European Federation of Pharmaceutical Industries and Associations

EFPIA White Paper on CMC development, manufacture and supply of pandemic COVID-19 therapies and vaccines

Executive Summary

This paper provides focused recommendations for CMC and GMP approaches to support the development of new COVID-19 pandemic medicines.

In considering how to address the challenge of expediting the development of new medicines, EFPIA has worked with regulators for a number of years[1,2,3] on innovative CMC approaches and principles that can facilitate rapid science and risk-based development of new high-quality medicines. Building on these earlier interactions, EFPIA intends that this paper can be used by regulators and companies to implement such accelerated CMC approaches for the development and supply of COVID-19 medicines.

Introduction

The EFPIA Medicines Adaptive Pathways to Patients (MAPPs) initiative is a framework addressing accelerated, adaptive approaches to development approval and the lifecycle of new medicines. It aims at faster translation of scientific breakthroughs to new, high quality medicines.

In considering how the challenge of expediting the CMC development of new medicines can be met, EFPIA proposed in its 2017 MAPPs CMC paper[1] key principles and strategies to facilitate rapid science and risk-based development of new, high quality medicines. These were expanded upon using experience of real case studies at the EMA/FDA 2018 PRIME/BT Quality workshop[2] and the 2017 EMA prior knowledge workshop[3]. Most recently, many significant and impactful proposals to address the need for rapid development and supply of COVID-19 medicines have been made in the 2020 IFPMA communication to ICMRA "*Collaborative, coordinated scientific assessments between national medicines regulatory agencies enhance speed of regulatory approvals*."[4]

This paper is intended to support implementation of the MAPPs/acceleration CMC principles developed by regulators and industry to-date in development and supply of COVID-19 therapies and vaccines. It includes detailed recommendations that should be acceptable for development and supply of all such COVID-19 medicines.

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[1] EFPIA-EBE White Paper on Expedited CMC Development: Accelerated Access for Medicines of Unmet Medical Need – CMC Challenges and Opportunities (Final Version - December 2017)

[2] Stakeholder workshop on support to quality development in early access approaches, such as PRIME and Breakthrough Therapies, 2018

[3] Joint Biologics Working Party / Quality Working Party workshop with stakeholders in relation to prior knowledge and its use in regulatory applications, 2017

[4] See "*Appendix 1: Collaborative, coordinated scientific assessments between national medicines regulatory agencies enhance speed of regulatory approvals*" IFPMA, May 2020

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The 1st intent/standard approaches in this document should form the basis of rapid discussion and dialogue with the EMA QWP, BWP and IWG, and such discussions should form the basis of specific actions and dialogue with global regulatory authorities in US and elsewhere.

Problem Statement

The innovative pharmaceutical industry is focused on rapid discovery, development and delivery of new vaccines and therapeutic treatments to address the COVID-19 pandemic, which has emerged as an unprecedented threat to global health. Billions of people are impacted by the COVID-19 pandemic and the rapid development, manufacture and large-scale supply of vaccines and therapeutic treatments for COVID-19 can address this crisis.

Given the scale of the worldwide patient population at risk from COVID-19, industry needs to proactively address the Quality (CMC/GMDP) and regulatory aspects associated with the manufacturing and logistical demands of rapidly providing billions of doses of new medicines and vaccines to save lives. This is an unprecedented challenge and requires new thinking.

In Europe, the EMA have begun this transformation by looking in detail at the challenges presented by COVID-19 to the supply of vital medicines for acute treatment of COVID-19 therapies[5], and the development of new products[8]. Similar programs and guidance are under development by FDA in the US and, more globally, through dialogue that has begun between industry and ICMRA.[4] Such initiatives are a welcome beginning and specific elements are noted below where linked or aligned to the recommendations in this paper.

A Paradigm Shift - EFPIA's Principles and Tactics for MAPPs applied to the development and supply of all COVID-19 therapies and vaccines

In considering how the challenge of expediting the CMC development of new medicines can be met, EFPIA proposed in its 2017 MAPPs CMC paper[1] principles that will facilitate rapid science and risk-based development of new high-quality medicines. Expanding upon these principles to the development and supply of COVID-19 pandemic medicines, the following points must be considered:

- Fundamentally, the principle that accelerated CMC approaches must always ensure product quality and patient safety whilst enabling the earliest access for patients, is unchanged for COVID-19 medicines.
- EFPIA's assessment of the situation has identified areas where current paradigms will need to adapt radically to support development. The current status of implementation of approaches to accelerated CMC development, approval and supply of new medicines is not enough for a pandemic of the scale of COVID-19 since therapies and vaccines must reach billions of patients in a very rapid timescale.
- Early decision making and agreement with regulators on CMC development and supply (including how to scale-up, scale out and implement post launch changes) is essential.
- Detailed, case-by-case discussion of all accelerated Quality/CMC elements of the development, commercial application and global supply of therapies may not be achievable in a highly accelerated, pandemic setting. CMC strategies proposed in the EFPIA MAPPs paper should be accepted by all parties as the backbone of CMC approaches for COVID-19 medicines.

