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REVIEW ARTICLE

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

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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 the implementation of strategies for the quality-related aspects of accelerated development and supply: (1) the substantial need to advance reliance or collaborative assessment; (2) the need for early decision making and streamlined engagement between industry and regulatory authorities on CMC matters; (3) the need to further facilitate 'post-approval' changes; (4) fully exploiting prior and platform knowledge; and (5) review and potential revision of legal frameworks. The recommendations in this publication are intended to contribute to the discussion on approaches that can result in earlier and greater access to high-quality pandemic vaccines and therapies for patients worldwide but could also be useful in general for innovative medicines addressing unmet medical needs.

**Keywords** analytical · anti-viral · chemistry · cleaning · CMC · commercial · comparability · control · controls · conventional · COVID-19, coronavirus · distribution · formulation · GMP · good manufacturing practice · importation · inspection · manufacturing · packaging · presentation · process · shelf-life · stability · strategy · validation · vaccine · regulatory · reliance/collaborative assessment · regulatory authority collaboration · parallel development

## Introduction

At the time of writing (March 2022), billions of people have been, and continue to be, impacted by the COVID-19 pandemic, with over 100 million cases reported world-wide and in excess of 2.8 million deaths (1). Mass vaccination programs have been initiated in many countries creating the need for the greatly accelerated expansion of the supply of rapidly-developed vaccines. The rapid expansion of supply is also an expectation for the newly developed antiviral COVID-19 therapeutics. This publication reflects on previous work by industry and regulators on approaches to accelerate the Chemistry, Manufacture, and Controls (CMC) aspects of development and Good Manufacturing and Distribution Practices (GMDP) for the supply of new therapies and vaccines (2–7), and on guidance developed to date for the development of medicines for COVID-19 (8–16), in the context of the lessons beginning to emerge from the global response to the pandemic crisis. Such interactions provide

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the foundation and framework for ongoing dialogue to establish common working principles and consultation mechanisms for industry and health authorities.

Several critical approaches for improving the rapid development and supply capacity of vaccines and therapies for effectively responding to future pandemics are discussed. These reflections and recommendations are intended to stimulate ongoing discussion among stakeholders (including industry, regulators, and patient groups) on measures that could facilitate public health responses in future pandemics, and that could also be valuable in non-pandemic situations. The recommendations and discussion points proposed within, augment and expand on the vaccine-specific recommendations proposed by McGoldrick *et al.* (17, 18)

One of the most challenging issues faced by companies introducing innovative medicines for use in the COVID-19 pandemic was having to engage each authority and their respective governmental distribution organizations to negotiate regulatory criteria for authorization and distribution in each market. Companies found that differences in expectations between different regions could not be managed during parallel, simultaneous submissions due to resource constraints. A critical observation from the industry perspective is the importance of prospectively establishing principles for alignment and collaboration of regulatory authorities with their respective governmental distribution organization before the next pandemic.

### Challenges Faced by Industry during the Pandemic

Conventional product development generally relies on a sequential approach to understanding product attributes and developing process knowledge that connects the quality attributes and material characteristics of the drug substance, raw materials, and other product and packaging components with associated manufacturing processes and supply chain operations. All accelerated clinical development programs result in the compression of time available for the development of CMC quality attributes and the establishment of a robust product control strategy that reliably provides products to patients.

It is understood that the discovery and approval of new medicinal products in a pandemic crisis can only be enabled by accelerated clinical programs. To support such accelerated clinical programs and the subsequent commercial distribution, the technical and regulatory challenges to develop manufacturing and supply chain capacity to deliver safe and effective products should not be underestimated.

Before the current pandemic crisis, industry and regulators had been collaborating for several years to explore innovative CMC and Good Manufacturing Practices (GMP) approaches and principles that can facilitate the rapid science- and risk-based development of new, high-quality medicines (2–7). Various science- and risk-based approaches have been identified that could facilitate more rapid generation of the CMC information required. While good progress was being made in this work, global harmonization of principles for accelerated CMC development to support early patient access has not yet been demonstrated and significant differences exist in pre- and post-approval regulatory expectations for medicinal products supplied through early access initiatives in Europe, United States of America (US), Japan, and China. Reducing regulatory differences will improve accelerated access to these new products for global populations; regions that maintain local requirements (not aligned with, or in addition to those agreed in e.g., International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)) may inadvertently delay patients' access to these innovative medicinal products.

In non-pandemic situations, products developed under accelerated programs may warrant limited manufacturing and supply chain capacity to serve relatively small patient populations. However, the COVID-19 pandemic demonstrated the clear need to rapidly develop a sustainable supply capacity of billions of doses of new, life-saving vaccines. This unprecedented challenge demanded alternative, compliant, approaches to ensure a supply chain to meet this huge global demand. Furthermore, both industry and regulators have found that it is important to reassure the public that although new therapies and vaccines have been developed rapidly, corners have not been cut. The same standards for quality, safety, and efficacy are being applied, and these early-access products are subject to rigorous regulatory review before approval/authorization.

Given the scale of the worldwide patient population at risk of COVID-19, standard (sequential) approaches to CMC development and supply could not deliver the medicines required by patients in a timeframe aligned with innovation in clinical programs. Parallel, accelerated clinical and CMC development efforts for a COVID-19 vaccine have required large, 'at-risk' investments ($billions) in manufacturing and supply infrastructure, both before the safety and efficacy of the vaccine were confirmed, and after authorization for emergency use, to rapidly expand the supply. There is therefore an opportunity to consider how even greater agility can be supported to meet the quality, global regulatory, and logistical demands for new medicines in pandemic situations.

