International Federation
of Pharmaceutical
Manufacturers & Associations

IFPMA

IFPMA policy briefing on:

Regulatory agilities applied to regulatory processes[1]

[1]Processes for submission, review and approval of applications for marketing authorization and post-approval changes

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 in regulatory processes have been key to allow the **rapid development, assessment, approval of 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 these agilities** 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 to 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 regulatory agilities has been key not only to allow the rapid development, assessment, approval of and access to safe COVID-19 and non-COVID-19 related pharmaceutical products, but also to facilitate the continuity of regulatory activities, highly impacted by the health emergency.

In some instances, the pandemic led to the emergence of new regulatory practices whilst in others, it rather accelerated existing trends in regulatory processes such as the increased digitalization of ways of working or the use of rolling reviews.

The experience of the pandemic has offered unprecedented learnings on which the biopharmaceutical industry and the NRAs (National regulatory Authorities) can build on to enhance 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 regulatory processes. Therefore, with this paper, IFPMA aims to outline important trends in regulatory agilities that emerged 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.

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 regulatory processes*

Digitalization

Trends: Overall, the digitalization of the regulatory ecosystem has been a major enabler of regulatory agilities worldwide. **Digitalization and remote working** have facilitated increased connectivity among all stakeholders during the pandemic as well as the continuity of regulatory activities, especially thanks to virtual meetings and online platforms.

The increased **use of digital methods and electronic documents**, such as e-submission of applications, use of e-signatures and e-documents, such as e-records for GMP activities and eCPP (Certificate of Pharmaceutical Product), also facilitated the continuity of regulatory activities.

The use of **digital tools to capture endpoints** has been of value to assess COVID-19 patient experience, overcoming shortcomings of traditional endpoints.

In addition to allowing increased interconnectivity, streamlined and faster processes, digitalization is also linked **to important sustainability advances** such as a decreased need for travel and decreased use of paper (such as in the case of e-labeling).

Challenges: The increased digitalization of working practices may be hindered by technological issues such as poor internet connections or sub-optimal technology infrastructures. There was also a sentiment of increased workload by the different stakeholders.

> We do not see digitalization as linked to only pandemic situations, in fact we see **digitalization** as a key opportunity **to strengthen regulatory systems holistically in the longer term**.
>
> *Excerpt from interview with Rebecca Lumsden - FIFARMA*

In some **countries with limited infrastructure such as in Africa**, there might be issues in accessing technologies, so for instance virtual meetings might still not always be possible. Additionally, some NRAs still require hard copies of documents signalling a need for change in this area.

Harmonization

Trends: ICMRA (International Coalition of Medicines Regulatory Authorities) has had an important role in supporting **alignment and convergence in the COVID-19 pandemic response** at the global level, by promoting appropriate information-sharing and collaboration.

Challenges: The **lack of convergence and harmonization** in evidence requirements, review and approval processes, with multiple global regulatory pathways and different benefit/risk assessments at country level, contributed to difficulties in timely access to medicinal products globally.

The **lack of convergence and harmonization** was flagged as a challenge by stakeholders in different regions: in **Africa**, together with fragmented regulatory systems; in **Latin America**, where some NRAs require documentation normally not required by other NRAs; and in the **European Union** where national regulatory requirements and approaches are still perceived as limiting the European harmonization of guidance.

Ways of working, Decision-Making, Reliance

Trends: The majority of NRAs implemented **risk-based regulatory agilities** in their decision-making processes, in order to enable rapid availability of products (COVID-19 related or not). Common risk-based approaches related to the evaluation and approval of products included: rolling submissions and reviews, expedited approvals, approvals in the absence of certain data submitted at a later stage for regular marketing authorization, as well as exceptional authorizations such as CMA (conditional marketing authorization) or EUA (emergency use authorization).

Collaborative assessments have also emerged to maximize efficiency in the evaluation of COVID-19 treatments and vaccines among various NRAs; an example is the EMA (European Medicines Agency) OPEN Pilot allowing WHO and NRAs outside the European Union to take part in EMA scientific evaluations, sharing scientific expertise, promoting transparency and tackling common challenges.

Reliance in decision-making was used by NRAs of different maturities, with the benefits of better managing resource capacity and expertise. The industry may expect more predictable approvals and patients may get timely access to safe and effective medicinal products. Using reliance may also strengthen trust among NRAs and support increased efficiency of regulatory systems. Generally, appropriate sharing of information between regulatory agencies happened more frequently whilst reliance on assessment reports from other agencies or joint assessment was somewhat less common.

Particularly in Africa, **reliance is important** because not every health authority has the level of maturity necessary to deal with pandemic situations.

