Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review

How to accelerate the supply of vaccines to all populations worldwide? Part II: Initial industry lessons learned and detailed technical reflections leveraging the COVID-19 situation ☆

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ABSTRACT

Vaccine discovery and vaccination against preventable diseases are one of most important achievements of the human race. While medical, scientific & technological advancements have kept in pace and found their way into treatment options for a vast majority of diseases, vaccines as a prevention tool in the public health realm are found languishing in the gap between such innovations and their easy availability/accessibility to vulnerable populations. This paradox has been best highlighted during the unprecedented crisis of the COVID-19 pandemic. As part of a two series publication on the vaccine industry's view on how to accelerate the availability of vaccines worldwide, this paper offers a deep dive into detailed proposals to enable this objective. These first-of-its-kind technical proposals gleaned from challenges and learnings from the COVID-19 pandemic are applicable to vaccines that are already on the market for routine pathogens as well as for production of new(er) vaccines for emerging pathogens with a public health threat potential. The technical proposals offer feasible and sustainable solutions in pivotal areas such as process validation, comparability, stability, post-approval changes, release testing, packaging, genetically modified organisms and variants, which are linked to manufacturing and quality control of vaccines. Ultimately these proposals aim to ease high regulatory complexity and heterogeneity surrounding the manufacturing & distribution of vaccines, by advocating the use of (1) Science and Risk based approaches, (2) global regulatory harmonization, (3) use of reliance, work-sharing, and recognition processes and

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(4) digitalization. Capitalizing & collaborating on such new-world advancements into the science of vaccines will eventually benefit the world by turning vaccines into vaccination, ensuring the health of everyone.

Contents

1. Introduction

Borders between countries have been invented by humans, for humans. Other living organisms on earth don't recognize such artificial borders but move depending on the best places to live (climate, environment, food). Outbreaks due to microorganisms such as viruses or bacteria, know no borders and can cause pandemics. Such disease outbreaks have always existed, with devastating impact on humans and society. This has been aggravated by the technologies humans have developed for circulating across the planet, with little restriction and as fast as possible [1]. Apart from the scientific challenge to find effective and safe vaccines to the current pandemic, the COVID-19 situation has exacerbated a number of regulatory challenges which impact the timely supply of vaccines to all populations who need them.

This article is Part II of a two part discussion (see Fig. 1) and presents a technical evaluation of specific practical regulatory flexibilites, focused on manufacturing and control, which are being considered to overcome barriers to the timely access of vaccines.

2. Background and scope

Over the past decades, the worldwide scientific, legal and regulatory environment has significantly evolved creating an extremely complex situation for vaccine manufacturers to navigate.

Much has been advocated in the international arena to develop more regulatory convergence and collaboration mechanisms including reliance, joint reviews and ultimately leading to harmonization and mutual recognition among agencies. However, harmonization takes years and we are still a long way from worldwide convergence, harmonization and reliance. Conse-

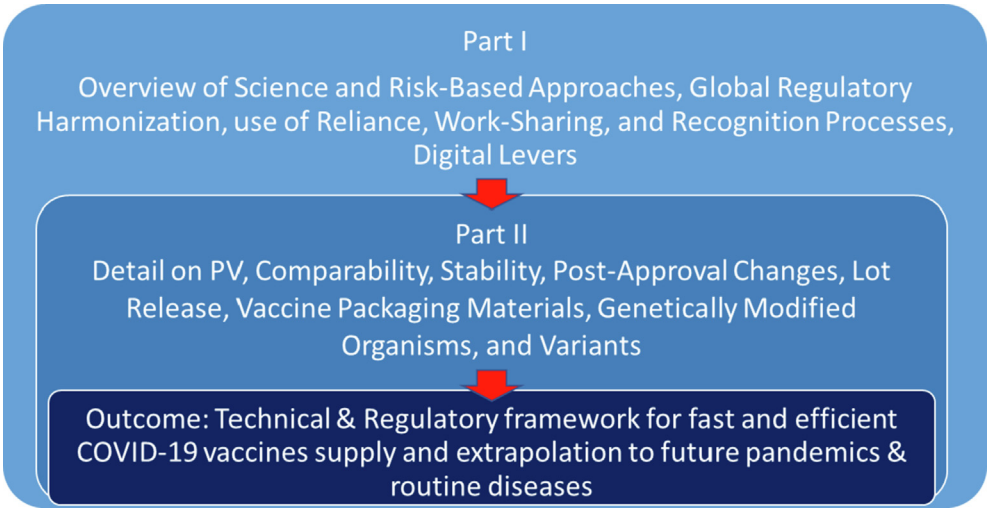

Fig. 1. How to accelerate the supply of vaccines to all populations worldwide – Part I and II.

quently, the global environment is still highly heterogenous, serving to limit equitable and timely access to vaccines.

COVID-19 is the most recent pandemic. The scientific community and pharmaceutical industry have strongly responded, resulting in the development and authorization of multiple vaccines within a year. In just a few months after approval, over 400 million [2] have been vaccinated. Bringing online such huge manufacturing capacity in a short timeframe has logically come with considerable "growth pains". However, there are agile ways of working outside of the standard approaches, and we must push the acceptance of these approaches globally.

