International Federation of Pharmaceutical Manufacturers & Associations

IFPMA policy briefing on:

Regulatory agilities applied to quality[1]

[1] Processes to ensure the quality and supply of medicinal products

Extraordinary measures have been applied by National Regulatory Authorities (NRAs) and the pharmaceutical industry to face the challenges brought by the **COVID-19 pandemic emergency.** A variety of agilities related to Quality processes have been key to allow the **rapid development, assessment, approval, manufacturing, and access to safe and effective COVID-19 and non-COVID-19 related medicines and vaccines.**

This policy briefing summarizes **trends in reported experiences (from primary and secondary research) in the use of regulatory agilities applied to quality** observed since the start of the pandemic, **some reported challenges** to their implementation and **forward-looking recommendations**, whether to prepare for the next pandemic or strengthen standard normative processes to accelerate patient access to safe and effective medicines and vaccines.

Introduction

The COVID-19 pandemic has posed unprecedented challenges to all healthcare stakeholders and society at large. The implementation of a variety of agilities in quality related processes has facilitated the rapid development, assessment, approval, manufacturing and distribution of safe COVID-19 and non-COVID-19 related pharmaceutical products. The pandemic has in particular highlighted the importance of using agilities to minimize disruptions in the global supply chain, risks of drug shortages, and to allow NRAs and manufacturers to rapidly increase manufacturing capacity for producing medicines without compromising their safety and quality.

In some instances, the pandemic led to the emergence of new practices and ways of working whilst in others, it accelerated existing trends in quality related processes such as the increased digitalization of ways of working.

The experience of the pandemic has offered unprecedented learnings on which the biopharmaceutical industry and the NRAs (National Regulatory Authorities) can build to enhance quality related activities in the standard normative regulatory process as well as to improve pandemic preparedness.

The pharmaceutical industry is committed to playing a central role in the continuous efforts to improve quality related processes across the whole supply chain. Therefore, with this paper, IFPMA aims to outline important trends in the reported use of regulatory agilities related to quality during the COVID-19 pandemic, challenges related to the implementation of these agilities as well as policy recommendations that should be taken to improve the standard normative process and to prepare for future pandemics.

The main themes of this paper are grouped under four categories centered around maximizing efficiency, increasing collaboration, improving practicalities and supporting sustainability.

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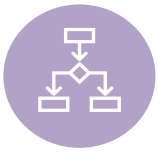
A series of recommendations to strengthen the standard regulatory processes and to prepare for future pandemics are outlined at the end of this policy briefing. These recommendations are built upon the learnings and experiences of the COVID-19 pandemic and are centered around maximizing efficiency, increasing collaboration and improving practicalities. Recommendations for the use of agilities should apply to all products. The complete list of recommendations can be found in the document: *IFPMA Recommendations: Regulatory agilities applied to quality processes*

> **The electronic CPP is not included in the legislation, but NRAs are accepting it during the Covid-19 pandemic,** and it does not look like the paper version will come back, so in a way this will make other NRAs adapt quicker to the new normality.
>
> *Excerpt from interview with Lorena Mauro - FIFARMA*

> [*In **remote inspections***] There is a need for **procedures that guarantee information security, reliability, transparency and privacy**. You may have to manage time zone differences and simultaneous translations. There is a need to define the information to be reviewed and for which regulatory processes the remote or hybrid inspections would be acceptable: for pre-approval or post-approval and under what circumstances?
>
> *Excerpt from interview with Rebecca Lumsden - FIFARMA*



Digitalization

Trends: The increase in **virtualization of working practices** and the **use of virtual tools** have been key trends during the pandemic, with remote working, remote assessments and inspections and use of e-documents such as e-payments, e-labeling, e-certificates, e-records for GMP (Good Manufacturing Practice) and e-CPP (Certificate of Pharmaceutical Product) being common features.

The pandemic led companies and inspectorates to use innovative tools to find alternative options to inspections requiring physical presence. Virtual media, collaborative platforms and new tools, such as digital presence, were helpful to enable assessments of quality**.** Virtual tools were vastly used in inspections during the pandemic as they can maximize efficient use of resource, they allow inspections to be carried out on non-consecutive days and allow industry experts to take part in inspections from different locations. The use of **virtual tools and hybrid approaches (virtual and on-site)** increased in both domestic and foreign inspections globally.

Challenges: **Lack of access** to appropriate **technology infrastructure,** such as internet accessibility, in settings with scarce resources limited the implementation of agilities related to quality processes.