## Discussion

### Can We Create a Paradigm Shift in CMC for the Development and Supply of Pandemic Therapies and Vaccines?

In considering how the challenge of expediting the CMC development and supply of new medicinal products can be

met and can evolve (not specifically for pandemic situations), industry and regulators have established many key principles via dialogue in stakeholder workshops and proposals in published literature. In 2016, a joint industry and US Food and Drug Administration (FDA) group published a reflection on Manufacturing Readiness for Breakthrough Drug Development (2), which proposed important principles for acceleration. In a related article in 2017, the European Federation of Pharmaceutical Industries and Associations (EFPIA) proposed further detailed principles to facilitate rapid science- and risk-based development of new high-quality medicines (3). These were expanded upon using the experience of real case studies at the European Medicines Agency (EMA)/FDA 2018 PRIME/Breakthrough Quality workshop (5) and the 2017 EMA prior knowledge workshop (4). Most recently, in 2020, EFPIA expanded upon these principles in a further paper (6) on the development and supply of COVID-19 pandemic medicines. In 2021, the EMA published, for consultation, a draft CMC acceleration toolbox (7), based on lessons of the 2017 and 2018 workshop discussions.

The primary conclusions drawn from these engagements have been consolidated (Table I) into a series of potentially impactful approaches to enable the accelerated CMC development and supply of pandemic medicines. These are proposed for discussion between industry and regulators to agree on principles that could be incorporated in, for example, harmonized guidelines to enable accelerated CMC development, especially in pandemics. The principles described in Table I must always be applied within a science- and risk-based framework and need to be considered in relation to local legislative requirements. In some cases, revision of the legal framework may be necessary to enable the implementation of some or all of the principles in Table I so as to facilitate the rapid supply of life-saving therapies and vaccines.

In developing the recommendations consolidated in this publication, the following core principles have been considered:

- Fundamentally, the principle that accelerated CMC approaches must demonstrate product quality and patient safety is unchanged. Indeed, for COVID-19 pandemic medicines, the quality expectations (specifications) for supply under emergency use were the same as for commercial supply under a marketing authorization. The application of these acceleration approaches should carefully consider the benefit/risk for patients (19). For example, in a pandemic, therapeutic treatments may be needed for critically ill patients, whereas vaccines are administered to healthy subjects, some of whom may be at very low risk of the pandemic infection.
- Many expectations for CMC development enshrined in global and regional guidance are essential. However, the application of innovative, state-of-the-art, science- and risk-based approaches to CMC development, manufacture, and supply can enable and have enabled, safe, high-quality medicines to be delivered more rapidly than by using conventional approaches.
- Innovative science- and risk-based approaches should be applied across both the development and post-approval commercial manufacturing stages of the product lifecycle. As well as developments that enable rapid clinical programs and accelerated approval, supply on the scale required for pandemic medicines requires an equal focus on the post-approval phase (whether for emergency use or full marketing authorization), an area in which the authors believe the COVD-19 pandemic experiences can provide useful insights.
- Effective dialogue and collaboration between developers and regulators on CMC development and supply (including how to scale manufacturing and implement post launch changes) is essential to facilitate early decision-making and alignment. In a pandemic setting, there will be multiple companies developing products on accelerated timelines and seeking dialogue with multiple regulatory agencies. The International Coalition of Medicines Regulatory Authorities (ICMRA)-Industry Workshop on Enabling Manufacturing Capacity in the COVID-19 Pandemic (20), highlighted the very positive benefits of dialogue for accelerated development of COVID-19 medicines and suggested there are opportunities to further enhance this collaboration and dialogue for both industry and regulatory agencies.

## Could Regulatory Guidance and Initiatives for CMC/GMDP Related to COVID-19 and Future Pandemics Be Developed in Advance?

In response to the COVID-19 pandemic, regulators rapidly issued guidance and introduced processes to facilitate the development of new therapies and vaccines. An opportunity for future pandemic preparedness is for globally-harmonized regulatory guidance to be developed in advance, to avoid the duplication of effort associated with the development of potentially non-aligned guidance by individual regulatory agencies.

In Europe, the EMA began to issue guidance in 2020 to address the challenges presented by COVID-19 to the supply of medicines for the acute treatment of COVID-19 patients and the development of new COVID-19 medicines. Similar programs and guidance were developed by FDA and many other countries globally. Regulatory agencies collaborated through organizations, such as ICMRA, and this also created

**Table I** Accelerated CMC/GMDP Approaches for Development and Supply of New Medicines in a Pandemic Such as COVID-19

| | 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 |
|---|---|---|---|
| 1 | Formulation, Presentation (drug/device combination) and Packaging | Commercial formulation and container-closure system developed and optimized; comparability to pivotal clinical formulation demonstrated in dossier<br>Presentation optimized for patient population, required usability studies completed | Use of clinical formulation and presentation, or limited optimization of selected market form<br>Especially for vaccines, a single presentation defined for markets world-wide. Post-launch strategy defined for multiple presentations<br>Where relevant, comparability of launch formulation to pivotal clinical formulation demonstrated in dossier<br>Potential for initial use of "maximum protection pack" to mitigate limited shelf-life<br>Potential use of a Post Approval Change Management Plan to demonstrate comparability of planned changes, e.g. (1) moving to a commercial formulation from the approved pivotal clinical formulation<br>(2) Introducing an improved patient convenience presentation (e.g., vial to pre-filled syringe or auto-injector) may be in development, with usability studies using a representative labeling ongoing, complete data (and, for EU, a Notified Body opinion) available before launch |
| 2 | Use of clonally derived cell lines for biological drugs | Non-clonal cell lines are used for non-clinical studies | Non-clonal cell lines from pools of stably transfected cells may be used for non-clinical and First-In-Human studies provided safety measures regarding potential bacterial and viral contamination of the cell substrates have been considered. The non-clonal cell line should be qualified with regard to Transmissible Spongiform Encephalopathy and viral safety in accordance with relevant guidance documents such as EMA/410/01 rev 3, ICH Q5A, and ICH Q5D. The switch to a clonally derived cell line should be made as soon as possible thereafter within clinical development, with an appropriate risk-based analytical comparability assessment performed. Should analytical comparability not be demonstrated, the impact on non-clinical and clinical data should be assessed and appropriate action taken, which may include additional studies |