As often is the case with catastrophes, COVID-19 can act as an accelerator for preparation to improve the supply of vaccines when the next pandemics occur. There are also lessons that can be applied to improving the routine ways of working, better ensuring consistent supply of vaccines for all diseases.

A first article (PART I) was written which covers the overarching themes and general proposals to address the regulatory concerns. The objective of this article is to provide deeper insights into the Vaccines Europe (VE)/International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) Task Force activities, supported by the Developing Countries Vaccine Manufacturing Network (DCVMN), on what improvements could or should be considered moving forward for preparing for the next pandemic, as well as continuously improving the supply of vaccines outside of outbreak or pandemic situations.

3. Methods

With the emergence of SARS-CoV-2 virus, an international organization was put into place for COVID-19 vaccines called the COVAX Facility. COVAX is the vaccines pillar of the ACT Accelerator, co-led by the Coalition for Epidemic Preparedness Innovations (CEPI), Gavi, the Vaccine Alliance, and the World Health Organization (WHO). Its goal is to enable access to safe and effective Vaccines to the most vulnerable in all participating economies [3]. Within the COVAX organization, a Regulatory Advisory Group (RAG) was established, made up of regulators from 10 nations, available to provide feedback and regulatory guidance on COVID-19 vaccine development and activities. COVAX has also established multiple SWAT's (Support Work to Advance Teams): groups of experts focused on resolving technical issues and challenges common across all COVID-19 vaccine development projects to promote and accelerate vaccine development. The Manufacturing SWAT, with representatives from the VE/IFPMA Task Force, focused on the following (3):

- "Regulatory strategy and the identification of manufacturing capacity for initial manufacture and increase in the supply of vaccines.
- Supply chain strategy to include securing raw materials, mutually agreed labelling and alignment with COVAX partners.
- Support for batch release assays (including potency assay requirements); mutual recognition of the process for timely national batch release; and support for additional analytical capacity"

In order to inform the Manufacturing SWAT, VE and IFPMA set up a task force to share multi-national vaccine manufacturers concerns and views and develop solutions. Several working groups provided proposals to assist the COVAX Facility RAG in providing "guidance for regulatory science challenges related to SWAT team activities, towards harmonization and streamlined processes where feasible." [3]

4. Results

These proposals are an aid in streamlining specific regulatory processes. Below we review eight elements, as introduced in the first paper (PART 1), touching on process validation, comparability, stability, post-approval-changes, lot release, genetically modified organisms, labeling & packaging, and variants. In all, divergence and heterogeneity between guidelines and regulations in the different countries have a negative impact on timely access for patients to effective, safe vaccines of high quality.

4.1. Process validation

Before any pharmaceutical product is released for use in patients, manufacturers must demonstrate with data and information that their manufacturing process is capable of consistently producing products with acceptable quality using commercial scale conditions.

With respect to the drug product, traditional process validation normally occurs when pharmaceutical development and/or process development has concluded, after production scale-up (with three consecutive commercial scale lots) and prior to marketing of the finished product [4]. ICH Q7 & Q11 [5] eliminates the ability to use small scale models, requires full study information in the initial filing, and prior knowledge can only be used as supportive information. Based on these requirements, the traditional process validation approach for a new vaccine adds several additional months or even years to the global technical development timelines. In a pandemic situation, flexibility on the provision and type of Chemistry, Manufacturing and Controls (CMC) data packages in initial regulatory filings would clearly be beneficial, taking into consideration the overall benefit/risk of the product.

An illustration of a more flexible process validation approach, is the unprecedented scale at which vaccines for COVID-19 are manufactured: many developers required multiple drug substance (often two or more) and drug product (often three or more) sites simultaneously which may be located around the globe, highlighting the need for a common approach across different regulatory agencies. Additionally, some sites may have been recently renovated or re-purposed to accommodate the manufacturing process for the newly introduced COVID-19 vaccines.

Process validation is an important element of ensuring control, both within a site and across sites. Given the need to perform relevant validation on processes and manufacturing scales for making commercial supply during an accelerated clinical development, process validation by necessity is one of the latest steps in process development and will be rate limiting for regulatory approval.

ICH Q9 [5] provides risk-based approaches to validation. However, different National Regulatory Authorities (NRAs) have developed their own requirements for the types of data required and timing for availability of that data. If all relevant NRAs could accept a level of risk (based on ICH Q9) for defining the appropriate levels of validation for equipment, process and analytical methods at time of submission, it would allow vaccine manufacturers to manage some aspects within their Pharmaceutical Quality System (PQS) [6]. It equally would allow the NRAs to receive data as post-approval commitments, as suggested in recent (draft) guidance documents [7,8].

