

Global management of CMC Post-Approval Changes for COVID-19 vaccines

5 October 2020

Background

The need to accelerate the development and manufacture of COVID-19 vaccines, and to ensure fair and equitable access for every country in the world is recognised both by the industry and by the European Commission^{1,2}.

There is no doubt that COVID-19 vaccines can only be approved with the provision of sufficient Chemistry, Manufacturing and Controls (CMC) data to guarantee their quality, safety and efficacy based on science and risk-based principles. However, the accelerated development of these vaccines presents a challenge in terms of the provision of CMC and Good Manufacturing Practices (GMP) information, and their review by regulatory authorities.

In addition, the current worldwide regulatory landscape is characterized by a high heterogeneity in terms of regulatory review, approval processes and timelines. In the context of the COVID-19 pandemic, this will present an important challenge for manufacturers to supply vaccines to all populations in a timely and equitable manner unless appropriate processes are considered.

Due to the accelerated development, it is anticipated that a lot of CMC information will have to be submitted post-approval to complement the initial Marketing Authorisation, and that a significant number of post-approval changes (PACs) will be needed to reflect the timely addition of manufacturing and testing capacity. There is a high risk that COVID-19 vaccines could experience shortages or discontinuities in supply as a result of difficulties in meeting standard regulatory lifecycle management expectations. This could even be exacerbated if heterogeneous regulatory requirements from Health Authorities worldwide result in some differences in the approved manufacturing process (e.g. duration of a manufacturing step) or control strategy of the vaccine.

1. Supply of vaccines to EU is impacted by global regulatory complexity

As mentioned above, the unprecedented acceleration of the COVID-19 vaccine development will result in the submission of many post-approval changes (PACs) to reflect the timely addition of manufacturing and testing capacity. In the EU, these PACs will have to be submitted to authorities for approval in line with the current EU Variation Regulation 1234/2008, either by using Post-Approval Change Management Protocols (PAMPs) or

¹ <https://www.vaccineseurope.eu/wp-content/uploads/2020/09/vaccines-europe-statement-on-the-safety-of-covid-19-vaccines.pdf>

² https://ec.europa.eu/international-partnerships/topics/eu-global-response-covid-19_en

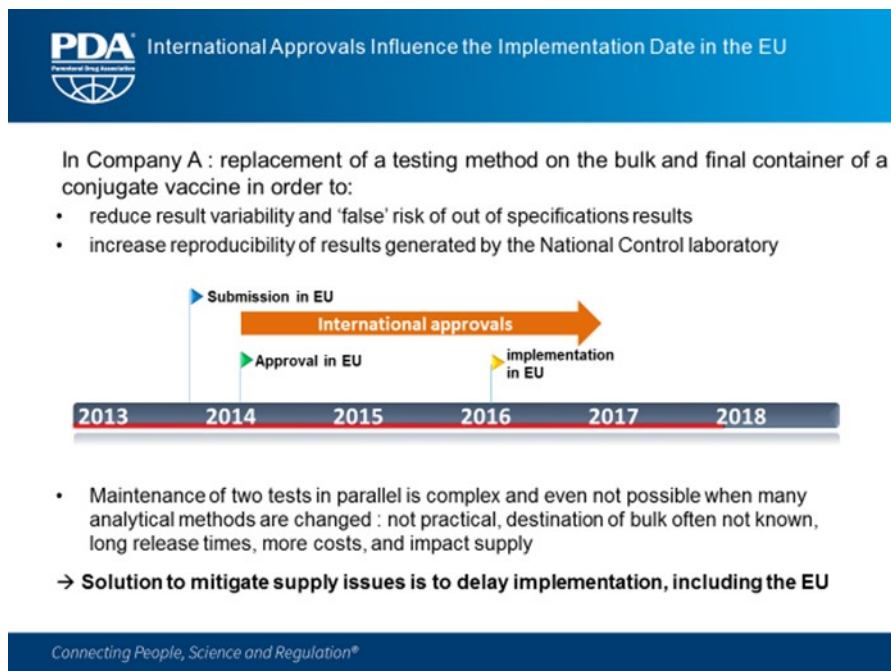
through the “regular” variation submission process. Likewise, PACs will have to be submitted in countries outside of the EU according to the national regulations.

Due to the complexity of manufacturing and control of vaccines and the limited number of manufacturing facilities, vaccine manufacturers cannot manage at the same time 2 different versions of a manufacturing and control process, i.e. the one prior to the PAC, pending the regulatory approval from Health Authorities and the one bearing the PAC, once individual regulatory approvals are obtained. In addition, once a PAC is implemented in production, manufacturers do not come back to the previous manufacturing version. As a consequence, vaccine manufacturers usually estimate a PAC implementation date which combines 3 main criteria:

1. the expected time needed to obtain approval from a majority of regulatory authorities worldwide
2. the expected vaccine demand
3. the stockpile possibilities, pending regulatory approvals, in order to avoid any shortage

As a consequence, once a PAC is approved in the EU, vaccine manufacturers usually do not implement the change as soon as it is approved but wait until the change has been approved by a majority of regulatory authorities worldwide. The fastest countries (including EU) are then penalized by the slowest ones.