Collectively, these considerations require a paradigm shift in how accelerated CMC development and supply is progressed globally. In the light of this, and in order to deliver the paradigm shift required, the following recommendations are made by EFPIA:

- For regulators and companies globally to further develop and fully implement all recommendations from the EMA/FDA 2018 PRIME/BT Quality workshop[2], the 2017 EMA prior

[5] QUESTIONS AND ANSWERS ON REGULATORY EXPECTATIONS FOR MEDICINAL PRODUCTS FOR HUMAN USE DURING THE COVID-19 PANDEMIC, EMA, 2020

knowledge workshop[3] and the EFPIA MAPPs CMC paper[1] for all potential COVID-19 therapies and vaccines.

- For simplification and global coordination of mechanisms and guidance to support flexible science and risk-based approaches for post-approval changes to enable the rapid scale-up or scale-out needed to supply medicines on an unprecedented scale (further details see below, point 3).
- That mutual reliance of unprecedented scope and scale for Quality is required. Work-sharing and reliance between FDA and EMA are expected to be at the core of such approaches, but that eventually a coordinated use of available Quality expertise globally would be required. As a minimum, such approaches would address Quality elements such as importation testing for vaccines and medicines globally, (virtual) GMP inspections, GDP, etc. and would ideally include full reliance for GMP oversight and Quality review of medicines applications and variations between regions.

Next steps: Recommended approaches for Industry and Regulators

Through the drafting of the MAPPs paper[1] and the discussions related to accelerated Quality development, industry and regulators agreed on a number of principles for CMC acceleration. The 2017 Prior Knowledge and 2018 PRIME/Breakthrough Therapy workshops also included a large number of real case-studies and examples highly relevant to the rapid development and supply of COVID-19 medicines, including the learnings from the development of pandemic vaccines for Ebola and many biological and chemical oncology drugs.

Whilst excellent progress was made, some of these approaches still require practical implementation following agreement by regulators and industry and there are also additional key topics that industry have highlighted since the publication of the summary reports of the workshops which will be key to further accelerating CMC development and supply.

It is also acknowledged that the level of acceptance of new acceleration paradigms should carefully consider the risk/benefit ratio. For example, therapeutic treatments may be needed by critically ill patients, whereas vaccines are administered to healthy subjects, some of whom may be considered at very high risk in a pandemic. Nevertheless, most of the CMC acceleration principles here reported can be applied to therapies and vaccines[6], and in the current emergency there may be ways of generating and providing information or updates to facilitate ongoing development outside of the standard approaches.

Taking stock of what has been learned and agreed to-date, EFPIA makes the following points:

1. The need for early decision making, and to streamline engagement with regulatory authorities on CMC matters

It is vital for the development and commercial supply of COVID-19 medicines that the strategy for CMC development (in the pre-and post-approval phases) is agreed early.

For this reason, a fundamental principle of MAPPs and the PRIME and Breakthrough Therapy programs is that early and frequent dialogue between industry and regulators are essential to agree product specific approaches to CMC development. However, there are currently over 200 therapies[7] and vaccines under development for the treatment or prevention of COVID-19 and that number is expected to grow significantly. As such, companies and regulators cannot allocate the resource or time required to discuss every CMC development program 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 (on the basis of science and risk) as broadly applicable to accelerated CMC development and supply can be implemented as efficiently as possible, without the necessity for prior agreement with multiple regulatory agencies.