A risk-based validation approach should also take prior knowledge into account. For example, the process validation might be accelerated based on knowledge gained from similar products manufactured with the same well-characterized platform technology (such as mRNA, viral vector vaccines, or recombinant proteins). Knowledge from lots manufactured prior to Process Performance Qualification (PPQ) batches (incl. pilot scale and clinical batches)

could then be used to confirm the critical process parameters previously identified for the vaccine platform, hence reducing or even removing the need for full scale product-specific data. Agencies generally accepted that PPQ data could be provided post-approval and some even allowed the use of pre PPQ batch for administration to patients, controlled within the company PQS. Similarly, new or repurposed facilities and equipment validation, as well as updated aseptic and cleaning processes (when needed), could be provided post-approval. When there is extensive prior knowledge on a particular manufacturing process and it comprises extensive in-line, on-line or at-line controls, continuous process verification could be used to validate the manufacturing process and reduce timelines, as an alternative approach to traditional process validation [8]. As every dose of vaccine is precious, use of alternative batches shown to be of acceptable quality, should be considered.

Finally, drug substance and drug product validation may be decoupled: under certain circumstances, the drug product validation may be conducted using drug substance lots manufactured prior to drug substance validation, for example drug substance lots manufactured under cGMP for clinical studies, with sufficient demonstrated comparability of earlier drug substance lots to the drug product lots intended for validation [8].

The use of science and risk-based approaches, convergence on data requirements, and flexibility on the provision and type of data packages in initial regulatory filings for process validation would clearly be beneficial to accelerating access to vaccines.

4.2. Comparability

Given the challenges associated with the COVID-19 emergency, comparability assessment of vaccines may be on a critical path. For instance, the number of batches used in the clinic and the urgency with which these studies are being executed result in a limited historical dataset to establish statistically based acceptance criteria which are typically applied for comparability assessment.

The following options for comparability strategies and engagement of Regulatory Agencies can provide a structured path to be rapidly assessed for the individual platforms/products during development and lifecycle:

- The use of a risk-based analytical comparability assessment of manufacturing changes, for instance:
  - evaluate Critical Quality Attributes (CQA's) related to the changes known to possibly impact safety and/or efficacy
  - matrixed and bracketed approaches
  - assess reinforcing characterization testing, if needed
- Use of release data, degradation data, and/or characterization data to demonstrate comparability, as appropriate.
- Comparing CQA's for post-change lots and pivotal study lots demonstrating clinical efficacy, linking the post change to efficacy. Assessing manufacturing variability in clinical trials and appropriate dose selection (as per discussion at 2018 EMA/FDA early access workshop [9]) would support definition of such patient-driven acceptance criteria for comparability.
- Demonstrate preservation of CQA's without process consistency requirements where prior knowledge is limited and/or in the absence of statistically based acceptance criteria. This is in line with ICH Q5E, stating "the goal of the comparability exercise is to ascertain that pre- and post-change drug product is comparable in terms of quality, safety, and efficacy."
- Emphasis on reliable analytical comparability in evolving process understanding and manufacturing facilities requires special attention to the analytical strategy. Analytical method changes could take place either due to company needs (e.g., evolving knowledge, cross-testing site transfers/ changes) or considering transfer to National Control Laboratories (NCLs). Keys to addressing this are:
  - minimize risks through a robust reference standard strategy, representative lot selection for comparability and for method bridging if needed, privileging clinically proven lots, extensive characterization and assessment of best storage conditions for reference standard)
  - definition of minimum set of tests (platform-specific [10,11]) and analytical method purpose and performance expectations (product-specific)

Building strong, quality risk-based comparability strategies is key to support fast access and sustainable lifecycle management.

4.3. Stability of vaccines during storage and distribution

The major challenge of ensuring stability of vaccines is to control the rate of antigen degradation to provide an acceptable shelf life during storage and worldwide shipments [12,13,14]. Rapid development of COVID-19 vaccines presents a challenge to provide initial stability information where limited, or no data will be available at the time of filling the commercial scale batches. Also, shelf-life extension, process scale-up and manufacturing site additions are likely to ensure supply sustainability. Nevertheless, expiry dating will be required for packaging/labelling.

Stability is frequently on the critical path for vaccines. The rigid application of ICH Q5C [5] indications, like the core stability data package and requirements for real-time data, is not compatible with the accelerated vaccine development and industrial plan needed for urgent global supply of COVID-19 vaccines. In cases of incomplete data sets, using prior knowledge and accelerated stability modeling studies to base claims on shelf life will be critical for manufacturers. In this context, the use of kinetic-based modelling approaches, along with the increased use of platform knowledge, make stability modelling a robust approach for vaccine stability assessment [15,16,17]. On balance, stability modeling approaches leverage accelerated stability studies to accurately predict shelf-life at the intended storage conditions and impact of temperature excursions (cold-chain breaks) during storage and shipments [18,19].

Post approval commitments to provide complete shelf-life data may be acceptable with appropriate justification in some markets (such as FDA Guidance For Industry on Development and Licensure of Vaccines to Prevent Covid-19 [20]). Yet, it is not clear to what extent the vaccine manufacturers will be allowed to leverage prior knowledge and scientific approaches to set the vaccine expiry date at initial authorization and submit confirmatory stability data generated on commercial batches as post approval commitments.