The time it currently takes to get approvals from all countries worldwide can go up to 4 years³. The real-life example below illustrates that it took 2 years after the EU approval to implement the change of a testing method in the EU⁴.



³ The complex journey of a vaccine – Part I; The manufacturing chain, regulatory requirements and vaccine availability; IFPMA; 2014

⁴ 2018 PDA conference on Vaccines / Malaga-Spain / Vaccine life cycle management complexity / A Deavin & T Gastineau

Even though one could expect that, under those exceptional COVID-19 circumstances, timelines will be significantly reduced, it remains crucial that an efficient global regulatory system is set up to enable the review and approval of PACs in a predictable, expedited and harmonized way in order to allow the production and distribution of vaccines in a timely and equitable manner. Any delay and lack of visibility about reviews and approvals in all countries in the world will impact the global supply of vaccines (including in the EU).

2. Global alignment: a key enabler for accelerating the supply of vaccines

There are multiple reasons why regulatory reviews and approvals are not provided in a timely manner, thereby jeopardizing the timely implementation of PACs and consequently the timely supply of vaccines. The reasons include but are not limited to:

- Regulatory processes are different depending on countries
- Numerous countries in the world require approval of the PAC in a reference country (usually the country of origin where the vaccine is manufactured) before starting their own review
- Lots of countries are not using reliance mechanisms to approve PACs that have already been reviewed and approved by a country of reference
- Countries may have different requirements for PAC approval compared to the country of reference (e.g. some countries are requiring longer real-time stability data at the time of submission)⁵
- PACs review and approval timelines vary from country to country and are often unpredictable⁵

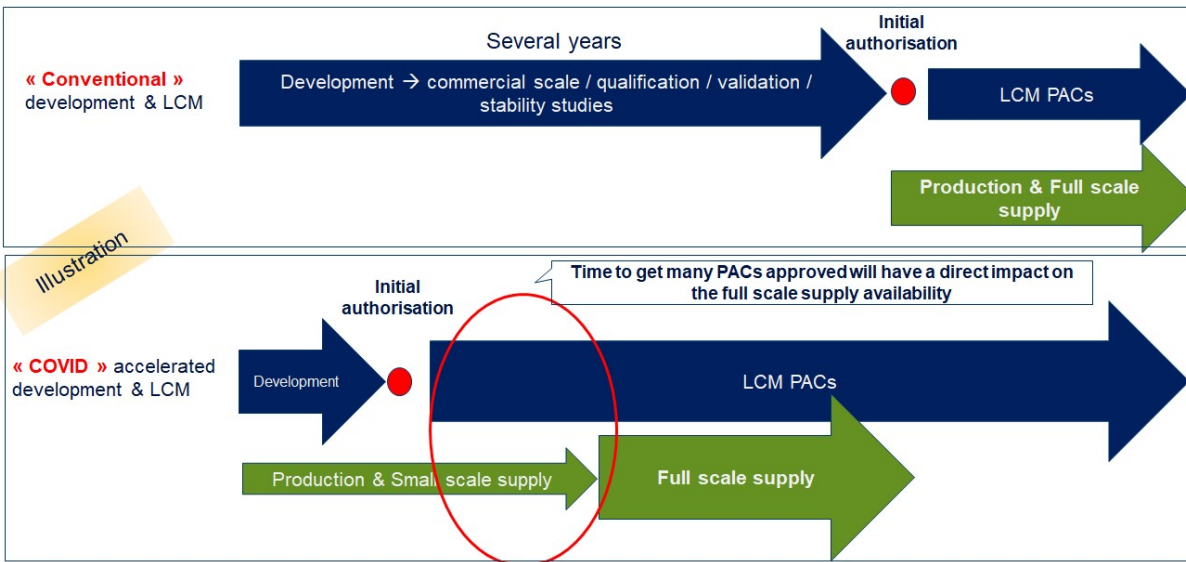
Global alignment on regulatory requirements and timelines, as well as the development of reliance mechanisms in the post approval space are key for improving the review and approval of PACs and ensuring timely supply of high quality vaccines worldwide.

3. The supply of huge volumes of COVID-19 vaccines depends on an efficient worldwide management of PACs

As indicated in the background section, it is anticipated that, due to the accelerated development phase of vaccines against COVID-19, numerous PACs will be needed, which will add to the challenge of meeting the global demand of such critical vaccines.