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[6] Vaccines Europe *paper "Assessment of barriers and bottlenecks to the rapid development and authorization of COVID-19 vaccines",* May 2020

[7] See https://milkeninstitute.org/covid-19-tracker

2. Simplification and global coordination of regulatory mechanisms and guidance to support science and risk-based approaches for post-approval changes

At the 2018 PRIME/BT workshop there was recognition of a need to develop regulatory tools and procedures to facilitate the registration of accelerated development products. Amongst these were:

- Avenues for provision of data during post-authorisation in addition to the established procedures (i.e. PACMPs, variations, recommendations, Annex II conditions)
- PACMPs (flexibility in timelines, detail and scope, specific guidance on PACMP application for ATMPs)
- CMC development plans (or 'quality lifecycle plans') specific to PRIME quality packages as a tool to describe the Quality development and product lifecycle planning.
- Continuation of PRIME/BT product support in the post-authorisation phase and opportunities for communication, even into inspection areas

It is clear that accelerated development, use of Emergency Use Procedures and supply of COVID-19 medicines will be impacted by all of these elements and that need for global supply to billions of patients will bring increased challenges for lifecycle management and post-approval changes. Examples of these challenges include:

- Challenges in scaling-up manufacturing to meet patient demand
- Challenges in modifying control strategies to accommodate evolving process understanding
- Challenges in demonstrating comparability because of limited batch history
- Challenges with the ongoing acceptability in the post-approval changes and inspections of novel approaches accepted in the original application (e.g. use of extensive modelling in establishing a shelf-life or retest period)
- Challenges in modifying or implementing approved PACMPs as a result of evolving process understanding

It is important to recognise that for most accelerated COVID-19 medicines, development will be ongoing during assessment and into the product lifecycle. While it is acknowledged that recommendations in the EMA initiatives paper[8], such as rapid scientific advice, rolling review and proposals for compassionate use are positive steps forward, it must be clear how these will be applied during CMC review and for post-approval changes.

These tools will help expedite upfront agreement to CMC requirements. Rolling review is seen as essential for CMC information, particularly in areas of process validation, evolving control strategies and stability.

However, there are many cases where the product & process understanding, control strategy and supply chain maturity at the time of filing may be evolving rapidly, necessitating significant post-approval change in order to achieve a "business as usual" steady state. Presentation of the plan of how to achieve full product maturity could help the reviewer understand not only the original file, but also facilitate change post-approval. Addressing these needs could help to ensure rapid patient access to COVID-19 products and help mitigate any potential supply outages without increasing the risk to patients.

Considerations of the role of post-approval commitments to ongoing studies under a robust Pharmaceutical Quality System to confirm and/or update the product control strategy, shelf life etc. should be further enablers for the recommendations in this paper.

Overall, in order to ensure rapid and secure global supply of COVID-19 preventative and therapeutic products, it is considered necessary to recognise the particular needs of CMC and to adopt new tools for product registration and lifecycle management with urgency.

3. Embedding the use of Prior and Platform Knowledge

Prior knowledge is an indispensable tool for rapid 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[3] and at the 2018 EMA/FDA workshop on Quality considerations related to PRIME/Breakthrough Therapy[2] that prior and platform knowledge is an established scientific tool available to accelerate many CMC deliverables for development and supply, including:

- Informing risk assessments
- Identification of CQAs
- Control Strategy (including identification of CPPs)
- Manufacturing Process validation
- Informing assessments of comparability
- Justifying shelf life and the overall stability strategy
- Leveraging platform analytics
- Use of 1st intent container closure systems and devices
- Viral Safety

Table 1 in this paper also includes additional examples of the use of prior and platform knowledge.

In the context of COVID-19 driven CMC development and supply and the further, 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 application of regulatory flexibility based on the use of prior knowledge wherever appropriate.

Regarding the use of prior knowledge, it is advised that:

- The relevance and application of prior knowledge should be confirmed as soon as possible (e.g. during agency kick-off meetings, Scientific Advice).
- It should be agreed which aspects of product-specific data prior knowledge is used to complement or substitute for, and how any remaining uncertainties arising from the use of prior knowledge will be addressed post-approval. In this manner, prior & platform knowledge can significantly help to justify greater flexibility in the compilation of quality data allowing certain quality data to be accepted supported by prior knowledge or deferred into the post-initial authorisation phase.
- Regulators should also consider how to allow most efficiently cross-referencing and/or re-using data from previous assessments to further facilitate development.

Thus, to facilitate global development and supply of COVID-19 medicines, diligent implementation of prior and platform knowledge will be essential.

1st intent, recommendations for Regulators and Industry

In Table 1 below, industry experts have summarized some of the most impactful approaches for CMC/GMP acceleration and supply and make recommendations as to how these should be generally applied to the development and supply of COVID-19 medicines.

This table is not intended to be comprehensive.