Additionally, lifecycle management of vaccines creates changes requiring regulatory approvals that can be lengthy [21]. An example of this is seen when new manufacturing sites or capacity increase changes requiring demonstration of comparability between batches and technology transfers.

The use of advanced modelling approaches, along with the increased use of platform knowledge, make stability modelling a robust approach for vaccine stability assessment. On balance, stability modeling approaches leverage accelerated stability studies to accurately predict shelf-life at the intended storage conditions. Various Health Authorities in Europe, North America, South America and Asia are already aware of these methods for predicting shelf life and shelf-life extensions for various vaccines. Even if such modeling approaches are still not strictly described in the official guidelines, they are aligned with nonlinear regression methods and kinetic models can usually be proposed as supplementary data in dossiers.

Up to now, general feedback from the regulatory agencies is positive when explaining the approach and sharing examples/publications. Taking advantage of stability modeling approaches can provide the shelf-life estimation for vaccines, especially in a pandemic context, during which long-term experimental data are not available. Additionally, timelines for approval of PACs can be greatly reduced using stability modeling methods, comparing long-term stability predictions of batches.

4.4. Post-Approval changes

Post-approval changes (PACs) are inevitable and necessary throughout the life of a drug product to increase capacity, secure supply chain, implement new knowledge and drive continual improvement. Many PACs require regulatory agency approval by individual countries before implementation. Because of global regulatory complexity, our past experiences with individual PACs usually take years [22] for full worldwide approval even when they reduce patient risk, improve compliance, or enhance the manufacturing process or test methods. The consequence of this can reduce supply security or continual improvement and innovation. This can lead to potential drug shortages for patients and possible compliance risks for companies [21].

Due to accelerated development and the overall complexity of vaccines, a significant increase in the number of post-approval changes has to be managed within a short period of time. An innovative solution is needed for this global problem, especially with a high heterogeneity in terms of regulatory review, approval processes and timelines [21]. This creates situations where manufacturers must, where possible, segregate pre- and post-change batches to the countries where those processes are either approved or unapproved, ultimately fracturing supply chains and limiting the fungibility of supply. Or they are forced to delay implementation of the change. Fig. 2 illustrates the real-life level of complexity of a routine life cycle management of PACs for a given vaccine licensed worldwide [23].

The extent of operational and regulatory flexibility is subject to product and process understanding (ICH Q8 and Q11) [5], application of quality risk management principles (ICH Q9) [5], and an effective PQS (ICH Q10) [5], all enabled by an appropriate knowledge management. ICH Q12 [5] also provides a harmonized approach regarding technical and regulatory considerations for lifecycle management. The Parenteral Drug Association's One Voice of Quality group, gathering the Chief Quality Officers of more than 25 multinational pharmaceutical companies, published [24] a standard approach for the steps necessary to establish and demonstrate an effective PQS to fully leverage the risk-based approach to PACs. The benefit is focusing regulatory resources on PACs that may have a potential to impact product quality as it relates to safety and efficacy and eliminating regulatory submissions and approvals for low and moderate risk changes that can be handled by an effective PQS.

Global alignment is needed on technical dossier content as well as on PACs reporting categories and mechanisms, data requirements, rapid review and approval timelines, allowance for multiple sites to be registered at all stages, expectations with regards to implementation, and the use of regulatory tools such as Post Approval Change Management Protocols (PACMPs).

Manufacturers could provide agencies with a target implementation period or use a standard 30 days post submission implementation while approvals are ongoing. A distinction must be made between the implementation of a PAC in production or quality control (that the manufacturer can proceed with at risk, while waiting for regulatory approvals), versus, the actual release of the first batch bearing the PAC on the market. The ability to implement a change rapidly is vital to mitigate the risk of delayed local regulatory approvals and avoid any potential vaccine shortage.

The WHO Good Regulatory Practices [25] aims to provide "a set of principles and practices that are applied to the development, implementation and maintenance of regulatory instruments – including laws, regulations and guidelines – in order to achieve a public health policy objective in the most efficient way". Both regulators and industry should focus on what really matters, which is the timely access to safe and efficacious medicines for patients, and so accelerating the management of CMC PACs is crucial. Multiple approaches to improve the management of PACs at the global level should be considered, including reliance, science/risk-based approaches, and removing regulatory barriers.

