ICMRA-Industry Virtual Workshop Report on Enabling Manufacturing Capacity in the COVID-19 Pandemic

Background and Objectives of the Workshop

The COVID-19 pandemic has affected almost every facet of daily life, with over 200 million registered infections globally and over 4 million deaths, both of which are significant underestimates. Due to the scale and impact of the COVID-19 pandemic, it was soon apparent that safe and effective vaccines and therapeutics would be required to ultimately help limit the threat to global public health. Thanks to the extraordinary efforts of the global scientific community, including, but not limited to the pharmaceutical industry, medicines regulators, and academic researchers, safe and effective vaccines and therapeutics were developed and authorised within a year of the first reported cases of COVID-19. However, the unprecedented stress that COVID-19 has imposed on the global drug supply chain warrants immediate actions to implement flexible approaches that will allow regulators and manufacturers to rapidly increase manufacturing capacity for production of COVID-19 therapeutics and vaccines to meet global demand, as well as avoid or mitigate drug shortages for non-COVID-19-related products, without compromising patient safety or product quality.

On July 7 and 8, 2021, ICMRA and Industry representatives conducted a joint workshop with focus on pharmaceutical quality and manufacturing, as part of a joint international effort to accelerate the availability of lifesaving COVID-19 therapeutics and vaccines. The overall aims of the workshop were to (i) enhance Regulators' understanding of specific challenges faced by manufacturers seeking to increase manufacturing capacity for COVID-19 therapeutics and vaccines; (ii) improve Industry's awareness of current regulatory approaches that have been used to enable the rapid increase of manufacturing capacity for the production of COVID-19 therapeutics and vaccines; and (iii) identify opportunities for further collaboration, alignment, and/or harmonization to enable more efficient and effective global regulatory response to the current and future public health emergencies. The following report provides a summary of main areas of discussion and key messages identified during each session of the workshop.

Day 1: Joint Regulator and Industry Participation

Regulatory flexibilities to support the rapid increase in manufacturing capacity

Representatives
Regulators
Sean Barry (HPRA)
Evdokia Korakianiti (EMA)

Following opening remarks from Emer Cooke and Greg Perry on behalf of ICMRA and IFPMA, respectively, a presentation was delivered outlining key regulatory and scientific tools, that were used to support the rapid increase in manufacturing capacity and post-approval changes (PAC) associated with COVID-19 related therapeutics and vaccines. Figure 1 provides a summary of the main scientific and regulatory tools used. Results from a survey designed to determine which regulatory flexibilities are most commonly utilised were also presented (see Appendix I).

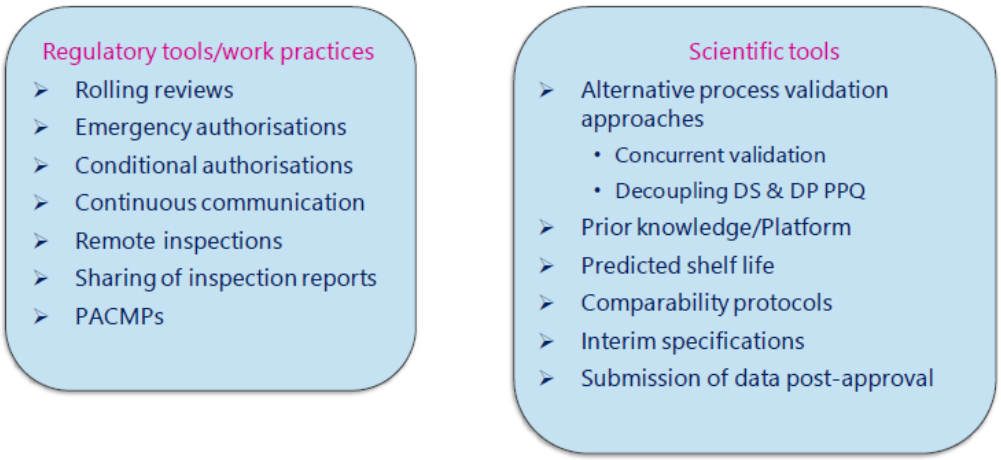

Figure 1: Summary of the key regulatory flexibilities used to support the rapid increase in manufacturing capacity and post-approval changes associated with COVID-19 related vaccines and therapeutics