Excerpt from interview with Philip Tagboto, AREPI

In regions such as **Africa, Latin America & Caribbean**, where some NRAs might not have the capacity to deal with health emergencies, use of reliance is particularly important. Additionally, WHO-led global assessment and NRA approvals accelerated access in Low-to-Middle-Income Countries.

Risk-based approaches have also been implemented in relation to **PACs** (post-approval changes) with the use of PACMPs (post-approval change management protocols) between manufacturers and NRAs allowing manufacturers to quickly implement changes.

Finally, it should be stressed that the implementation of risk-based approaches did not come at the expense of **regulatory standards**, which are to be preserved at all times. Maintaining effective regulatory standards is also key to support public confidence in the regulatory processes to develop safe medicinal products.

Challenges: **Limited or inadequate data** can make rapid risk-based approaches, which are already resource intensive processes, particularly challenging, making it important for applications to be supported by robust and sound scientific evidence. Moreover, during the pandemic, some **NRAs were also unfamiliar or uncomfortable with risk-based approaches**, due to lack of expertise or requirements for evaluating new technologies. NRAs were also expecting complete dossier information, which might have resulted in delays in decision-making activities.

In some instances, **COVID-19 products were prioritized** over other applications, creating delays and backlogs in other disease areas.

Concurrent reviews, such as Project Orbis, during the pandemic were **not used as much as some had hoped**, due to the speed with which things needed to be reviewed and because these were not designed for emergency use authorizations, but for regular reviews.

Excerpt from interview with Janet Vessotskie, PhRMA

Early-dialogue, Transparency

Trends: During the COVID-19 pandemic, **real-time information sharing and collaboration** were key to informing NRAs and WHO regulatory decisions, requirements, communications and plans for COVID-19 products, especially through ICMRA.

The health emergency was generally characterized by **increased levels of communication** among stakeholders. Communication among **NRAs and sponsors** was often more frequent, faster, earlier in the regulatory processes and less formal compared to non-emergency times. Sponsors were able to engage with NRAs as soon as they were planning submissions and such interactions allowed **swift alignment** on data requirements for submissions as well as on regulatory agilities that could be implemented.

Enhanced levels of engagement and interactions were also seen **between health authorities and the public.** An example of this was the launch of the "WHO Health Alert" on WhatsApp to provide **up-to-date information** on the pandemic to patients. **Enhanced transparency** was thus not only important to maximize alignment on regulatory processes and agilities between NRAs and sponsors, but it was also critical to support public confidence around the maintenance of good regulatory standards and safety of approved medicinal products as well as to provide general guidance to patients related to the pandemic.

Challenges: In some countries, stakeholders lamented **lack of transparency** and of clear, rapid engagement pathways with NRAs.

Finally, in many instances**, public confidence was easily dented** around the globe by inconsistent, or unclear communication, which led to widespread movements doubting the efficacy and safety of medicinal products aimed to fight the pandemic.

In **Latin America**, **information sharing among authorities was not sufficiently strong** and despite PAHO compiling information on regulatory actions, different countries flagged the need for more bilateral information sharing with memorandums of understanding.

> [*To maintain trust among stakeholders*] There is a need to **accelerate communication between different stakeholders**. In person interactions still have that big effect, so stakeholders need to consider how to have these discussions.
>
> *Excerpt from interview with Shinji Hatakeyama- Japan*

Evidence

Trends: NRAs allowed **evidence agilities** at time of submission, giving sponsors the possibility to provide data at a later date and thus allowing faster development timelines and expedited regulatory approvals. NRAs also provided helpful guidance to the industry on data needed for COVID-19 therapeutics and vaccines.

Because of travel restrictions, the use of **novel evidence such as RWE** (real world evidence) or digital tools for capturing endpoints has been accelerated to facilitate diversity and inclusion.

Challenges: One of the main challenges was generating **robust scientific evidence** which was needed to support regulatory decisions using a risk-benefit approach.

Lack of convergence and harmonization and divergent data requirements among NRAs were also challenges for sponsors which limited access to vaccines and treatments.

> In Latin America, preparation of information, including translation, requires time and resources which can cause delays in submission of documents; additionally, NRAs will often require **additional documentation that may not be normally required by other NRAs.**
>
> *Excerpt from interview with Rebecca Lumsden - FIFARMA*

PACs

Trends: Several agilities in relation to PACs have been applied during the COVID-19 pandemic by different NRAs such as expedited procedure for extensions of indications for approved medicines being repurposed against COVID-19 and postponement of certain PACs.

Notably, the development of **PACMPs** between manufacturers and NRAs, allowed manufacturers to move quickly to implement changes.

In the **United Kingdom**, waivers were granted for the requirement of leaflet mock-ups for variations. In **Africa**, waivers were granted for renewals and variations requirements such as samples; renewals and PACs were also prioritized over new drug applications to ensure supply. In the **Asia region**, 'grace periods' for PACs implementation were given.