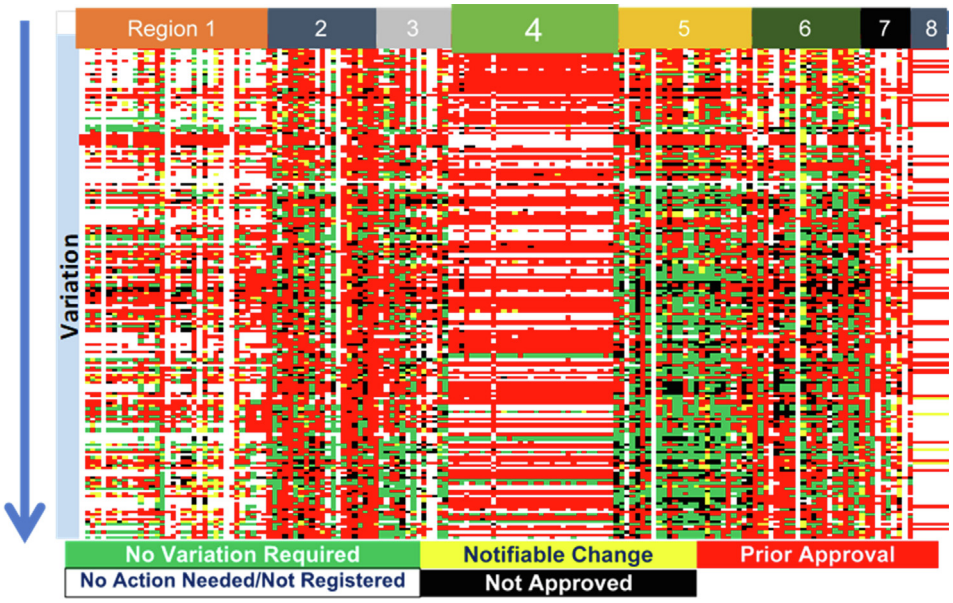

Fig. 2. A highly worldwide regulatory heterogeneity for managing Post Approval Changes. Note: Each single column represents one country and each single line represents one PAC. Each color represents a reporting category depending on the nature of the PAC. Apart from the EU (Region 4) where procedures are harmonized and mutual recognition processes exist, all other countries in the world have different regulations for managing PACs.

4.5. Challenges with lot release of Covid-19 vaccines to the general population

Vaccines often require National Control Laboratory (NCL) release testing, and in most cases, a formal release by the competent authorities. This is a unique situation compared to the thousands of other pharmaceutical products. This results in the batch being tested by the original releasing authority (refence NCL) in the country where the vaccine is manufactured and tested again in one or multiple receiving countries by their Control Laboratories without assurance of conclusions based on the same test methods and specifications. Initial COVID-19 vaccine batches will have a short shelf life upon regulatory approval due to limited stability data. Therefore, time executing additional NCL testing beyond the reference NCL would inevitably reduce remaining available shelf life for the vaccine, potentially resulting in insufficient time to reach the populations or the discard of expired doses. Where speed to market is essential, the duplication of testing will not be beneficial to the population. Below are potential options to eliminate additional testing through the adoption and alignment of batch release reliance.

To expedite supply, the World Health Organization (WHO) provided recommendations for batch release of Prequalified vaccines or Emergency Use Listing according to the published "WHO Operational Tool for efficient and effective lot release of SARS-CoV-2 (COVID-19) vaccines" [26]. In this document WHO expresses that access to prequalified vaccines should rely on lot release certificates of the reference NCL. Industry supports adoption of this proposal and additionally advocates for the allowance of a higher degree of batch release recognition even if no legally binding obligation exist.

The WHO also has a network consisting of NRAs and NCLs, from over 40 countries, and is open to new members subject to signing a confidentiality agreement. This network could work as a batch release alliance for reliance and/or recognition to reduce redundant testing. As per the WHO reference document, an issued NCL lot release certificate will be provided to recipient countries by the manufacturer of the vaccine lot. The certificates may be either in the form of a WHO model certificate, national release certificate or an EU Official Control Authorities for Batch Release (OCABR) certificate (basis for lot release reliance within Europe and recognized in many countries outside Europe). An expanded alliance with NCL members recognizing a batch release certificate from a reference NCL could be a significant step promoting timely supply of vaccine to the world population and prevent shortened shelf-life.

4.6. Vaccine packaging Materials: Label, carton and leaflet

Integral to the distribution and safe use of vaccines are the packaging materials: label, carton and package insert (leaflet), which are regulated by NRAs. Rarely can the label/carton/leaflet for one country be used for another country.

Each country requires approval of packaging materials for vaccines prior to distribution in that country. Waiting for approvals before printing packaging materials slows down vaccine introduction and eliminates pre-positioning for distribution. Vaccines (like mRNA vaccines) requiring extreme cold storage conditions must be labeled and packaged immediately after filling and inspection; delaying filling for specific markets until approval can cause considerable delays or even loss of doses.

A critical point is the need to maximize flexibility of global vaccine supply chains. The presence of country-specific packaging materials severely limits the interchangeable use of global vaccine supplies, segregating supplies into small allotments only available for individual countries.

Additionally, updates to labeling and leaflet information as additional information becomes available (e.g. clinical data, stability, etc.) will be challenging under the current regulatory system, further fracturing supply chains.

The WHO 30 October 2020 working version 2.1 paper "Barcodes, QR codes and Vaccine Vial Monitors in the context of COVID-19 vaccines" [27] lays out a recommendation for addressing some of these challenges. Independent and prior to the WHO work, a group of packaging experts from IFPMA were convened to determine how to achieve maximum speed and flexibility of COVID-19 vaccine supply. One thing became very clear: the key to maximizing flexibility and speed of supply (while minimizing stranded supply and wastage due to expired materials) is to avoid country-specific markings or requirements on the printed label, carton and insert, including country-specific languages and printed data that could require updating.