Key Messages

i) The majority of agencies have adopted the use of various regulatory and scientific tools to enable the rapid increase of manufacturing capacity COVID-19 products.

ii) While there is sharing of information between regulatory agencies, reliance on assessment reports from other agencies or collaborative assessment is somewhat less common.

iii) There has been extensive exchange of information on GMP compliance amongst International Regulators, paving the path for more reliance between International Partners. Remote inspections have been a useful tool complementing GMP compliance verification.

iv) Regulatory flexibilities and early approval do not represent a reduction in regulatory standards, rather, greater process and product knowledge and understanding *enables* manufacturers to better leverage flexibilities in data requirements. Irrespective of the flexibilities applied, the dossier will eventually be completed with the full data required.

Science and Risk-based Approaches to Enable the Rapid Increase of Manufacturing Capacity for COVID-19 Therapeutics and Vaccines

Representatives
Industry
Connie Langer (Pfizer, presenting on behalf of Industry)

The challenges faced by industry regarding post-approval site transfers conducted to increase manufacturing capacity of COVID-19 related vaccines and therapeutics were outlined. Major difficulties identified by industry included data generation, dossier preparation and submission, the volume and heterogeneity in queries received from regulatory agencies regarding submissions, in addition to pre-approval site inspections.

Key Messages

The following regulatory mechanisms and flexible chemistry, manufacturing and control (CMC) approaches were identified as being critical to rapidly increase manufacturing capacity for COVID-19 therapeutics and vaccines from an Industry perspective:

i) Establishment of quick, frequent, and continuous communications/engagement

ii) Full or partial reliance on assessment reports of regulatory authorities from other regions

iii) Acceptance of alternate process qualification/validation approaches, such as leveraging of platform data and prior knowledge, concurrent validation, decoupling drug substance (DS) and drug product (DP) validation, and/or continuous process verification

iv) Approval of PACs in the absence of full data

Presentation of Regulator and Industry Case Studies

Representatives	
Regulators	*Industry*
Stelios C. Tsinontides (US FDA)	Matt Popkin (GSK)
Raphael Sanches Pereira (ANVISA)	Boris Zimmermann (Genentech/Roche)
Maria Baca-Estrada (Health Canada)	Graham Cook (Pfizer)
Evdokia Korakianiti (EMA)	

A range of case studies were presented, detailing regulatory and industry perspectives on flexibilities to facilitate the approval of CMC related changes that address manufacturing capacity issues associated with COVID-19. Specifically, regulators presented on their experience of technical transfer requests, a change in primary packaging, an amendment to a new drug substance manufacturing site, and the addition of a new manufacturing and testing facility. Industry case studies focused on the challenges and opportunities for comparability and analytical testing; the potential to accelerate CMC related assessment of stability and shelf-life using predictive modelling for biologics; and the use of alternative validation approaches combined with greater reliance on prior knowledge and enhanced collaborative regulatory review practices as priorities to address challenges to increasing manufacturing capacity.

A summary of the key challenges, accomplishments and recommendations based on the collective regulatory experiences as detailed in all case studies submitted in advance of the workshop are outlined below.

Key Challenges

- Expedited timelines
- Level of engagement (e.g., scientific advice, rolling reviews, and/or ad hoc meeting)
- Limited resources
- Limited/incomplete data packages without justifications
- Lack of transparency
- Regulatory decisions requiring increased communication
- Limited harmonization of product specifications
- On-site inspection challenges
- Manufacturing facilities' readiness for inspection

Major Accomplishments

- Risk-based/prioritization approaches (e.g., downgrading supplements to facilitate assessment based on available product/process knowledge)
- Accelerated assessments and approval (e.g., approval of three finished product manufacturing sites in less than a week)