**Table I** (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 |
|---|---|---|---|
| 3 | Comparability for changes to chemical drugs | Bioequivalence studies (e.g., for bridging between small-scale clinical formulation and large-scale production formulation) are completed in accordance with regional Health Authority expectations. For drugs that are highly soluble, the ICH M9 guideline provides a globally agreed standard for *in vitro* demonstration of bioequivalence. All other drugs are subject to the national/regional bioequivalence requirements. These are not harmonized globally, meaning that multiple bioequivalence studies can sometimes be required | Since a typical bioequivalence study may take 6 months to complete, considerations for demonstration of bioequivalence for new medicines in a pandemic situation may be based on a scientific assessment of the potential impact of any drug product change on clinical performance. Broader application of biowaivers, biorelevant *in silico* and *in vitro* tools, and<br>*in-silico* Physiologically Based Pharmacokinetic (PBPK) models may be used to ensure that:<br>• Bioequivalence is based on the identification of product quality attributes critical for *in-vivo* performance which are at the heart of considerations for comparability<br>• Bioequivalence requirements when bridging between formulation changes and changes due to process optimizations and scale-up, are focused, where appropriate on *in vitro* and in silico assessment with tests and acceptance criteria agreed on a product-specific basis to allow biowaivers for BCS Class 2 and 4 drugs |
| 4 | Comparability for changes to biological drugs and vaccines | Full analytical comparability assessment, including extensive characterization and stability data<br>Clinical comparability studies proactively planned and performed to prevent delays that would be incurred if they are scheduled after analytical comparability results become available | A risk-based analytical comparability assessment of manufacturing changes may be performed to evaluate a subset of high-risk CQAs that are known (via prior/platform knowledge) to have an impact on safety and/or efficacy at the levels exposed to the patient (when administered at the desired dose). The use of release, stability, and/or characterization data to demonstrate comparability will depend on the changes being made (see section on stability)<br>The comparability strategy may vary depending on the nature of the change and supporting process. Companies may demonstrate the comparability of quality attributes (analytical comparability) (per ICHQ5E), without the additional requirement of process consistency (29)<br>In a pandemic situation, where only a few doses are likely to be administrated to the patient, clinical comparability studies may not be required unless the analytical assessment finds significant differences in high-risk CQAs that could impact safety and/or efficacy<br>Post-change lots could be compared to lots used in the pivotal study in which clinical efficacy has been demonstrated, thereby supporting comparability based on product quality with a link to the patient without a need to obtain further clinical exposure |

**Table I** (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 |
|---|---|---|---|
| 5 | Analytical procedures | Developed and fully validated | Procedures may be developed and qualified as suitable for their intended purpose<br>Science and risk-based approaches may be applied to bridging/equivalence studies needed to support changes to analytical procedures and technologies occurring late in development or post-approval. The impact on the stability data should be assessed<br>Validation approaches used in the clinical phase (e.g. analytical qualification rather than full validation) may be appropriate, where justified, for commercial supply of accelerated medicines<br>Establishment of an analytical target profile (ATP) can facilitate rapid optimization of analytical procedures and/or changes to implement alternative analytical procedures and technologies (30)<br>Rapid implementation of post-approval changes to analytical procedures and reference standards may be supported by the use of lifecycle management tools and processes (e.g., Post Approval Change Management Plans from ICH Q12)<br>Prior/platform knowledge of both the product and analytical technology can be used to simplify technology selection and validation |

**Table I** (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 |
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| 6 | Control strategies for impurities in chemical drugs | Impurities identified, risk assessed, and controlled<br>Synthetic route and process changes can result in the presence of new impurities that are qualified in animal safety studies<br>Requirements defined in ICH Q3A/Q3B guidelines provide some flexibility in the qualification of impurities but the presence of a new impurity greater than the qualification limit often triggers the need for further animal testing, even though such tests may be of limited value because of their inability to detect any toxicity associated with impurities at the levels tested<br>Extensive experimentation (e.g., through spike/purge investigations including variations in manufacturing process conditions and input materials and the accompanying iterative design and execution of analytical procedures) is used to identify potential non-mutagenic and mutagenic impurities and establish suitable control strategies, including the development of test procedures. Even where the risk is assessed to be low, there may be the need to develop highly sensitive methods to assess mutagenic impurities | Impurities identified, risk assessed, and controlled<br>The ICH M7 Guideline describes flexible control options, with Option 4 allowing the use of purge calculations (i.e., assessment of the interrelationship between the properties of a mutagenic impurity and the processing conditions) to determine the fate of the impurity without the requirement for specific analytical data<br>Where calculations show the risk to be very low (Barber *et al.*. (31)), this approach can be employed for all mutagenic impurities, including those that are part of the 'cohort of concern', during the development of pandemic medicines<br>A framework similar to the risk–benefit considerations described in ICH S9 may be considered for therapies used in a pandemic. ICH Q11 describes approaches that may be used in defining which impurities present a risk and need to be controlled. Such justifications can come from first principles considerations or models (e.g., based on solubility, chemical reactivity, and other relevant factors). In pandemic situations, these approaches may avoid the need for animal testing to qualify impurities, given the delays that such studies may introduce in development programs and the value of such studies in detecting toxicity<br>For new impurities arising from synthetic route and process changes to new chemical drug treatments for use in a pandemic, it may be possible to establish a baseline threshold of 1 mg/day, rather than the dual limits defined in ICHQ3A/B (1 mg or 0.15%, whichever is the lower), based on the conclusions from Harvey *et al.*. (32), that non-mutagenic impurities at levels of 1 mg/day have been established as safe over a lifetime. Modification of limits, based on the duration of treatment, and aligning this to a modified form of Haber's Law was also proposed in the publication<br>Combining these proposals could significantly reduce the risk associated with changes to the manufacture of the active substance delaying approval due to the presence of new low-level impurities that present a very low risk, especially for short-duration treatments likely to be required in a pandemic<br>Higher level of control by specification/testing (potentially including intermediates) may be needed until sufficient data are available to support greater reliance on process control |