Despite the clear benefits linked to **remote/hybrid inspections**, several challenges were also associated with them and at times, depending on the circumstances, remote/hybrid inspections have been considered more burdensome to carry out compared to on-site inspections. Challenges for remote/hybrid inspections include: high amount of documents requested; difficulties to find documents; unclear filenames; risk of technical issues impeding or delaying inspections; lack of direct interaction among stakeholders; decreased visibility on body language and context; longer time for preparation; more documents requested in advance; and privacy related issues.

Decision-making, Ways of working, Reliance

Trends: During the pandemic, several agilities have been introduced to enable rapid increase of manufacturing capacity for production of COVID-19 related products whilst ensuring quality of these products. Working practices heavily leveraged **digitalization**, leading to an increase in remote working, distant assessment and batch certification, remote/hybrid inspections and e-communication among NRAs and applicants.

Risk-based approaches were often utilized to improve efficiency in decision-making. Examples included: taking different approaches to **expedite CMC** (Chemistry, Manufacturing and Controls) **changes**, including concurrent process validation and post approval commitment to submit additional information; grouped supplements and derogations to labeling requirements as a result of CMC changes. Risk-based approaches were also applied when **planning and conducting inspections**, when considering the number of inspectors, the scope of inspections as well as inspection site history. Risk-based approaches were also used for GMP (Good Manufacturing Practice) compliance verifications and certifications.

Using reliance proved helpful to increase efficiency **when conducting inspections**. Reliance was facilitated by guidance issued by PIC/S (the Pharmaceutical Inspection Co-operation Scheme) which for instance outlined a process for desktop assessment of compliance with GMP, by the WHO GBT (Global Benchmarking Tool), and by information and data sharing among the different stakeholders. **Waivers on inspections** were often granted for sites in a country where a formal MoU (Memorandum of Understanding) was established or where the inspectorate was a participating authority in PIC/S, provided that all tools required (e.g., on-site, remote, paper-based, reliance on prior knowledge) were applied appropriately.

Given the disruptions on the supply chain caused by the pandemic, various measures were taken to **secure supply of medicinal products and avoid shortages**. Different authorities applied agilities on imports of medicine without compromising GMPs and GDP (Good Distribution Practice).

Decision-making, Ways of working, Reliance (cont.)

In the **European Union**, common trends included remote working for qualified person and responsible person, agilities for testing on imports, extension of applicable GMP certificates, remote assessment for GMP certificate validity extension and authorization of new sites, and implementation of green lanes to ensure smooth flow of goods. The **United States** adopted risk-based approaches for manufacturing and to which current GMP inspection activities could be delayed, reduced or modified. In the **United Kingdom,** GxP (Good Practice) documents were approved using alternative methods (when working remotely), only essential on-site GxP inspections were conducted, and agilities for qualified person declarations for variations and initial applications were granted. In the **Asia** region, a single license was adopted for multiples sites, in line with ICH and WHO guidance. In **South Korea**, exemptions on CPP submission were given. In **Africa**, requirements for product release were reduced, import and export processes were prioritized as well as renewals and PACs (post-approval changes) over new drug applications.

Challenges: The pandemic heavily impacted the **global supply chain** causing considerable market disruptions and a decrease in production and exportation of both raw materials and finished products across countries, highlighting the importance of a diverse supply chain. Manufacturing activities were particularly affected by the scarcity of raw materials, supply constraints and the lack of workforce readiness to face the challenges of the pandemic.

Risk-based approaches sometimes proved difficult due to sponsors providing **limited data initially** and **some NRAs being unfamiliar and uncomfortable** with science-and risk-based approaches, ultimately causing delays in decision-making processes.

Limited capability and capacity of manufacturing sites, due to increased demand, also caused some drug shortages. Additionally, given the **variation in complexity of site transfers,** it was difficult to establish a one-size-fits-all approach on regulatory expectations for these transfers. For instance, there were **different opinions on the interpretation of the legislation in different countries,** on whether remote assessments could be used to legally confirm GMP compliance and capability of a site to manufacture a product.

For remote facility assessments for PAI (pre-approval inspection), NRAs adopted various approaches, but **the use of "alternative tools" impacted reliance** practices leading to an inspection backlog. Additionally, at times, foreign inspections still target sites in countries with recognized inspectorates, e.g PIC/S participating authorities.

Early-dialogue, Transparency

Trends: During the COVID-19 emergency, there was an extensive **exchange of information** (pursuant to agreements protecting the confidentiality of information) **on GMP compliance** amongst regulatory bodies. In particular, reliance practices were facilitated by the WHO and PIC/S, including information and appropriate data sharing as well as sharing of inspection reports.

Generally, NRAs showed efforts to increase communication, be transparent and provide guidance to manufacturers, which ultimately also facilitated reliance practices.