Learnings/Recommendations

- Clarity on the detail and data required for expedited assessment should be provided.
- It is important to prioritize requests/data requirements with maximum impact on supply due to limited resources.
- Supporting data, prior knowledge and site readiness are necessary to leverage regulatory flexibilities.
- Timely, open and regulator communication between industry and regulators is fundamental to fully utilize the potential of regulatory flexibilities.
- There should be close liaison between industry and regulators on supply chain plans as they form and change.
- Companies should have an effective pharmaceutical quality system (PQS) that proactively focuses on managing change and continuous improvement, in addition to reducing quality issues leading to complaints, shortages, and/or quality-related adverse events

Panel Discussions

Representatives	
Moderators	
Sau Lee (US FDA); Markus Goese, Roche (EFPIA); Lorraine Nolan (HPRA)	
Regulators	*Industry*
Stelios C. Tsinontides (US FDA)	Matt Popkin (GSK)
Karl Cogan (HPRA)	Boris Zimmermann (Genentech/Roche)
Raphael Sanches Pereira (ANVISA)	Graham Cook (Pfizer)
Maria Baca-Estrada (Health Canada)	Connie Langer, (Pfizer)
Evdokia Korakianiti (EMA)	Thierry Gastineau, Sanofi Pasteur (Vaccines Europe)
Paula Walker (MHRA)	Diane Wilkinson, Astra Zeneca (Vaccines Europe)
Mohammed A. AlMuteri, (SFDA)	Suresh Jadhav, Serum Institute of India Pvt. Ltd. (DCVMN)
Derek Smith (US FDA)	Rajiv Desai, Lupin Ltd. (IGBA)
Brendan Cuddy (EMA)	Steve Mendivil, Amgen (PhRMA)
Mohammed Alaqeel (SFDA)	Caroline Bell, Kindeva Drug Delivery (PBOA)

Regulatory and Industry representatives participated in three separate panel discussions, with particular focus on:

1. Concepts, challenges, and approaches highlighted in the Regulatory and Industry case studies, lessons learned to date, and mechanisms that could be retained in a post-pandemic environment;
2. Challenges related to the lifecycle management of COVID-19 therapeutics and vaccines, the unique application of specific lifecycle management tools, and opportunities to optimize the use of such tools to expedite patient access to COVID-19 products; and
3. Current challenges and near-term solutions or recommendations related to regulatory oversight of manufacturing facilities during the COVID-19 pandemic, including utilization of alternative tools (e.g., remote inspections) and reliance practices for inspection reports and other GMP documents.

Key Messages from Panel Discussions

i) The following were identified as the most important enablers (or pre-requisites) to maximize the effect (or impact) of the regulatory flexibilities introduced in response to the COVID-19 pandemic to support manufacturing and PACs.

Regulator Position	*Industry Position*

• Supporting Data (Scientific/Regulatory):
  ○ Demonstrated manufacturing experience
  ○ Platform approaches
  ○ Prior knowledge
  ○ Sufficient characterization
  ○ Demonstrated product understanding
  ○ Appropriate control strategy
  ○ Scientific advice
  ○ Use of specific obligations and post approval change management protocols (PACMP)
• Site readiness for inspection and manufacturing
• Remote inspection whenever possible
• Open, transparent formal (e.g., scientific advice) and informal (ad-hoc meeting) communication between regulators and industry
	• Remote approaches to inspection
	• Use of a risk-based approaches to streamline CMC regulatory packages (use of alternative/limited data/prioritization of data requirements)
	• Full or partial reliance on assessment reports
	• Use of a 'global' regulatory process (e.g., WHO EUL, 80 countries recognizing review/approval)
	• National regulatory authorities (NRAs) following WHO recommendations
	• Flexibility on importation testing
	• PACMPs
	• Quick, frequent, and continuous communications/ engagement

ii) The following key bottlenecks limiting the use of regulatory procedures and flexibilities introduced in response to the COVID-19 pandemic to support manufacturing and PAC were identified.

