in production and testing site readiness

The scale of pandemic product demand warrants investment in site-readiness and often requires non-EU/EEA inspections of sites in reduced timeframes.

- Substantial company site investment is done 'at-risk' in the pandemic, even before knowing the results of key clinical trials. This investment by companies including also in third party sites, is critical to facilitating rapid authorisation and ensuring sufficient, timely post-authorisation manufacturing capacity and resilience.
- Good manufacturing practice (GMP) [4] describes the production standard for medicines, ensuring their consistent high quality. It applies to commercial production of COVID-19 vaccines and generation of key site-specific data before authorisation. The EMA coordinates inspections to verify compliance with these standards.
- Due to pandemic travel-restrictions, distant (remote) inspections or extensive interactions and reliance on inspections from trusted international partners often replaced on-site EU inspections. Sometimes on-site inspections are still required, e.g., 'new' sites/activities, where major issues/ lack of EU regulatory conformity is highlighted, justifying early EMA engagement. Existing GMP certificate validity was also extended and flexibilities to facilitate the activities of the Qualified Person were granted. A risk-based approach has been used to permit distant inspections etc., and to postpone inspections for biological starting material sites. Despite this, the GMP expectations for these sites and for other parts of product development were not lowered.
- Early interactions with the European Directorate for the Quality of Medicines and Healthcare – EDQM [5] (responsible for coordinating the Official Medicines Control Laboratory- OMCL) are necessary. Timely transfer of relevant quality control tests to an OMCL permits the required independent verification of the quality of each vaccine batch.

5. Learning: Early regulatory engagement reduces the likelihood of GMP bottlenecks delaying authorisation and post-authorisation supply.

CMC Lifecycle- post-approval planning

The CMC post-approval changes with greatest impact relate to production scale-up, testing, storage, transport and usage (e.g., *refrigerated storage, ready-to-use formulations). Changes may also be required to respond to emerging variants.*

- Experience has demonstrated that commercial production sites and supplies of raw materials e.g., media/ container closures, are initially insufficient to satisfy the exceptional demand. Therefore, well-mapped planning for production scale-up and quality-control testing should already begin pre-submission of a Marketing Authorisation Application (MAA).

- A plan allows prioritisation of critical post-approval changes, understanding the need for inspection thus helping to avoid review bottlenecks.
- To streamline and accelerate changes further, applicants can use post-approval change management protocols (PACMP), most optimally included in the initial MAA. This way, conditions and criteria for introduction of certain types of future changes can be predefined.
- Timely consideration of data requirements for improvements to storage, transport conditions, packaging, formulation and dosing, can facilitate early registration.
- Finally, regarding emerging variants,[6] whereas a new COVID-19 strain presentation could heavily rely on the existing manufacturing process, strain-specific adaptations are required. Platform data from multiple COVID-19 variants in the company's production system can support a strain-switch.

Learning: Efficient life-cycle planning should begin pre-submission and be built into the initial MAA dossier to *maximise market supply.*

6. Where do we go from here?

- To conclude, we consider that early engagement on CMC and site-readiness aspects facilitates timely dossier finalisation. Early engagement reduces the likelihood of GMP bottlenecks delaying authorisation and post-authorisation supply. CMC flexibilities can be tailored to the vaccine allowing filing of some data post-approval if justified by alternative supporting data/ information and dossier maturity should coincide with clinical trial read-outs. Furthermore, supply chain and life-cycle planning should be undertaken in parallel to dossier development to maximise market supply.
- Enhanced communication and advanced planning between regulators and companies is therefore key to success. We estimate that the pandemic response required the most resource-intensive effort by the pharmaceutical industry and the European Regulatory network in modern times, therefore efficient, targeted resourcing is critical. On the regulatory side, resources had to be allocated for the intense planning and enhanced communication/ transparency that the pandemic necessitated in addition to the increased workload from the accelerated review of these products.
- Differing regional CMC requirements have challenged global COVID-19 vaccines' development and supply. Regulatory activities are governed by different legal frameworks. However, opportunities for greater international collaboration including mutual reliance (i.e. GMP) and collaborative review initiatives are being explored, particularly within the context of International Coalition of Medicines Regulatory Authorities (ICMRA), which is also supporting interactions between international regulators' and industry to further understand and exchange COVID-19 lessons learned, aiming to continue uninterrupted vaccine supply.[7] In the meantime, ad hoc interactions between regions on CMC aspects, are beneficial. Companies are encouraged to share advice received from other regulators so that differences can be resolved jointly. Data digitalisation initiatives will also foster greater convergence and better handling of product life-cycle changes.[8]
- Pandemic Lessons learnt and scientific advancements provide a timely opportunity to inform how the EMA's flexible 'risk-based' approach to CMC requirements during COVID-19, can offer sustainable solutions for future medicinal products for unmet medical needs and during public health crises. Recent analysis by industry [9,10] highlight similar areas to the ones identified in our analysis e.g., use of 'risk-based' approaches and prior knowledge, the need for rapid regulatory approaches and frameworks to accommodate pandemic vaccines and their supply challenges, as well as further areas, including for greater engagement and harmonisation. The Agency will continue to involve industry stakeholders in discussions regarding specific lessons learnt and pandemic preparedness.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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