Table 1: Recommended accelerated CMC/GMP approaches for development and supply of COVID-19 therapies and vaccines

	Topic	Critical path CMC activity and traditional approach	Accelerated CMC aligned approach for COVID-19 therapies and vaccines
1	**Process and product and supply chain changes, scale-up, scale out**	Implementation of significant numbers of post-approval changes will be required for many medicines (e.g. therapies and vaccines for COVID-19, supportive care therapies for COVID-19 patients (e.g. respiratory relief medicines for ICU patients) and to support maintenance of supply chains impacted by the need to manufacture COVID-19 medicines) in order to enable supply on the scale required. Accelerated, harmonized approaches to enable efficient introduction of changes are essential to COVID-19 patients.	• Data requirements and timings for post approval changes should be agreed early and efficiently through informal or formal scientific advice and globally, minimizing delay, repetition and inconsistency by leveraging reliance mechanisms. • Such requirements should always be science and risk-based, taking into account considerations such as the control strategy and companies' approaches to ongoing process verification. • Tools such as those described in ICH Q12 (e.g., the use of general/broader PACMPs for types of change, the concepts of established conditions and product lifecycle management plans) should be implemented for COVID-19 medicines in all ICH regions.
2	**Accelerated approaches to development of the commercial Specification**	Efficacy, quality, and safety principles are paramount and testing methods and specifications are established based on standards and ranges from the experience gathered from testing results of the lots used in pivotal clinical trials.	• There will be limited number of clinical lots as well as reduced amount of process characterization data available at the time of submission. Consequently, regulators and Industry should establish interim commercial specifications defined on the basis of patient risk, supported by prior knowledge. • Approval of specifications wider than the available batch data will be necessary to ensure uninterrupted supply. • In such cases applicants should provide a plan for how specifications will be further developed and evaluated over time and revised if required. A flexible PACMP is a helpful tool to support updates to specifications over the lifecycle

	Topic	Critical path CMC activity and traditional approach	Accelerated CMC aligned approach for COVID-19 therapies and vaccines
3	**Control strategy considerations specific for Vaccines**	Given the unique and complex nature of vaccines, it is important to integrate product understanding, process control strategies and analytical control strategies, and ensure a structured approach for evolving knowledge in pandemic situation. Current worldwide heterogeneity with regards to CMC requirements in particular, including Pharmacopoeias, as well as regulatory processes represents limiting factors in terms of having the maximum industrial flexibility adapted to the demand, without any added value for patients, and does not allow to maximize the use of our industrial assets. For instance, there are more than 40 pharmacopoeias in the world. Meeting the specific requirements of each of them is not possible and is a barrier to industrial and supply flexibility Compared to other modalities, vaccines are diverse products, hence the level of risks/ acceptance associated to the proposals may vary depending on the prior knowledge and degree of complexity of product and process	Deliver vaccines based on an expected Target Product Profile (including presentation, shelf life, storage conditions), as provided by WHO[8] and agree on the minimum data required at time of submission, with product-specific considerations based on available prior knowledge (within and across companies) and stability prediction studies; this may be different depending on the vaccine platform. Acknowledge evolution of product, process and control strategy along the development, and lifecycle of the vaccine, leveraging risk- based approaches (ICH Q8), and tailored comparability packages. Coherently, adopt phase- appropriate expectations for specifications prioritizing safety and potency assessment privileging *in vitro* testing. Agree with regulators on the use of innovative technologies during development and after launch ensuring reliable and high- throughput product and process monitoring. Leverage on dose finding to support product understanding/ control strategy evolution. Utilize risk-based approaches (based on ICH Q9) for defining the appropriate levels of validation for equipment, process and analytical methods at time of submission, applying thinking in terms of benefit to patient. Establish a global approach regarding release testing by Official Medicines Control Laboratories (OMCL), that includes mutual recognition between countries, to avoid delays in availability of COVID-19 vaccines in EU and non- EU countries. Define strategy for multiple presentations, ideally fitting all markets.