Regulator Position	*Industry Position*
• Limited or inadequate data without justification that make risk-based approaches to assessment difficult • Lack of engagement/ communication/ transparency • Limited capacity/resources • Changing timetables	• Lack of regulatory reliance • Application of existing legislation to a pandemic • Volume of NRAs' questions • Full national release testing of vaccines • Expectations of complete dossier information • CMC requirements for different NRAs (i.e., lack of harmonisation) • Lack of clear, rapid engagement pathways • Conducting on-site pre-approval inspections during pandemic

iii) Ultimately, the most effective regulatory flexibilities were identified as the following.

Regulator Position	*Industry Position*
• Use of PACMPs, or similar, to expedite PACs • Remote inspections • Rolling review • Expedited timelines to meet public need • Labelling flexibilities • Conditional marketing authorisation / emergency use authorisation / or similar regulatory mechanism to meet urgent public health need • Use of risk-based, post-authorisation obligations to collate CMC-data (e.g., what is the most/least critical data required for approval)	• Establishment of quick, frequent, and continuous communications/ engagement with regulators • Specific reliance practices: Full or partial reliance on assessment reports of regulatory authorities from other regions • Process Qualification/Validation Data: leveraging of platform data and prior knowledge, concurrent validation, decoupling DS and DP validation, and/or continuous process verification • Approval of PACs in the 'absence of full data' (with certain data provided at a later date)

Day 2: Regulator Discussion, Reflections and Next Steps

Following a recap and open discussion between regulators on a range of issues identified during Day 1 of the workshop, in addition to the ICMRA Leadership Panel outlining their perspectives on the issues highlighted, a number of next steps to enable manufacturing capacity and streamline regulatory assessment were discussed. Specifically, opportunities for further collaboration, alignment, or harmonization to enable more efficient and effective global regulatory response to the current and future public health emergencies were explored.

To further understand the context of the appetite for greater reliance and collaboration between regulatory agencies under both pandemic and non-pandemic conditions, a more detailed survey of the ICMRA membership was proposed. This information will be used to optimise the design of several potential pilot projects exploring collaborative assessment of COVID-19 related post approval CMC changes. Key focus areas for potential pilots included i) collaborative distant/remote and local inspections (i.e. collaborative 'hybrid' approach between regulatory agencies that utilizes desk-based inspection supported by technology from one agency, together with inspectors from the regulatory agency of the host country where the facility is located carrying out an on-site visit); and ii) collaborative assessment of COVID-19 related post approval CMC changes, including PACMPs. Further details on the scope and implementation strategy (e.g., type of engagements among different regulatory agencies) are subject to active consultation with participating regions, and endorsement by the ICMRA Executive Committee. Key objectives for any proposed pilots to enable manufacturing capacity and streamline regulatory assessment include:

- Identification of best practices and standards.
- Identify misalignments, differences, and potential areas for alignment or harmonization across regions.
- Provide opportunities for collaboration and dialog for industry participants interested in global regulatory filing.
- Build upon and improve the communication and collaboration framework between different regulatory agencies to enable more efficient and effective global regulatory mechanisms.

Conclusions

The milestone ICMRA-Industry workshop provided an opportunity for an exchange of views between regulators and the pharmaceutical industry on the regulatory flexibilities introduced to enhance the manufacturing capacity of COVID-19 products.

Adapted regulatory procedures were used to safely accelerate the authorisation of COVID-19 therapeutics and vaccines and facilitated the unprecedented efforts of the pharmaceutical industry to make available lifesaving COVID-19 products.

Key enablers and bottlenecks limiting the use of regulatory flexibilities, in addition to the most effective mechanisms that enabled increased manufacturing capacity, were identified.

Opportunities for further collaboration, alignment, or harmonization to enable a more efficient and effective global regulatory approach to enabling increased manufacturing capacity were also identified. It is hoped that the workshop will serve as a catalyst for further collaboration between regulatory agencies and between regulators and industry, and that such collaboration will lead to greater convergence and further efficiencies in global CMC assessment and inspection activities. Two pilots are being considered for launch to optimise the design of future collaborative interactions.