Several NRAs relied on **MRA** (Mutual Recognition Agreement) **or Confidentiality Agreements** to review inspection reports by other agencies and reliance on inspections was facilitated by **PIC/S** (the Pharmaceutical Inspection Co-operation Scheme) **issued guidance**, which outlined a process for **desktop assessment** of compliance with GMP.

In **Latin America**, the lists of products needed for COVID-19 medicines, personal protective equipment and medical devices were made available on NRAs' websites and a dashboard to track vaccines safety evaluation criteria was also published. In **Brazil and Colombia**, guidelines and requirements for remote inspections were established while onsite international inspections could be performed.

Evidence

Trends: During the COVID-19 pandemic, fast-track reviews and approvals allowed manufacturers to initially provide less comprehensive data than normally required, in consultation with NRAs and under the condition that all the comprehensive data was provided at a later stage. Thus, during the pandemic, fast-track reviews and approvals proved critical to speed up development and access to medicines whilst maintaining usual standards of safety/efficacy.

Flexible approaches to CMC data requirements were applied globally, for instance with relation to process qualification or process validation data. For drugs in fact, a streamlined data package based on risk was allowed, whilst for biologics and vaccines, leveraging of platform data and prior knowledge, concurrent validation, decoupling drug substance and drug product validation, and/or continuous process verification were allowed.

In the **European Union** agilities were applied to testing on imports as well as to quality variations. In the **United Kingdom** re-testing on imports was omitted. In **Africa**, product release requirements were reduced.

Challenges: One of the main challenges that emerged was the **lack of harmonization and divergent data requirements and processes** among NRAs, which ultimately limited access to vaccines and treatments. For instance, traditional approaches to process validation can take six or more months to complete. Many NRAs require the submission of twelve or more months of real-time stability data and will not allow manufacturers to utilize accelerated stability testing, modeling, extrapolation, and/or prior knowledge as surrogates for real-time testing. Another challenge was the **limited harmonization** of products specifications (including biosafety) and **full national release testing** of vaccines.

PACs (Post-approval changes)

Trends: Due to the accelerated development and the complexity of COVID-19 therapeutics and vaccines, a high number of PACs were needed in a short timeframe to enhance manufacturing processes and expand supply to fight the pandemic.

Risk-based approaches leveraged **PACMPs** (post-approval change management protocols) between manufacturers and NRAs, a regulatory tool proposed by ICH Q12, which effectively allowed manufacturers to quickly implement changes.

Several agilities related to PACs were implemented globally, for instance several approaches to CMC changes such as concurrent process validation and post approval commitment with some information submitted after approval, grouped supplements and derogations to labeling requirements could be applied as needed.

> Some PACs mean a new registration in some countries, so imagine the complexity of that.
>
> *Excerpt from interview with Lorena Mauro - FIFARMA*

In the **United Kingdom**, the requirement to submit leaflet mock-ups for variations was waived and post-approval transfer of product were allowed to additional manufacturing facilities. In **Africa**, waivers were granted for renewals and variations requirements such as samples, product release requirements were reduced, and renewals and PACs were prioritized over new drug applications to ensure supply. In the **Asia** region, 'grace periods' for PACs implementation were given.

Challenges: NRAs themselves recognized the difficulty in ensuring regulatory compliance in multiple regions while rapidly expanding the supply chain. Introducing multiple manufacturing sites post-approval was challenging due to different national requirements and manufacturers flagged that NRAs often had **different post-approval expectations** for the same PAC, that the same change had to be approved by multiple NRAs, and that PAI for post-approval site transfer were challenged by travel restrictions.

In **Africa**, hard copy and/or legalized documents were requested. In the **Asia** region, it was flagged how the complex addition of multiple sites was not linked to an enhancement of the value of regulatory oversight.

Labeling & packaging

Trends: Several agilities were applied to labeling and packaging. Labeling agilities proved very important when there was increased demand for medicinal products, transport disruptions and other factors impacting the normal flow of products.

E-labeling was widely adopted and, as a result of CMC changes, derogations to labeling requirements could be applied as needed.

In the **European Union** e-labeling as well as single language formats were adopted. In the **United Kingdom**, facilities with Manufacturers Specials (MS) licences considerably increased the 'packing down' of large packs of licensed medicinal products into smaller quantities for retail sale. **Japan, Chinese Taipei** (pilot limited to certain categories of products) **and Singapore** all adopted e-labeling and **Japan** is currently leading the way as it planned to eliminate paper in August 2021 with a two-year transition period to a paperless system to be reached in July 2023.