[8] *WHO Target Product Profiles for COVID-19 Vaccines* 9 April **2020**

	Topic	Critical path CMC activity and traditional approach	Accelerated CMC aligned approach for COVID-19 therapies and vaccines
			It is important to have support from health authorities in advocating for harmonization of Pharmacopoeias and have COVID-19 vaccines to meet only one single standard, globally recognised. More broadly, health authorities should provide increased support advocating for global harmonization requirements, regulatory processes, and mutual reliance of unprecedented scope and scale between regions.
4	**Science and risk-based methodologies for determining stability/shelf life**	Stability is frequently on the critical path for drug substance and/or drug product development and medicine supply. Changes during development (many of which may be unplanned/"*late breaking*" during development or post launch for COVID-19 medicines) could be delayed by having to wait for real time stability data. The rigid application of ICH Q1 and Q5C principles (whose scope is in support of marketing applications), together with the core stability data package exemplification and requirements for real time data, can impact the start of clinical investigations and impact decisions to make changes during development. Alternate stability approaches can support rapid development by taking the 'real time' stability study clock off the critical path, allowing data generation under normal conditions to become confirmatory rather than pivotal in developing product understanding and may also be used in support of a proposed change. Similarly, real-time stability data to determine the storage condition and shelf-life of investigational	There should be acceptance of the use of alternative approaches to the determination of stability than that defined in ICHQ1 and Q5C, and in regional guidance in support of all development and registration activities and post approval changes where required, including: • Alternate design of studies e.g. reduced studies where justified on the basis of utilisation of prior knowledge including relevant company knowledge, 1st principles and the scientific literature • Use of accelerated (but relevant) conditions of temperature and humidity to provide increased knowledge more rapidly • Taking a science and risk-based approach to the definition of what is a "representative" batch of API or Drug Product (e.g. based on scientific justification of the impact of changes in process of scale-up) • Use of (or greater use of) extrapolation and/or data modelling to predict stability under normal storage conditions more rapidly and to establish shelf-lives for product registration and for post approval changes • Post-change comparability stability studies done using accelerated conditions on representative material • 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.

	Topic	Critical path CMC activity and traditional approach	Accelerated CMC aligned approach for COVID-19 therapies and vaccines
		materials should be taken off the critical development path.	• In general, the provisions of ICH Q12 Chapter 9 (Stability data approaches to support the evaluation of CMC changes) should be fully leveraged post-approval and be acceptable to the regulatory agencies. • Similarly, the stability, storage condition and shelf-life of investigational materials can also be supported using accelerated approaches, again taking real-time stability off the critical development path. • Deferral[5] in the EU of routine stability testing, where justified, to focus resources on product release testing is also a welcome consideration to liberate vital resources for ensuring continued supply of crucial medicines used for treatment of patients infected with COVID-19

5	**Additional stability/shelf life considerations for biological drugs and vaccines**	There are additional considerations for justifying shelf life for biological drugs and vaccines which can significantly impact medicines' development and availability, including:
		• The need to identify stability-indicating CQAs for the stability program.
		• The need for a minimum 6 months data for 3 lots, at minimum of pilot scale. PPQ lots would typically be used on stability and used for launch.
		• Shelf-life being restricted by the need for real-time, real condition data with no extrapolation. Minimum workable shelf-life requires 18 months stability data but 24 months is desired to optimise supply/demand from initial commercial batches (e.g. PPQ runs).
			• Focus stability testing on the most critical stability-indicating PQAs, considering the mode of action; when possible, use method options with reduced assay variability to improve monitoring of PQA trends, e.g. ligand (antigen) binging assay rather than cell-based assays. This may also speed up assay development.
			• Streamline stability and modelling approaches to stability and shelf-life determination, for example:
			  ○ When there is sufficient product-specific stability data, accept 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.
			  ▪ Available, 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, kinetically and statistically analysed to support extrapolation and estimate impact of potential temperature excursions (cold chain breaks)

	Topic	Critical path CMC activity and traditional approach	Accelerated CMC aligned approach for COVID-19 therapies and vaccines
			○ When there is insufficient data for direct extrapolation of stability data and prior knowledge exists, accept extrapolation to a maximum time-point of suitable prior knowledge stability data, e.g. 3 months product-specific data extended to a shelf-life based on transferable prior knowledge data from like-molecules and the stability specification.
6	**Science and risk-based approaches to Comparability for changes to biological drugs and vaccines**	Full analytical comparability assessment, including extensive characterization and stability data	It is recommended that companies perform a risk-based analytical comparability assessment of manufacturing changes, to evaluate a subset of high risk CQAs that are known (via prior/platform knowledge) to have 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 later section on stability). In addition, the comparability strategy may vary depending on the nature of the change and supporting process evolution. In case where prior knowledge is limited, companies should apply a "clinical development" type approach to comparability aimed at demonstrating the preservation of quality attributes, without the additional requirement of process consistency.
		Clinical comparability studies proactively planned and performed to prevent delays that would be incurred if they are scheduled after analytical comparability results become available	In a pandemic situation, where only a few doses are likely to be administrated to the patient, clinical comparability studies should not be required. The exception would be if the analytical assessment finds significant differences in high risk CQAs that could impact safety and/or efficacy. 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.
7	**Comparability for chemical drugs: considerations**	A typical BE study takes 6 months from start to finish and therefore it is essential to streamline approaches to demonstrate bioequivalence for oral drug products through broader application of biowaivers. These can safely be extended beyond the current boundaries of	It should be the founding principle that considerations for demonstration of bioequivalence should be based on scientific assessment of the potential impact of any drug product change on-clinical performance.