Appendix: Common flexibilities utilised by regulatory agencies to facilitate to rapidly increase capacity for COVID-19 therapeutics manufacturing

CMC Changes to Rapidly Increase Capacity for COVID Therapeutics Manufacturing	FDA	EMA	PMDA	TGA	MHRA	HC	SMC	ANVISA	HSA	ANMAT	SFDA
Current Mechanisms and Approaches											
What are the available mechanisms offered by Regulatory Authorities for expedited assessment?											
• Establishment of quick, frequent, and continuous communications/engagement with manufacturers to discuss their requests and provide regulatory recommendations and advice	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
• Rolling submissions or other expedited regulatory actions	Y	Y	Y	Y	Y	Y	Y	M[1]	Y	Y	Y
• Comparability protocols or post-approval change management	Y	Y	Y	Y	Y	Y	Y	M	Y	Y	Y
• Providing public guidances or guidelines to clarify regulatory expectations on how assessment of critical drugs or biologics will be prioritized during the pandemic	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
• Approval of post-approval changes in the absence of full data (with certain data provided at a later date)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
• Dedicated resources to handle the extensive lifecycle management	Y	Y	Y	Y	M	Y	Y	N	N	Y	Y
• Reliance on assessment carried out by other regulators or participation in joint assessment programmes	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
• Specific reliance practices ○ Sharing of assessments between regulatory authorities from other regions	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
• Specific reliance practices ○ Full or partial reliance on assessment reports of regulatory authorities from other regions	Y	N	N	M	Y	Y	Y	Y	Y	N	Y
• Specific reliance practices ○ Participation in joint assessment programmes	Y	Y	N	Y	Y	Y	Y	Y	Y	N	N

[1] In ANVISA, we do not have rolling submissions, but we have mechanisms for prioritizing analysis.

What flexible approaches to CMC data requirements may be considered?											
• Analytical method validation ○ Risk based approach depending on the type and extent of proposed changes (e.g., platform validation of methods for biologics)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
• Process Qualification/Validation Data ○ For drugs, reduced data package based on risk	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
• Process Qualification/Validation Data ○ For biologics, leveraging of platform data and prior knowledge, concurrent validation, decoupling DS and DP validation, and/or continuous process verification	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
• Process Qualification/Validation Data ○ Limited process qualification based on risk	Y[2]	Y (CMA)	Y	Y	Y	Y	Y	Y[3]	Y	Y	Y[4]
• Control Strategies ○ Interim specifications	Y[1]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y[4]
• Control Strategies ○ Alternative in process controls[5]	Y	Y	Y[6]	Y	Y	Y	Y	Y	Y	Y	Y
• Adventitious agents (for biologics) ○ Leveraging of platform knowledge to reduce viral clearance studies	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y
• Stability data ○ For small molecules and biologics, alternatives to establishing a shelf life based only on real-time data	Y	Y	Y[6]	Y	M	Y	Y	M	Y	Y	Y

[2] For FDA, this is only used for Emergency Use Authorization (EUA).
[3] For ANVISA, this is only used for Emergency Use Authorization (EUA).
[4] For Saudi FDA, this is only applicable for conditional approvals of COVID-19 vaccines and therapeutics.
[5] For example, alternative in-process controls include monitoring a larger number of process parameters in a predefined range.
[6] No for vaccines.

What are the regulatory tools available for facility assessment in lieu of inspection?											
• Desk-based review of documents requested from the facility	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
• Review of inspection reports by other agencies via a Mutual Recognition Agreement or Confidentiality Agreements	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
• Remote interactive assessment or Distant Assessments o Acceptable tools/Technology	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y[4]

What approaches have been used to expedite CMC changes?											
• Concurrent Process Validation & Post approval commitment (additional information to be submitted after approval per commitment)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
• Grouped supplements	Y	Y	N[7] M[8]	Y	Y	Y	Y	M	Y	Y	Y
• Derogations to labelling requirements as a result of CMC changes	Y[1]	Y	Y[9]	Y	Y	Y	Y	Y	Y	Y	Y[4]

Y = Yes;

N = No;

M = Maybe

[7] For COVID-19.

[8] For other pandemics.

[9] PMDA: This is applied only for products under Special Approval for Emergency.