Challenges: Despite the added value of e-labeling, also recognized by the WHO, regulations globally are still moving at different speeds with its implementation.

Environment

Trends: Travel restrictions linked to the COVID-19 pandemic contributed to **increased levels of digitalization of ways of working** for both NRAs and industry. The use of digital tools, such as during quality inspections, helped maintain business continuity and decreased the need to travel contributing to reduce environmental pollution.

The use of **electronic signatures, electronic documents and e-labeling,** in addition to facilitating access to information, decreases the need to use paper.

Recommendations

Efficiency

Digitalization

Standard Normative Process	Pandemic Preparedness
• Embrace virtual working and digital methods (institutionalize the use of e-documents such as eCPP, e-records for GMP).	• Centralize e-documents and make them available securely.

Ways of working, decision-making, reliance

Standard Normative Process	Pandemic Preparedness
• Consider risk-based approaches to improve efficiency, such as remote/ hybrid inspections as necessary. • Use reliance for remote/hybrid inspection and highlight duplicate regulatory GMP/GDP inspections / ISO-certification. • Institutionalize new measures for GMP (Good manufacturing practice) during technology transfer. • Support diverse supply chain.	• Implement risk-based approaches (accelerated process for GMP certification and real-time data review). • Embrace alternate process validation approaches (e.g. drug product validation activities or concurrent validation) • Use reliance for reducing redundancies in inspection, encourage implementation of the harmonized PIC/S and WHO guideline.

Harmonization

Standard Normative Process	Pandemic Preparedness
• Harmonization of remote/hybrid inspections adopting best practices and enabling higher-level guidance.	• Streamline and standardize requirements / data packages internationally. • NRAs and industry to develop/revise harmonized guidelines reflecting science-and risk-based approaches.

Collaboration

Early dialogue, transparency

Standard Normative Process	Pandemic Preparedness
• English as inspectorates' language, where possible. • Inform companies if reliance is used (also for pre-approval inspection).	• Adopt global trust repository for traceability of products and GMP certificates. • Maintain continuous communication with NRAs on submissions, supply chain and needs. • Increase collaboration for remote/hybrid inspections.

Practicalities

Evidence

Standard Normative Process	Pandemic Preparedness
• Allow alternate process validation approaches and defer the submission of certain processes. • Conduct comparability testing focusing only on critical attributes that may be impacted by the site transfer and that utilize a limited number of lots.	• Implement evidence agilities (e.g. accelerated stability testing, predictive stability modeling) and accept some level of risk based on ICH Q9. • Use reliance for reducing redundancies in inspections, encourage implementation of the harmonized PIC/S and WHO guideline.

PACs

Standard Normative Process	Pandemic Preparedness
• Industry to ensure site readiness and in-depth product knowledge. • Adopt best practices and reporting categories from ICHQ12. • Increase global harmonization when appropriate.	• Use risk-based agility for data requirements • Maximize collaborative review and reliance, and develop a global PACs framework. • Clear prioritization of changes based on public health and supply impact.

Labeling and packaging

Standard Normative Process	Pandemic Preparedness
• Adopt e-labeling • Harmonize national requirements for product labeling and information to minimize safety risks.	• Allow derogations to labeling requirements as a result of CMC changes. • Maximize labeling agilities in times of increased demand and disruptions to the normal flow of products.

Sustainability

Environment

Standard Normative Process	Pandemic Preparedness
• Institutionalize use of electronic documents such as eCPP and adopt use of e-labeling to decrease the need to use paper.	• Conduct hybrid and/or remote inspections with virtual tools to reduce need for traveling.

Background

IFPMA represent research-based biopharmaceutical companies, and regional and national associations across the world. Clarivate is a global leader in providing trusted insights and analytics to accelerate the pace of innovation. This document captures the lessons learnt from primary and secondary research on the use of regulatory agilities emerged from the COVID-19 pandemic, enriched by shared experience from the IFPMA Steering Group. This document does not aim to provide an exhaustive overview of agilities and challenges experienced worldwide and regionally.

Acronyms

CMC (Chemistry, manufacturing and controls)
CPP (Certificate of pharmaceutical product)
GBT (WHO Global Benchmarking Tool)
GDP (Good distribution practices)
GMP (Good manufacturing practices)
GRP (Good Regulatory practices)
ICH (International Council of Harmonization)
ISO (The International Standards Organization)
MRA (Mutual Recognition Agreement)
MoU (Memorandum of Understanding)
NRA (National regulatory authority)
PAC (Post-approval change)
PACMPs (Post-approval change management protocols)
PAI (Pre-approval inspection)
PIC/S (The Pharmaceutical Inspection Co-operation Scheme)

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