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	for bioequivalence	BCS/ICH M9 leveraging on the rapidly evolving set of biorelevant *in-silico* and *in-vitro* tools. Prior agreement of the tests and acceptance criteria to be used on a drug specific basis using a science and risk-based approach will be essential both for ensuring timely and widespread patient access to: • existing oral therapies effective against COVID-19 itself or therapies essential for ongoing supportive treatment of COVID patients, that will need to be manufactured at greater scale to meet the increased demand; novel oral therapies proven effective against COVID 19, e.g. for including rapid bridging between small scale clinical formulation and large-scale production formulation, and to enable scale-up/scale out and optimization of manufacture.	Furthermore, regulators and industry should accept appropriate utilisation of advanced biorelevant *in-vitro* tools and *in-silico* Physiologically Based Pharmacokinetic (PBPK) models to ensure that: • Bioequivalence is based on the identification of product quality attributes critical for *in-vivo* performance which are at the heart of considerations for comparability • 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; Clinically relevant control strategies are developed to support rapid scale-up and supply chain robustness, and guarantee supply continuity for essential products like COVID-19 therapies, minimizing the risk of supply shortage.
8	**Justification of Control strategies for impurities in Chemical Drugs**	In accelerated development, both synthetic route and process changes are very likely to be required as the route is scaled up to commercial phase. This can result in the presence of new impurities that are not qualified in animal safety studies. Current approaches are framed by the requirements defined within ICH Q3A / Q3B although these guidelines provide some apparent flexibility in terms of qualification the presence of a new impurity greater than the qualification limit often triggers the need for further animal testing. Such testing significantly adds to development timelines i.e. a 28	As established in the 2017 paper by Harvey et al[9], it should be generally accepted that non mutagenic impurities at levels of 1 mg/day have been established as safe over a lifetime and hence for COVID-19 related treatments it should 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) Furthermore, the Harvey paper also presented a position in relation to the modification of limits based on duration of treatment, aligning this to a modified form of Haber's Law. Again, it is believed this is entirely appropriate in the context of COVID-19 related treatments and that the combination of these proposals would significantly reduce the risk associated with changes to the manufacture of the

[9] *Regul Toxicol Pharmacol.* **2017;** *84* 116-123 Harvey J; Fleetwood A; Ogilvie R; Teasdale A; Wilcox P; Spanhaak

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		day study in a rat will typically take up to 6 months to complete and report all findings. Such testing is standard practice despite the EMA recognizing the limited value of such tests and specifically their inability to detect any toxicity associated with impurities at the levels tested.	active delaying approval due to presence new low-level impurities that present a very low risk especially for short duration treatments needed to treat COVID-19. Overall, a framework similar to the risk-benefit considerations described in ICH S9 should be considered for COVID-19 therapies.
		Development of tests and other controls for possible non mutagenic chemical impurities require 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) to identify potential impurities and establish suitable control strategies. Such studies can be critical path activities for development of API supply chains and essential post approval route and process modifications required to support scale-up and supply. Such activities can be amplified where low-risk impurities are then included on specifications for API starting materials, intermediates and drug substance.	It should be generally accepted that: • A science and risk-based approach is appropriate to defining which impurities present a risk and need to be controlled as per ICH Q11. • Such justifications can come from 1st principles considerations or models (e.g. based on solubility, chemical reactivity and other relevant factors).
9	**Mutagenic Impurities**	ICH M7 already permits flexible control options allowing the use in the case of Option 4 assessment of the interrelationship between the properties of an Mutagenic Impurity and the processing conditions to determine the fate of the impurity without the	It is critical that this is employed in the context of COVID-19 medicines to avoid delay caused by the need to develop highly sensitive methods where calculations show the risk to be very low (Teasdale et al, Barber et al)[10] and that this approach can be employed for all MIs including those that are part of the Cohort of concern.