The figure below is representing this “accelerated” situation, compared to the “conventional” process.

⁵ Alignment in post-approval changes (PACs) guidelines in emerging countries may increase timely access to vaccines: an illustrative assessment by manufacturers. N Dellepiane et al. Vaccine: X 6 (2020)100075



Hereafter are some examples of PACs that will be needed to meet the demand of large quantities of vaccines:

- Batch size scale-up
- Addition of manufacturing and testing sites, facilities or suites
- Production of new cells / virus banks
- Shelf-life extension (at Drug Substance and Drug Product level)
- Change in product specifications
- Addition of new raw material and container closure system suppliers
- Manufacturing process improvements
- Analytical procedures improvements

While it is expected that numerous and more PACs than for a “conventional” vaccine development will have to be managed soon after initial approval, it is very difficult to provide accurate and reliable figures. Based on real-life examples from “conventional” development and life cycle management of vaccines, it is estimated that at least 20 CMC PACs, covering all the above cases, will have to be managed within the weeks and months after initial approval of a COVID-19 vaccine. According to the most advanced companies in terms of vaccine development against COVID-19, the number of PACs could even be much bigger, due to the accelerated development timelines. In addition, to address the global pandemic, it is expected that initial approval of COVID-19 vaccines will be granted in more than 100 countries within a few months timeframe while it usually takes a few to several years. The consequence is that the worldwide management of PACs will be extremely concentrated within a very limited period of time while it usually takes years. Assuming that more than 20 PACs will have to be reported in 100+ countries (depending on local regulations), it means that, for a single COVID-19 vaccine, more than 2,000 CMC variation dossiers will have to be managed worldwide within months instead of years. This situation will be further complexified by the worldwide heterogeneity of regulatory processes and approval timelines for initial approval and for approval of PACs.

Given the magnitude, the complexity and the excessively reduced period of time to manage PACs which will be critical to meet the worldwide demand, an efficient worldwide management of PACs will be crucial. Anticipating this situation is key to successfully address this challenge.

4. Potential approaches for global alignment

Multiple approaches to improve the management of PACs at the global level should be considered as soon as possible in order to ensure sufficient and timely supply of COVID-19 vaccines. Some concrete proposals are provided hereafter:

- Agreement on approaches that can demonstrate comparability of COVID-19 vaccines during development and lifecycle
- Alignment on data requirements and timings for PACs in order to avoid repetition and inconsistencies and minimize delays. Such requirements should always be science- and risk-based, taking into account considerations such as the control strategy and companies' approaches to ongoing process verification. Upfront alignment should facilitate reliance mechanisms, as fostered by WHO⁶, for the review and approval of PACs
- Using tools such as those described in ICH Q12 and already implemented in some regulations. This is the case for PACMP in the EU. However, one of the current limitations for the use of PACMP is the fact that this mechanism does not exist in the vast majority of countries. Developing those mechanisms beyond ICH regions could facilitate the management of some PACs
- Use of Exceptional Change Management procedures, as proposed by EMA for changes in the manufacturing and/or control sites and changes in suppliers of starting materials, reagents, intermediates or active substances that are necessary to prevent/mitigate shortages of supplies in the EU, could be explored for global application
- Use of (or greater use of) extrapolation and/or data modelling to predict more rapidly stability under normal storage conditions and to establish shelf-lives for product registration and for post-approval changes should be considered globally
- Use a science- and risk-based approach to support changes in analytical methods and technologies, for example in bridging/equivalence studies, with 'the same' interpretation accepted globally.

Vaccines Europe does acknowledge the high challenge that worldwide harmonization and review of local regulations may represent in a such short period of time. **Developing reliance mechanisms, by leveraging the WHO draft principles and recommendations on Good Reliance Practices⁶ is likely a more efficient way to streamline the overall process and make a best use of resources.**

⁶ Good reliance practices in regulatory decision-making: high-level principles and recommendations. WHO Working document QAS/20.851 June 2020

5. Conclusion

Vaccines Europe welcomes the efforts made by EU Authorities to address the challenges related to the development and supply of COVID-19 vaccines from a global perspective².

Considering the time it may take to engage discussions with all Health Authorities worldwide and to come with an agreement on the best way(s) to efficiently manage PACs, we believe that there is a matter of urgency to consider this challenge and not to wait for initial licenses to be granted. Vaccines Europe encourages EMA and the EC to work with ICMRA and CEPI/WHO to find mechanisms allowing a timely review and approval of PACs in EU and globally.

Vaccines Europe remains open for any question and appropriate follow up, and thanks EMA to keep us informed about discussions on this very important topic.