**Table I** (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 |
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| 7 | Control strategies for vaccines | Vaccines may use diverse approaches to stimulate the immune system to produce antibodies and hence the level of risk may vary based on the degree of complexity and knowledge of the product and process<br>Integration of product understanding, process control, and analytical control strategies, is important for a structured approach to gather evolving knowledge<br>Lack of harmonization with regards to CMC global regulatory requirements | Harmonized CMC regulatory requirements, especially with respect to the control strategy for vaccines, may reduce manufacturing and supply complexity and facilitate global supply, especially if the supply of new (and /or existing) vaccines is constrained by the availability of suitable manufacturing capacity in a global pandemic situation<br>Principles described in ICH Q8-Q11 may be used to define and develop the control strategy, with product-specific considerations based on available prior knowledge (within and across companies), use of dose-finding studies to support product understanding/control strategy development, appropriate comparability studies, shelf-life and stability approaches (as described below), etc<br>Similar to other biologics, a Quality Target Product Profile (QTPP) may be used to define the vaccine (including presentation, shelf life, storage conditions as defined by WHO (12); the elements in the QTPP may vary depending on the vaccine platform<br>Specifications may prioritize product attribute safety and potency assessment using *in vitro* testing, rather than animal testing, etc<br>A company may seek regulatory approval for the use of innovative technologies during development and post-launch to ensure reliable, high- throughput product and process monitoring<br>Flexible approaches to the release of vaccines by Official Medicines Control Laboratories (OMCL) may be necessary for some countries. This may include deferring the completion of analytical procedure transfers until post-launch, mutual recognition between countries (where possible), etc<br>See below regarding pharmacopeial requirements. Supply of vaccines worldwide may be facilitated by meeting a single, globally-recognized standard and release by a suitable reference OMCL |

**Table I** (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 |
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| 8 | Commercial product specification | Established and documented<br>Supported by extensive dataset<br>Efficacy, quality, and safety principles are paramount. Testing methods and specifications are established based on standards and range from the experience gathered from testing results of the lots used in pivotal clinical trials | Established and documented<br>There will be a limited number of clinical lots representative of the product to be launched, as well as a reduced amount of process characterization data available at the time of submission. Consequently, regulators and industry may establish interim commercial specifications defined based on risk to the patient, supported by prior knowledge<br>Approval of specifications wider than the available batch data may be necessary to ensure uninterrupted supply. Specifications may include some parameters where the data will be reported but acceptance criteria are not defined<br>Applicants may provide a plan to evaluate and update specifications and to reassess the control strategy, based on pre-defined criteria (e.g., after *x* time or *y* batches) |

**Table I** (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 |
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| 9 | Shelf-life and stability data | Shelf-life at launch based upon the defined length of stability data on defined batch types/sizes (ICH Q1A and Q5C)<br>Limited extrapolation<br>Post-approval extension as further data is obtained | Real-time stability studies are likely to be on the critical path for new drug substances and/or drug product development and medicine supply in pandemics. Stability studies impact the start of clinical investigations and decisions to make changes during development, which could be delayed by having to wait for real-time stability data<br>Launch product will be supported by (ongoing) stability studies, but conventional stability data will be limited. A short shelf-life and/or atypical storage conditions may be applicable for urgent supply in pandemics<br>Use of alternative 'smart' risk-based stability' approaches to establishing the shelf-life and storage conditions for new products in pandemics may include:<br>•Use of reduced studies justified on the basis of utilization of prior knowledge including relevant company knowledge, first principles and scientific literature<br>•Use of accelerated temperature and humidity conditions<br>•Definition of a "representative" batch of API or drug product using science- and risk-based considerations of the impact of changes in process scale-up, for example<br>•Use of extrapolation and/or data modelling to predict shelf-life under normal storage conditions<br>•Post-change comparability stability studies using accelerated conditions on representative material<br>•To support a post-approval change, a commitment to initiate or complete ongoing, long-term stability testing on post-change batches can assure that the approved shelf-life and storage conditions continue to be applicable after implementing the CMC change<br>Similarly, the stability, storage conditions and shelf-life of investigational materials can also be supported using the above approaches<br>The principles described in ICH Q12 may be applied to confirm the established shelf-life and storage conditions for post-approval changes |

**Table I** (continued)

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| 10 | Additional Shelf-life and stability data for biological drugs and vaccines | Additional considerations for establishing the shelf-life for biological drugs and vaccines include:<br>•The need to identify stability-indicating CQAs for study in the stability program<br>•Typical regulatory requirements for a minimum of 6 months of data for 3 lots, at a minimum of pilot scale. Process Performance Qualification lots are typically used in stability studies and for launch<br>•Shelf-life is typically established from real-time, real-condition data with no extrapolation. (e.g., Minimum workable shelf-life requires 18-month stability data, with 24 months desired to optimize supply from initial commercial batches) | Stability studies are focused on the most critical stability-indicating quality attributes, considering the mode of action and primary routes of degradation<br>When possible, stability studies may use method options with reduced assay variability to improve monitoring of quality attributes trends, e.g., ligand (antigen) binding assay rather than cell-based assays. This may also accelerate assay development<br>Sufficient product-specific stability data may allow extrapolation to a shelf-life that is proportionate to the amount and quality of product-specific data and supporting prior knowledge data from like-molecules. For example, representative, development product data obtained under recommended storage conditions (i.e., +2°C/+8°C) and under accelerated conditions (i.e., +25°C, +37°C, or +40°C) may be pooled and statistical and kinetic analyses used to support extrapolation and estimate the impact of potential temperature excursions<br>When there is insufficient data for direct extrapolation of stability data, extrapolation to a maximum time-point based on suitable prior knowledge of stability data may be possible. A short shelf-life and/or atypical storage conditions may be applicable for urgent supply in pandemics |