The proposal covers the key aspects of packaging materials:

- LABEL: A generic, single language label provided for all markets. Statutory information in human readable format (putting this in barcode in addition is optional).
- CARTON: A generic, single language carton provided for all markets. Statutory, lot-specific information would be in human readable format and GS1 barcode format.
- SERIALIZATION: Using unique serialization numbers, where possible and without delaying release to the market, included on the carton only. Timing and capacity for doing so would vary for each manufacturer (implement immediately up to a maximum of 12 months), considering use of alternate manufacturing lines and contract manufacturers.
- INSERT: A generic, simplified insert supplied with each carton. Containing basic information in a single language. A QR code on the insert would point to a website with full country approved inserts in their desired language. Where an electronic insert is not acceptable in place of a paper insert, countries would be responsible for printing the website insert and distributed with the vaccine.

These proposals create a responsive, flexible and fungible global supply chain while still preserving safety, efficacy and quality of the vaccine.

Little has been agreed on globally, except by EMA that noted that the "blue box" statutes clearly stated specific requirements for carton format/printed contents. Similarly, FDA noted that these approaches may be acceptable for vaccines under Emergency Use Authorization (EUA), but not for fully licensed products. The WHO is expected to update their recommendations . In the meantime, developers were recommended to have individual discussions with National Immunization Programs on labelling and leaflet proposals.

4.7. Impact of genetically modified organism (GMO regulations on vaccine approval)

For medicinal products containing GMO or based on recombinant technology, separate GMO approvals are needed in addition to the typical regulatory approvals. The GMO regulatory framework is complex, with different regulations required at regional and at country levels, which hamper the rapid development and approval of GMO-based vaccines significantly. The process of acquiring GMO permits is time consuming. Many countries have their own GMO legislation which is not necessarily aligned. For some countries there is a lack of understanding of their regulations and processes and many have different positions with regards to the biosafety level (BSL). This has an impact on conducting clinical trials, manufacturing, and the transport of material between coun-

tries. As a result, vaccine developers face challenges as outlined below including recommendations to overcome them.

For COVID specifically, a GMO derogation has been installed temporarily which allows COVID-19 vaccines to be developed more quickly in the EU. However, this derogation was only effective for clinical trials in Europe, and not outside of Europe. A similar approach should be taken globally.

The challenges seen are:

- GMO permits are needed for the manufacturing facilities, often requiring inspections
- No alignment between bio-safety level (BSL) requirements between countries
- Many manufacturing platforms do not significantly change the organism between products, only the targeted antigenic transgene; however separate GMO application are required for each product
- The approval and classification of a GMO in one country currently does not aid in the approval of the GMO in another country
- Country specific environmental (risk) assessments are often required as part of the marketing authorization dossier covering the impact of exposure due to handling the vaccine.
- Shipment of GMO vaccines need to comply with transportation legislation in the sending, receiving or transit countries which can hamper fast distribution and reduce the flexibility of using capacities at different manufacturing sites

Reliance or recognition between countries and convergence towards single standards on GMO requirements could facilitate this complexity and save time and effort.

4.8. Variants

Experience suggests that fast track regulatory pathways that are clear and have highly accelerated authorization schedules, are critical enablers of the timely prevention of seasonal influenza strains; however, the lack of globally harmonized regulatory pathways for seasonal influenza makes the process of getting vaccines against new strains to market unnecessarily complex, slow and burdensome. For COVID-19, some regulators have worked in heroic fashion to provide scientific advice, regulatory guidance and high priorities for vaccine authorizations to meet the needs of the pandemic. Although these efforts are greatly appreciated, having fast-track globally converged regulatory mechanisms (based on reliance or mutual recognition) that can allow multiple countries to address COVID-19 variants on unprecedented timelines using the same application remains the ideal.

5. Discussion

The unprecedented speed with which vaccines are being developed for the pandemic have exposed regulatory hurdles for global and timely access. The current global regulatory processes are fragmented, which adds unnecessary delays and do not allow for a unified global product.

Throughout the previous sections, we have presented many opportunities to accelerate the regulatory process and provide quicker access to a global population. Some of the key themes seen throughout are science/risk-based approaches, global harmonization and convergence towards single standards, and reliance as discussed in the PART I article.

In the best of circumstances, these proposals would have been previously discussed and potentially accepted by regulators worldwide prior to an emergency. More recently they have been discussed with regulators, at the COVAX level, with good interactions and understandings [28]. At this stage however, there is little movement on a collaborative global level. On the contrary, regulators recommended that individual developers need to approach their relevant regulatory agencies to engage in a dialogue to explore the feasibility on any proposed exemptions (WHO Technical Brief: Regulation of Covid-19 Vaccines [28]). This results in each developer of a vaccine talking part in 100s of Agency meetings pre-submission, during review and post approval across 100 countries, addressing 1000s of questions from agencies and negotiation of 1000s of post approval submissions, all for just 1 vaccine.