[10] Barber, C.; Antonucci, V.; Baumann, J.-C.; Brown, R.; Covey-Crump, E.; Elder, D.; Elliott, E.; Fennell, J. W.; Gallou, F.; Ide, N. D. A Consortium-Driven Framework to Guide the Implementation of ICH M7 Option 4 Control Strategies. *Regul. Toxicol. Pharmacol.* **2017**, *90*, 22– 28

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		requirement for specific analytical data (i.e. purge calculations)	
10	**Analytical Procedures**	Development, validation technical transfer and post-approval changes to analytical procedures and technologies are essential tools for process understanding, QC and to support product and process changes. Even minor changes typically require regulatory activity.	Subject to appropriate risk assessment, it should be generally accepted that: • Analytical methods and technologies will more likely change during late development and post approval and that a science and risk-based approach should be appropriate in bridging/equivalence studies • The use of clinical-phase validation approaches for commercial procedures can be appropriate where justified, for example analytical qualification rather than validation initially, justified on a risk basis. Establishment of an analytical target profile[11] (ATP) can enable fast optimization of procedures and/or implementation of alternative analytical procedures and technologies and to facilitate changes • Fast implementation of changes to procedures and reference standards after launch can be supported by lifecycle management tools and processes (e.g. through the use of general PACMPs, including references to relevant sections of ICH Q12) • Qualification (demonstration of fitness-for-purpose) of non-pharmacopoeial methods can be an appropriate approach where justified. • Leveraging of prior- and platform knowledge (of both the product and analytical technology) can simplify technology selection and validation and that validation can be significantly streamlined by the use data generated during development.

[11] Using the Analytical Target Profile to Drive the Analytical Method Lifecycle, *Anal. Chem.* **2019,** *91*, 4, 2577–2585

	Topic	Critical path CMC activity and traditional approach	Accelerated CMC aligned approach for COVID-19 therapies and vaccines
11	**Alternative approaches to process validation**	Process validation is commonly a critical path activity for the commercial application and many post approval variations, in particular where such data is required as part of the application (e.g. for sterile drug products or novel manufacturing technologies). It is accepted that risks associated with process validation can be alternatively mitigated through provision of protocols, the product control strategy, concurrent validation (as in EU GMP Annex 15) and/or continuous process verification, particularly where there is extensive prior and platform knowledge, however, agreement of such approaches is often challenging to achieve.	It should be generally accepted that: • Concurrent validation should be recognized globally as a suitable tool for COVID-19 medicines to deal with assurance of manufacturing consistency for authorisation or post-authorisation, as already applied to synthetic products and recently confirmed by EMA.[5] This approach could also be applied when scaling up or out. • Process validation protocols can be simplified based on risk assessments where there is appropriate platform/prior knowledge (e.g. a focus on validation of critical steps only) and a suitable control strategy, supported by continuous process verification where appropriate and ongoing process verification. • It is acceptable to waive requirements for actual process validation data to be included in the application or variation where justified by risk assessment and where a suitable process validation protocol is supplied.
12	**Considerations for GMP**	Rapid development and lack of knowledge in accelerated scenarios may lead to GMP gaps, of low risk to the product compared with the patient benefit. If remediated prior to approval/ launch this may lead to delays, especially where first intent supply chains cannot be used, e.g. where companies use Contract Research/ Manufacturing Organizations (CROs/CMOs, oriented to IMP or early commercial supply) where process understanding and control is still developing and manufacture can rely more on process monitoring and manual oversight and there may be greater batch-to-batch variation.	Whilst it is essential that appropriate GMPs are in place for supply to patients, industry recognizes and supports the proposals related to GMP and GDP included in the EMA Q&A[5], and further notes that it should be generally accepted that: • Suitable approaches on GMP matters can be agreed between regulators (through reliance/collaborative scientific advice), e.g. on suitability of reprocessing or release of materials, streamlined validation. Such approaches would need to be viewed consistently in the context of future inspections by multiple authorities. • Acceleration may require that GMP considerations, typically associated with early clinical phase manufacture are accepted for early commercial supply for a limited period of time (for example, where less knowledge leads to more frequent interventions into manufacture to improve control and greater batch-to-batch variability).