**Table I** (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 |
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| 11 | Process development and validation | Complete package at launch<br>Process supported by extensive development studies<br>Prospective Validation and Continued Process Verification<br>Process validation data are required as part of the regulatory submission for sterile drug products or novel manufacturing technologies<br>Process validation data are also required for some post-approval changes | Process development studies less extensive and based on risk to product quality. Risk-based approaches (based on ICH Q9) may be used to define the appropriate levels of qualification/validation for equipment and process, including for vaccines<br>Concurrent validation and/or continuous process verification may be suitable tools for the assurance of manufacturing consistency for pandemic medicines<br>Process validation following accelerated development may be supported through a variety of approaches including:<br>•Platform knowledge, refined as experience is gained with more product-specific batches/materials<br>•Validation of normal operating ranges only<br>•Consideration of the product control strategy<br>•Provision of simplified process validation protocols, based on the use of risk assessments, appropriate platform/prior knowledge (e.g., a focus on validation of critical steps only), and the control strategy. Such protocols may be supported by continuous process verification or ongoing/continued process verification<br>Requirements for process validation data to be included in the regulatory submission could be waived where justified by risk assessment and a commitment to execute a suitable process validation protocol |
| 12 | Viral clearance validation for biological drugs | Validated in a small scale | Appropriate platform data may be included in the regulatory dossier, with a commitment to validate in a small scale prior to launch. See ASTM E2888 and E3042 standard practices for inactivation of rodent retrovirus |
| 13 | Cleaning method and validation | Cleaning method established and validated<br>Single-use systems (disposable manufacturing equipment) may be used, avoiding or reducing the need to develop and validate cleaning procedures | Cleaning method was established with appropriate verification through analyses on batch-wise basis<br>Single-use systems (disposable manufacturing equipment) may be used, avoiding or reducing the need to develop and validate cleaning procedures |

**Table I** (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 |
|---|---|---|---|
| 14 | Scale and sites of production and distribution | Commercial manufacturing site(s)—multiple sites may be approved. Commercial site has GMP license or is Inspection–ready<br>Conventional accelerated development programs may often result in launches to limited markets/patient numbers followed by expansion of supply as product approval is gained in more markets<br>Product lifecycle management plans may envisage the expansion of supply with transfers to manufacturing locations within or outside the company's network<br>Single-use systems (disposable manufacturing equipment) may be used, avoiding or reducing the need to develop and validate cleaning procedures | In global pandemics, the supply of new (and /or existing) therapies or vaccines may be constrained by the availability of suitable manufacturing capacity. Multiple approaches described in this guide may be applicable to addressing this issue<br>Commercial materials may be supplied from GMP-approved clinical supply (investigational medicinal product (IMP)) manufacturing sites without a commercial GMP license<br>Product history, PQS, and GMP status may support approval of the clinical site for commercial supply of medicines in a pandemic<br>In pandemic situations, the rapid expansion of supply may be required and significant numbers of post-approval changes may be required to support these activities (both scale-up, and scale-out technology transfer to other facilities)<br>Single-use systems (disposable manufacturing equipment) may be used, avoiding or reducing the need to develop and validate cleaning procedures, and also facilitating the rapid expansion of supply<br>In addition, significant numbers of changes may be required for the optimization of the product and manufacturing process<br>Product lifecycle management regulatory tools such as those described in ICH Q12 (e.g., the use of Post Approval Change Management Plans) may be valuable in facilitating changes for medicines in pandemics<br>Data requirements and timings for post-approval changes may be agreed through informal/formal mechanisms for scientific advice with a regulatory agency. Science- and risk-based approaches can be applied to define requirements in pandemics, taking into account considerations such as the control strategy, ongoing process verification, etc<br>Regulatory agencies may collaborate informally or formally to facilitate post approval changes to minimize delays and use regulatory agency resources efficiently (e.g., by adopting good reliance practices (24)) |

**Table I** (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<br>PAIs may be undertaken by some agencies prior to the approval/launch of a new product<br>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<br>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<br>There may be additional regional requirements (typically included in Sect. 3.2.R) that are necessary for dossiers submitted to some ICH members<br>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 nodule, as specified in ICH M4<br>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<br>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<br>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<br>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 |

**Table I** (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 |
|---|---|---|---|
| 20 | Importation testing | Many countries typically require testing on importation | It may be necessary in justified cases to deviate from the requirement for importation testing to avoid delaying the supply of the treatment or vaccine to patients. Importation testing may necessitate analytical method transfers to the receiving country, potentially diverting analytical expert resources from priority activities related to development and supply. For a product that is in limited supply, importation testing may consume a product that is needed by patients<br>Requirements for testing on importation may be waived for treatments and vaccines where release testing has been performed with satisfactory results and the product has been determined to be of suitable quality for patients and has been released |

**Table I** (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 |
|---|---|---|---|
| 21 | GMDP Considerations | Use of full GMP commercial manufacturing facilities and GDP distribution of the product | Accelerated development and supply from clinical or development manufacturing facilities may lead to GMP 'gaps' if used for commercial supply. Remediation of such gaps prior to approval/ launch may lead to delays<br>Appropriate GMDPs should be in place to assure the quality of medicines supplied to patients during a pandemic. Accelerated supply may require that GMDP approaches associated with early clinical phase manufacture are accepted for early commercial supply for a limited period of time<br>Remediation of identified GMP gaps could be addressed as part of post-approval lifecycle activities agreed between applicants and regulators, e.g., as part of a lifecycle plan<br>Limitations in product and process understanding may result in, for example, greater batch-to-batch variation and relatively higher numbers of deviations/investigations. More manual controls, enhanced monitoring, etc. may be necessary and consequently control strategies may be evolving, necessitating submission of post-approval changes<br>Normal GMDP operations may be compromised by the effect of the pandemic, necessitating adaptations to procedures and ways of working. Regulatory agencies may introduce adaptations to GMDP requirements and other regulatory procedures to facilitate ongoing operations related to the manufacture and supply of medicines in a pandemic and to avoid shortages (14)<br>Where possible, the collaboration between regulatory agencies regarding suitable approaches to certain GMP matters (e.g., suitability of reprocessing or release of materials, and validation) can facilitate global supply and consistency in the context of future inspections by different regulatory agencies |

one of the forums for dialogue with industry. In addition, the Access to COVID-19 Tools (ACT) Accelerator was launched in April 2020, by the World Health Organization (WHO) and partners, to accelerate development, production, and equitable access to COVID-19 diagnostics, and medicines (21).