We believe that more could be done. This will require more international and political willingness to move towards full harmonization. One such approach would be for ICH to create a pandemic playbook or guidance on flexibilities. But if one keeps the ultimate goal in sight which is timely access for patients wherever they are, this should be a strong incentive on its own.

As with other facets of global pandemic preparedness, a lack of unified global regulatory pathways adds unnecessary complexity and increases delays in product supply. Regulations supporting agility and speed for pandemic vaccines should be prioritized with other regulatory concerns prior to the next pandemic. Many of these processes would also be a benefit in non-pandemic situations.

Great progress has been made on application of some of these CMC approaches, to make early access to patients easier, through direct product discussions or via workshops with Agency members. More of this would be welcomed so we can help ensure we apply these pragmatic science risk-based CMC approaches to bring true clinical benefit to patients as soon as we safely can. Especially because it impacts each lot manufactured, the same approach should be implemented regarding the harmonization of batch release tests methods and specifications and global batch release process and data sharing tools (reliance). Great discussions took place at the joint ICMRA (International Coalition of Medicines Regulatory Authorities) – Industry workshop in July 2021 [29], and at the "Extraordinary ICDRA" (International Conference of Drug Regulatory Authorities) conference in September 2021 [30]. Both ICMRA and ICDRA conferences highlighted the pre-requisites needed for ensuring appropriate regulatory flexibility and the need to better develop reliance mechanisms respectively.

6. Conclusion

The COVID-19 pandemic has shown itself to be an unprecedented situation for vaccines. It has highlighted some hurdles that need to be negotiated in the worldwide regulatory flow for manufacturing, controls and batch release. This has led to the formulation of solutions, or regulatory flexibilities, that can overcome barriers and provide significant improvement for the benefit of all. The regulatory flexibilities described in this paper provides solutions to be better prepared to improve the supply of vaccines when the next pandemic occurs. Most of the lessons learnt can also improve the ways of working in order to provide a consistent supply of vaccines under a routine mode.

The ICMRA and ICDRA conferences did illustrate great willingness to improve ways of working, however, there is still work that must be done to provide the needed accelerated processes to continuously improve the timely supply of vaccines to all populations who need them, beyond borders.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing

interests: [Some of the participants in the authoring group own stocks in their company].

References:

[1] Excler JL, Saville M, Berkley S, et al. Vaccine development for emerging infectious diseases. Nat Med 2021;27:591–600. https://doi.org/10.1038/s41591-021-01301-0.

[2] Coronavirus (COVID-19) Vaccinations - Our World in Data, Project of the Global Change Data Lab; Website (sited 9-Jun-2021) https://ourworldindata.org/covid-vaccinations.

[3] The COVAX Pillar; WHO Website (sited 15-Apr-2021) COVAX: The vaccines pillar of the access to COVID-19 tools (ACT) Accelerator (who.int).

[4] EMA Guideline on process validation for finished products - information and data to be provided in regulatory submissions (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1, Corr.1), November 2016 https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-process-validation-finished-products-information-data-be-provided-regulatory-submissions_en.pdf.

[5] ICH Quality Guidances; Website (sited 15-Apr-2021) https://www.ich.org/page/quality-guidelines.

[6] WHO Technical Brief: Regulation of COVID-19 Vaccines – Synopsis from the August to November 2020 COVAX RAG meetings, February 2021 https://www.who.int/publications/m/item/annex-1st-technical-brief-regulation-of-covid-19-vaccines.

[7] FDA Guidance for Industry – Development and Licensure of Vaccines to Prevent COVID-19, June 2020 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/development-and-licensure-vaccines-prevent-covid-19.

[8] EMA Draft toolbox guidance on scientific elements and regulatory tools to support quality data packages for PRIME marketing authorisation applications, February 2021 https://www.ema.europa.eu/en/documents/scientific-guideline/draft-toolbox-guidance-scientific-elements-regulatory-tools-support-quality-data-packages-prime_en.pdf.

[9] Stakeholder workshop on support to quality development in early access approaches, such as PRIME and Breakthrough Therapies; 26-Nov-2018 Stakeholder workshop on support to quality development in early access approaches, such as PRIME and Breakthrough Therapies | European Medicines Agency (europa.eu).

[10] Analytical strategy options proposed by EDQM on recombinant viral vectored vaccines for human use https://www.edqm.eu/sites/default/files/medias/fichiers/COVID-19/recombinant_viral_vectored_vaccines.pdf.

[11] *WHO Evaluation of the quality, safety and efficacy of RNA-based 5 prophylactic vaccines for infectious diseases: regulatory 6 considerations (DRAFT)* https://www.who.int/docs/default-source/biologicals/ecbs/reg-considerations-on-rna-vaccines_1st-draft_pc_tz_22122020.pdf?sfvrsn=c13e1e20_3.