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			• Remediation of identified non-critical GMP gaps can be addressed as part of post-approval lifecycle activities where agreed between applicants and regulators, e.g. as part of a lifecycle plan.
13	**Pre-approval Inspections (PAI)**	PAIs can be undertaken by multiple agencies in a short period of time as part of pre-approval or pre-launch preparation. Such inspections are often performed in addition to routine GMP inspections and can be critical path activities	• For COVID-19 products PAI requirements and timing (e.g. post approval) would be considered on a risk-basis (e.g. would be waived where justified on the basis of recent inspection history). • If deemed necessary, PAI would be virtual or paper-based by 1st intent, • Manufacturing sites for COVID-19 medicines, if not previously inspected, would have no more than one single PAI (e.g. from one agency).
14	**Launch and commercial supply from Investigational Medicinal Product (IMP) manufacturing sites**	IMP manufacturing sites are ideally suited to rapid development activities. However, many IMP sites are not yet authorized to produce commercial products.	• It should be generally accepted that if a manufacturing site has already been inspected and authorized for the production of IMP, it has been appropriately demonstrated to have an adequate PQS and GMP status for commercial supply of COVID-19 medicines. • COVID-19 commercial materials can be supplied commercially from IMP GMP manufacturing sites without a commercial GMP license
15	**Global considerations (e.g. Pharmacopoeial)**	Specifications for materials (e.g. excipients) and products must meet national/regional Pharmacopoeial standards/requirements (e.g. Ph.Eur., USP, JP etc.). This is often a legal requirement. Different versions of products may be produced for different markets and/or duplicate testing performed for compliance with pharmacopoeial requirements (given that there are more than 40 Pharmacopoeias worldwide).	• Vaccines and pharmaceutical products will be developed and supplied in compliance with standards from one internationally-recognized pharmacopoeia. Regulatory adaptations may be needed to allow supply of e.g. a product complying with Ph.Eur. to the USA or a product complying with USP to Europe.

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16	**Importation testing**	Countries where the COVID-19 treatments and vaccines will be manufactured are yet to be defined and due to the global capacity that will be needed, a global supply chain will likely be required. Many countries would typically require testing on importation. This would lead to additional time before the treatment or vaccine can be supplied to patients.	EFPIA welcomes the provisions highlighted in the recent EMA Q&A5 which note that "*it may be necessary in justified cases to deviate from the requirement for importation testing…"* It is recommended that the general requirement of testing on importation is waived for all COVID-19 treatments and vaccines, relying on the tests performed at the exporting site of the manufacturer for the following reasons: • The product would already have been independently released and proven acceptable quality for patients • The additional time necessary for testing at importation would delay product availability • This transfer to a second analytical testing site would divert analytical expert resources from priority activities related to development and supply. • In a situation of limited supplies, such activities may divert product that is needed by patients. In this context, EFPIA welcomes the provisions highlighted in the recent EMA Q&A[5] reference is also made to the principles laid out in the IFPMA position paper[12]
17	**Global requirements for dossiers in addition to ICH CTD**	Although ICH M4Q defines a common set of CTD requirements across ICH regions for the Quality Module of a dossier, there may be additional regional requirements (typically included in section 3.2.R) that are necessary for dossiers submitted to some ICH members.	• CTD Dossiers for COVID-19 vaccines and therapies will contain only the core information required for the Quality Module, as specified in ICH M4Q(R1).

[12] IFPMA position paper: Appropriate Control Strategies Eliminate the Need for Redundant Testing of Pharmaceutical Products

Conclusions and Next steps

There has rarely been a greater need to consider benefit/risk to patients of CMC approaches in bringing COVID-19 therapies and vaccines to the waiting world population.

It is vitally important for industry and regulators to address the acceptability of justifications, data sets and positions taken on the basis of scientific assessment versus standard regulatory guidelines and approaches. Standard approaches, meeting all requirements of all guidelines in all regions cannot deliver the medicines required by the worldwide patient population at risk from COVID-19 in an acceptable timeframe.

Industry and regulators need to avoid delay and possible risks to patient supply. As such, CMC and GMP considerations for development and supply of high quality, affordable COVID-19 medicines may utilise alternative approaches and the "different", innovative approaches outlined in this paper must be considered as generally applicable.

It is further suggested that:

- At the earliest opportunity, EMA and EFPIA engage to discuss jointly the implementation of the CMC/GMP approaches discussed in this paper
- Furthermore, engagement via IFPMA, with ICMRA and WHO is sought without delay, to ensure global acceptance of such proposals to accelerate development and supply of life-saving medicines to patients.

Overall, the recommendations in this paper are intended to result in earlier and greater access to much awaited, high quality COVID-19 vaccines and therapies for patients worldwide, and to significantly reduce potential drug shortages. The opportunity to agree proactively to the application of these proposed approaches will be vastly beneficial to all those working to deliver vital medicines with necessary haste.

Contributions

The contribution of the following EFPIA MAPPs CMC sub-team members to the development of this white paper is acknowledged:

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