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 WHO and involves experts from across the industry. CMC considerations have been discussed in the COVAX Manufacturing Support Work to Advance Teams (SWAT) including process validation; comparability strategies; stability prediction; specifications setting and testing strategies; post-approval changes; batch testing and release processes; and inspections (22). Some of the key questions are also discussed and addressed in WHO periodic publications, for example, the 1st Technical Brief: Regulation of COVID-19 Vaccines Synopsis from the August to October 2020 COVAX RAG meetings (13). Several such CMC aspects are common across different therapeutic modalities and aligned with the recommendations of this publication. It is particularly urgent to implement such recommendations for vaccines, due to the CMC and regulatory challenges for fast and global (equitable) supply: multiple manufacturing sites/ technology transfers are needed, with evolving analytical, product, and process knowledge; and there are different risks associated to acceleration options, depending on the vaccine platforms. Virus variants make such challenges even more severe, requiring fast and extensive vaccination with existing vaccines, to minimize virus spread, and, at the same time, accelerated development of new or modified vaccines and therapeutics against variants. Successful implementation of CMC strategies would be supported by harmonization of regulatory frameworks for accelerated approvals and reliance on Stringent Regulatory Agencies (SRA) or WHO Prequalification; alignment on data requirements and timings for Post-Approval Changes (PACs); and a global mechanism for recognition of other National Control Laboratories (NCLs) testing. WHO is currently providing valuable recommendations to address the above points, prompting further dialogue among regulators (16, 23).

### What Is the Role of Emergency Use/Conditional Marketing Authorizations?

Pandemic situations may require that non-critical (low risk to patient safety or efficacy) data normally provided at the initial submission stage, are provided (or have to be available) after the authorization of new medicines. Although this can be enabled by using regulatory tools such as protocols that commit to obtaining defined data and standards and may be provided in an initial submission, such an approach might not be the most efficient and rapid approach to the provision of information for accelerated medicines. Fundamentally information supporting the quality of vaccines or therapies used in clinical studies (i.e., 'Investigational New Drug (IND)-like' information) should form the basis for authorization for emergency use, and this authorization is updated as more comprehensive information becomes available. Provision of such information will often be a condition of the authorization for emergency use and this information will be consolidated into a full dossier submitted as a marketing authorization application. This concept is aligned with the principles of emergency use or conditional marketing authorizations (CMAs). Emergency use authorizations (EUAs) have been an essential regulatory tool for the rapid development and approval of the first generation of COVID-19 vaccines and the approval of the first new therapeutic treatments in the US (9). Under an EUA, unapproved medical products can be used in an emergency to treat or prevent serious or life-threatening diseases. Of note is that the EUA-like procedure in the European Union (EU) is not managed centrally by the EMA but is issued by each Member State's competent authority. There is no specific guidance on the CMC requirements for emergency use, and, since the review and approval/authorization are on a national basis, the CMC requirements could potentially differ between member state authorities. In a pandemic, any differences in expectations for quality information between the Member States could adversely affect access to such medicines.

Manufacturing supply chains designed to supply materials for clinical studies will need to evolve and expand to meet the increasing requirements during emergency use and thereafter for full marketing authorization. This will likely require multiple technology transfers and the specifications and control strategy may be refined accordingly during these phases of the early product lifecycle. This is likely to necessitate ongoing dialogue between the manufacturer and regulatory agencies during this evolutionary development.

## Recommendations: Implementation of General Strategies for CMC/GMDP Acceleration to Enable the Development and Supply of Pandemic Therapies and Vaccines

The key publications (2, 3, 6), workshop reports (4, 5), and draft guidance (7–12) describe several best practice approaches for CMC for early patient access and pandemic supply. Furthermore, the development of these materials has documented and highlighted several examples highly relevant to the rapid development and supply of pandemic medicines: including the learnings from the development of pandemic vaccines for Ebola and COVID-19, and many

biological and chemical oncology therapies. Whilst excellent progress has been made in developing core principles, challenges to practical implementation are still encountered despite the agreement between regulators and the industry. There are also additional topics (highlighted in the publications and reports) that need further advancement to enable accelerated CMC development and supply of new medicines for pandemic scenarios.

Reflecting on what has been learned and agreed to-date, the authors note the following:

1. *The substantial need to advance reliance/collaborative assessment*

Work-sharing and reliance between regulatory agencies is a well-established principle in the area of GMP, for example where Mutual Recognition Agreements establish a legal basis for recognizing inspectional activities by one regulatory authority to rely on the expertise of another authority (24). This helps optimization of resources in regulatory agencies and companies, providing a considerable benefit to patients by enabling medicine availability via global supply chains. In pandemics, it would be highly beneficial to extend the concept of collaborative use of available quality expertise to address CMC regulatory aspects of submissions (including EUA/CMA) and variations and thereby facilitate the optimal use of regulator and industry human expert resources globally. The use of Reliance/collaborative assessment processes could also be extended to other supply-related aspects, such as importation testing for vaccines and medicines, and to facilitate (virtual) GMP and pre-approval inspections.

The authors acknowledge that some progress has been made through schemes such as FDA Project Orbis (25) for oncology treatments and the recent EU OPEN program (26) and recommend that further collaboration by stakeholders should be fostered to tackle the significant legislative, procedural, and cultural barriers to global collaboration.