Labeling & Packaging

Trends: Agilities for labeling and packaging requirements proved to be beneficial for stakeholders in different regions. In particular, **exemptions and waivers** for labeling facilitated vaccine rollout worldwide.

The **European Union** allowed the inclusion of e-labels and single language formats for COVID-19 products. In the **United Kingdom** waivers were granted for the requirement of leaflet mock-ups for variations. **E-labeling** was also particularly used in the **Asia region**, especially in Japan, Chinese Taipei, and Singapore.

Challenges: Printing of labeling and leaflets delayed supply of emergency products, confirming how use of e-labelling could be beneficial to increase efficiencies.

Environment

Trends: Increased digitalization of ways of working and use of digital tools can have a positive impact on the environment, as the **adoption of virtual meetings, e-documentation and electronic signatures** can contribute to decreasing need for traveling and use of paper.

Some NRAs around the world adopted the use of **e-labeling** for COVID-19 products. Labeling agilities can be highly beneficial when factors such as increased demand and disruptions in transports impact the normal flow of products. In addition to simplifying regulatory information management, e-labeling helps to reach environmental sustainability goals (UN SDG 3, 12, 17) and its added value was also recognized by WHO.

Japan already eliminated paper labeling as of August 2021, with a transition period of two years, and aims to reach a paperless system in July 2023.

Recommendations

Efficiency

Standard Normative Process	Pandemic Preparedness
Digitalization	
• Improve technology facilities and embrace virtual working and digital methods. • Institutionalize the use of electronic documents such as eCPP.	• Leverage virtual working and digital methods as much as possible. Digitalization should be perceived as evolving with social and behavioral digital trends.
Ways of working, Decision-making, Reliance	
• For all products, adopt risk-based approaches throughout the product lifecycle to improve efficiency. • Reach international convergence on the minimum data package for applications. • Promote joint regional initiatives and reliance. • Encourage NRAs to share Public Assessment Reports.	• Develop fit-for-purpose 'ready-to-go' frameworks with risk-based approaches for submission, review and approval. • Implement a single dossier for global markets. • Be mindful of time and resources. • Temporarily suspend non urgent activities and restart them as soon a possible to avoid any backlog due to accumulation of activities.
Harmonization	
• Streamline and standardize requirements. • Integrate principles of Good Regulatory Practices and Good Reliance Practices and support WHO related activities.	• Avoid multiple emergency plans. • Streamline and standardize requirements. • Acknowledge regional differences.

Collaboration

Standard Normative Process	Pandemic Preparedness
Early dialogue, Transparency	
• Increase sharing of data between NRAs and between NRAs and manufacturers and promote transparency.	• Ensure early, frequent and transparent dialogue between the different stakeholders. • Ensure clear and timely communication when introducing agilities, especially to the attention of the public and healthcare professionals.

Practicalities

Standard Normative Process	Pandemic Preparedness
Evidence	
• Broaden the use of real-world data / real-world evidence • Further enable use of digital tools for capturing endpoints. • Enhance evidence generation to inform on diverse populations	• Weigh benefit/risk to guarantee quality, efficacy and safety of products, with ongoing generation of data. • Support global data convergence.
PACs	
• Enhance collaborative review and reliance practices, align on a unified set of queries for each PAC. • NRAs to fully implement and use ICH Q12 (International Council for Harmonisation).	• Exercise risk-based regulatory agility for the data requirements (e.g. waiver of samples). • Clear prioritization of changes based on public health and supply impact.
Labeling and packaging	
• Gradual implementation of e-labeling and removal of requirement for printed product information. • Share labeling between countries to improve supply chain resilience and efficiency.	• Implement an electronic central platform for sharing labeling. • Exemptions and waivers for labeling to facilitate emergency products rollout.

Sustainability

Standard Normative Process	Pandemic Preparedness
Environment	
• Increased digitalization to support environmental sustainability, such as virtual meetings and e-documentation.	• Leverage virtual working and digital methods as much as possible.

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

CBER (Center for Biologics Evaluation and Research)
CDER (Center for Drug Evaluation and Research)
CMA (Conditional marketing authorization)
CPP (Certificate of pharmaceutical product)
EMA (European Medicines Agency)
EUA (Emergency use authorization)
GMP (Good manufacturing practices)
HCP (Healthcare professional)
ICH (International Council of Harmonization)
ICMRA (International Coalition of Medicines Regulatory Authorities)
LMICs (Low and middle-income countries)
NRA (National regulatory authority)
PAC (Post approval change)
PACMPs (Post-approval change management protocols)
PAHO (Pan American Health Organization)
RWE (Real world evidence)

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