[12] Kumru OS, Joshi SB, Smith DE, Middaugh CR, Prusik T, Volkin DB. Vaccine instability in the cold chain: mechanisms, analysis and formulation strategies. Biologicals 2014;42:237–59. , https://pubmed.ncbi.nlm.nih.gov/24996452/.

[13] Kartoglu U, Milstien J. Tools and approaches to ensure quality of vaccines throughout the cold chain. Expert Rev Vaccines 2014;13:843–54. , https://pubmed.ncbi.nlm.nih.gov/24865112/.

[14] Dumpa N, Goel K, Guo Y, McFall H, Pillai AR, Shukla A, et al. Stability of Vaccines. AAPS PharmSciTech 2019;20:42. , https://pubmed.ncbi.nlm.nih.gov/30610415/.

[15] C. Roque, S.F. Ausar, N. Raham, D. Clénet, chapter Stability Modeling in QbD: Accelerating Formulation Development and Predicting Shelf Life of Products, PDA book "Quality by Design - An Indispensable Approach to Accelerate Biopharmaceutical Product Development", ISBN number: 978-1-945584-22-0, **2021.**

[16] Clénet D, Imbert F, Probeck P, Rahman N, Ausar SF. Advanced Kinetic Analysis as a Tool for Formulation Development and Prediction of Vaccine Stability. J Pharm Sci 2014;103:3055–64.

[17] Roduit B, Hartmann M, Folly P, Sarbach A, Baltensperger R. Prediction of thermal stability of materials by modified kinetic and model selection approaches based on limited amount of experimental points. Thermochim Acta 2014;579:31–9.

[18] Roduit, B., Luyet, C. A., Hartmann, M., Folly, P., Sarbach, A., Dejeaifve, A., Dobson, R., Schroeter, N., Vorlet, O., & Dabros, M. Molecules, 24(12), 2217, **2019.** Continuous monitoring of shelf lives of materials by application of data loggers with implemented kinetic parameters.

[19] D. Clénet, Eur. J. Pharm. Biopharm., 125:76–84, **2018**. Accurate prediction of vaccine stability under real storage conditions and during temperature excursions.

[20] Development and Licensure of Vaccines to Prevent COVID-19, FDA Guidance for Industry; June 2020. https://www.fda.gov/media/139638/download.

[21] Dellepiane et al., 2020, Alignment in post-approval changes (PAC) guidelines in emerging countries may increase timely access to vaccines: An illustrative assessment by manufacturers. https://doi.org/10.1016/j.jvacx.2020.100075.

[22] The complex journey of a vaccine; IFPMA Brochure; 17-Jan-2014. https://www.ifpma.org/resource-centre/the-complex-journey-of-a-vaccine-2/.

[23] PDA presentation "The Complexity of Post-Approval Change Management and New Regulatory Approaches: Relevance for Vaccine Products" PDA conference on Vaccines / Malaga-Spain / Vaccine life cycle management complexity / A Deavin & T Gastineau, 2018; Conference Link: https://www.pda.org/docs/default-source/website-document-library/eu-conferences/2018/04_vaccines/brochure.pdf?sfvrsn=1699898e_8.

[24] PDA, 'Effective Management of Post-Approval Changes in the Pharmaceutical Quality System (PQS) - Through Enhanced Science and Risk-Based Approaches Industry One-Voice-of-Quality (1VQ) Solutions ', 2020: https://journal.pda.org/content/early/2020/05/28/pdajpst.2020.011734.

[25] Good regulatory practices in the regulation of medical products (Annex 11); WHO; pages 255-285. https://apps.who.int/iris/bitstream/handle/10665/340323/9789240020900-eng.pdf.

[26] WHO WHO Operational Tool for efficient and effective lot release of SARS-CoV-2 (Covid-19) vaccines" version 1: 20 January 2021. https://extranet.who.int/pqweb/sites/default/files/documents/WHO_OperationalTool_EfficientLotRelease_v20Jan2021.pdf.

[27] Bar-codes, QR codes and Vaccine Vial Monitors in the context of COVID-19 vaccines; Working Version 2.1, 30 October 2020. https://www.who.int/publications/m/item/bar-codes-qr-codes-and-vaccine-vial-monitors-in-the-context-of-covid-19-vaccines.

[28] WHO Technical Brief: Regulation of COVID-19 Vaccines – Synopsis from the August to November 2020 COVAX RAG meetings, February 2021. https://www.who.int/publications/m/item/annex-1st-technical-brief-regulation-of-covid-19-vaccines.

[29] ICMRA-Industry Virtual Workshop Report on Enabling Manufacturing Capacity in the COVID-19 Pandemic; 8 to 9 July 2021 (sited 10-Nov-21). https://icmra.info/drupal/sites/default/files/2021-10/covid-19_manufacturing_capacity_ws_report.pdf.

[30] Extraordinary International Conference of Drug Regulatory Authorities (ICDRA); 20 to 24 September 2021 (sited 10-Nov-21). https://www.who.int/teams/regulation-prequalification/regulation-and-safety/regulatory-convergence-networks/icdra.