2. *The need for defining early key decision points and streamlined engagement between industry and regulatory authorities on CMC matters*

It is essential for the development and commercial supply of pandemic medicines that the strategy for CMC development and supply (in the pre-and post-approval phases) is agreed upon with regulators globally and early during development. Consistent expectations for the content of CMC development across regulatory authorities are necessary because key CMC decisions are highly inter-related and, combined with compressed timelines, may require careful consideration of trade-offs in areas of development. These trade-offs may include aspects such as optimization of the pharmaceutical dosage form, formulation, supply chain (including manufacturing, testing, batch release sites), manufacturing process, scale of manufacture, control strategy, process validation, and stability strategy. Many of these decisions need to be made early to fully exploit the opportunities to realize early patient access and facilitate supply. In addition, the industry cannot customize manufacturing and controls to satisfy individual regulatory expectations for each market whilst also meeting global demand with the required urgency. Furthermore, for complex products such as vaccines, release to the market involves the review of a manufacturer's production data and quality control test results by the relevant national regulatory authorities (NRA) and national control laboratories (NCL). This may be supplemented by confirmatory laboratory testing by the NCL, all of which add additional requirements to the timeline of CMC development and supply.

For these reasons, a fundamental principle of accelerated CMC development is that early and frequent dialogue between industry and regulators is essential to agree on the Applicant's planned, product-specific approaches to CMC development. But parallel dialogues—between a company and multiple regulatory agencies, and an agency and multiple companies—where regulatory expectations are not clear or aligned strains expert resources in both companies and agencies. There are currently approximately 600 therapies and vaccines approved or under development for the treatment or prevention of COVID-19 (27). As such, companies and regulators cannot allocate the resource or time required to discuss every critical decision on CMC development and supply individually. Hence, it is vital that CMC approaches, which may differ from those in ICH and regional guidelines but which have been discussed and agreed (based on science and risk) as broadly applicable to CMC development and supply for unmet medical needs, can be implemented as efficiently as possible. Globally harmonized agreement on the general principles of CMC acceleration for pandemic situations should streamline product development by reducing the number of interactions and prior agreements needed between industry and regulatory agencies. This would facilitate an efficient and collaborative response to pandemics.

3. *The need to further facilitate 'post-approval' changes*

Accelerated CMC development for early patient access means that work is continued into the post-approval/authorisation phase generally leading to more frequent and more significant post-approval activities. During the period of emergency use, the process for providing updates, confirmatory data, and optimizations/changes may not use conventional administrative approaches designed for making variations to Marketing Authorisations. In the context of this publication, the term 'post-approval' is used to encompass changes reported to regulatory authorities after authorization

for emergency use (by whatever mechanism is defined in the regulatory framework) and approval of a full marketing authorization.

In a global pandemic situation, this ongoing work is amplified by the need to rapidly expand supply to billions of patients, leading to increased challenges for lifecycle management and PACs. Examples of these post-approval CMC challenges include the following:

- Scaling-up of manufacturing, including expanding supplies of raw materials and manufacturing capacity of raw materials and components, to meet patient demand.
- Evolving and aligning the control strategy across markets to incorporate increasing knowledge and experience of the product and process.
- Demonstrating comparability pre- and post-changes when there is limited batch history.
- The ongoing acceptability (e.g., in the context of PACs and inspections) of approaches accepted in the original application (e.g., use of extensive modelling in establishing a shelf-life/retest period).
- Modifying or implementing approved Post-Approval Change Management Protocols (PACMPs).
- In the future, defining and revising the established conditions for a product, due to evolving process knowledge.

It is important to recognize that for many accelerated pandemic medicines, the generation of confirmatory data, and data to fulfil regulatory commitments associated with approval for emergency use, will be a continuous activity during assessment and into the initial phase of commercial product supply. It is acknowledged that recommendations already made for COVID-19 by regulators such as EMA (14) and FDA (9, 11), (including rapid scientific advice, rolling review, and proposals for compassionate use) are positive steps forward. The authors believe there are also opportunities to consider adapting such regulatory tools for review and approval of CMC PACs, including for products for unmet medical need. Although ICH Q12 Product Lifecycle Management reached step 4 consensus in November 2019, implementation of Q12 by ICH members had just started with the transition of the Expert Working Group to an Implementation Working Group when the COVID-19 pandemic emerged. Consequently, full understanding and experience of the regulatory tools described in the Q12 guideline that are intended to facilitate PACs and product lifecycle management have not yet been achieved across industry and regulatory agencies globally.

Reflecting on the above, the authors recommend:

- Improved planning and alignment among regulatory authorities to establish a harmonized and consistent approach for regulatory applications and inspection criteria for pandemic situations, as well as for acceleration of medicines for unmet medical needs.
- Continued efforts aimed at harmonization of requirements for post-approval changes (variations) globally, with a focus on science- and risk-based regulations and guidance.
- Optimization of the avenues for provision of data post-authorization in addition to the established procedures (i.e., via implementation of commitments agreed in marketing authorizations, use of PACMPs, and science- and risk-based variations regulations and guidance)
- Exploiting the full functionality of PACMPs (e.g., via greater flexibility in timelines, modifications and details, and broader scope), established conditions, and other tools described in ICH Q12 to facilitate product lifecycle management
- Ensuring that emergency use/conditional marketing authorizations allow specifications to evolve as product and process knowledge is developed. For example, allowing initial, interim acceptance limits that are wider than the available batch data, which may then be tightened as justified by the development of additional data that consider clinical relevance (28). In certain cases, impurities may be included in the specification while data are accrued to demonstrate their clearance (7). As outlined in Table I, Topic 8 (Commercial Product Specification), it is not considered viable to implement tight specification ranges that would incur an elevated risk of batch failure and unnecessary discard of an otherwise good product. Continuation of close collaboration between regulators and industry into the post-authorisation phase, including consideration of innovative approaches to meet GMDP requirements.
- Agreement with regulatory agencies on CMC development plans (or quality lifecycle plans') specific to accelerated products as a tool to describe the quality development and product lifecycle planning.

There will be many cases where the product and process understanding, control strategy and supply chain maturity at the time of filing for a pandemic medicine may be evolving rapidly, necessitating significant PAC to achieve a "business as usual" steady state. Transparent, ongoing communications for lifecycle management of accelerated development of pandemic products (note that plans may be revised frequently due to the dynamic situation during pandemics) could help to facilitate changes that are anticipated, such as those for scale-up and scale-out of production, as well as the delivery of commitments made as part of EUA or CMA approval.

Evolution of the tools to facilitate PACs will expedite upfront agreement to CMC requirements, rolling review of marketing authorisations, and the changes needed post approval to ensure ongoing supply. Addressing these needs

could help to ensure rapid patient access to pandemic medicines and help mitigate any potential supply outages without increasing the risk to patients. Overall, further collaboration and dialogue between industry and regulators would be beneficial to explore new tools and harmonised ways of working for product lifecycle management to facilitate the security of global supply of pandemic medicines.

4. Fully exploiting prior and platform knowledge

Prior knowledge is an indispensable tool for accelerated development of medicines because it provides extensive additional information and assurance beyond product-specific information.

It was explicitly recognized at the 2017 EMA Joint QWP/BWP stakeholder workshop on prior knowledge (4) and at the 2018 EMA/FDA workshop on quality considerations related to PRIME/Breakthrough Therapy (5) that prior and platform knowledge is a vital and underused scientific tool available to accelerate many CMC deliverables for development and supply, including informing risk assessments; identification of Critical Quality Attributes (CQAs); development of control strategy elements such as identification of Critical Process Parameters (CPPs); informing specification limits, informing comparability; selection of container-closure and device; process validation; and shelf life. Table I also includes additional examples of the use of prior and platform knowledge.

In the context of pandemic-driven CMC development and supply and under extremely shortened timelines, these tools become even more relevant, often simply due to the lack of alternatives. Consequently, it is of crucial importance for regulatory decision-making in a pandemic setting to strike a balance between the need for product-specific data and the use of prior knowledge, wherever appropriate.

Regarding the efficient use of prior knowledge, the following are suggested:

- The relevance and application of prior knowledge should be confirmed as soon as possible (e.g., through agency kick-off meetings or scientific advice).
- It should be agreed which aspects of prior knowledge are used to complement, or substitute for, product-specific data. A risk assessment should discuss any remaining uncertainties arising from the use of prior knowledge that will be addressed post-approval. In this manner, transferable prior and platform knowledge can significantly help to justify greater flexibility in the compilation of quality data, allowing certain quality data supported by prior knowledge, to be accepted or deferred into the post-initial authorization phase.
- An important regulatory question is how to enable the use of prior knowledge in an efficient way, avoiding the need for extensive 're-justification' of the knowledge. Aspects for further discussion between regulators and industry could include cross-referencing the prior knowledge data and/or re-using data from previous assessments to further facilitate development and specific regulatory processes such as platform technology master files.

Overall, to maximally facilitate global development and supply of pandemic medicines, diligent implementation of prior and platform knowledge will be essential**.**

5. Review and potential revision of legal frameworks

Considerable progress has been made to date with international harmonization activities under the umbrella of ICH, WHO, or Pharmaceutical Inspection Co-operation Scheme (PIC/S). Equally, harmonization work arising from the COVID-19 pandemic (e.g., via ICMRA) will remain a priority in the industry recommendations. Optimal agency review, approval, and product launch require a common structure to the submitted documentation, alignment on the type of required information, and mutual acceptance of internationally recognized standards, including pharmacopoeias. The use of well-proven harmonization mechanisms such as ICH can address the technical aspects, but perhaps other mechanisms to enable regulatory agencies to rely on the scientific assessments of experts in other agencies could also be important (24). It is acknowledged that the CMC early access approaches that are proposed in this publication, including the use of reliance practices, could necessitate some revision of the current legal frameworks of several agencies. It is therefore vital that any incompatibilities with the legal framework are identified, and the consequences for patients and pandemic preparedness can be discussed with legislators.

## Conclusions and Next Steps

Has there been a greater need for accelerating CMC approaches than in bringing COVID-19 pandemic therapies and vaccines to the waiting world population? The success achieved in the development and authorization of new vaccines and therapies for COVID-19 and the supply of billions of doses in very rapid timescales provides a rich set of experiences—positive and negative—on which to base future collaborative efforts by all stakeholders to introduce improvements facilitating accelerated CMC development and supply; ultimately enabling all stakeholders to be better prepared for the next pandemic emergency.

Learnings from the current COVID-19 pandemic provide an opportunity to define those CMC approaches (which may differ from approaches outlined in ICH and

regional guidelines) that build on prior knowledge and science- and risk-based approaches already discussed and agreed as broadly applicable to accelerated CMC development and supply. The authors have identified current approaches that could be adapted to support accelerated CMC development and supply for earlier patient access to pandemic medicines (Table I).

It is vitally important for industry and regulators to work together to explore how these approaches could be implemented efficiently in future pandemics. This would facilitate the dialogue between companies and regulatory agencies on the acceptability of such approaches, and the associated data requirements for specific development projects.

The authors also believe that it is critical for regulatory authorities to establish principles for regulatory authority collaboration and alignment prospectively, before the next pandemic. Companies found that having to engage with each regulatory authority and their respective governmental distribution organizations to negotiate regulatory criteria for authorization and distribution of innovative pandemic medicines in each market was a significant challenge, and the ICMRA Workshop report concluded that there are opportunities for further collaboration, alignment, or harmonization to enable a more efficient and effective global regulatory approach.

Overall, the recommendations in this publication are intended to contribute to the discussion on approaches that can result in earlier and greater access to high-quality pandemic vaccines and therapies for patients worldwide and significantly reduce potential drug shortages. The opportunity to further develop and agree on such approaches will be enormously beneficial to all those working to rapidly develop and deliver vital medicines as part of pandemic response, and such approaches could also be useful in a post-pandemic setting for innovative medicines addressing unmet medical needs.

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**Conflict of Interest** The authors are employees of their respective companies and declare that some of the participants in the authoring group own stocks in their company.

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