IFPMA International Federation of Pharmaceutical Manufacturers & Associations

Lessons from the regulatory agilities emerged during the COVID-19 pandemic: views from members of National Regulatory Authorities

Introduction

To address the COVID-19 pandemic, regulatory agilities were allowed and utilized by National Regulatory Authorities (NRAs) in an unprecedented manner to accelerate the development, assessment, and approval of medicines and vaccines. Since 2021, the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) has been exploring common regulatory agilities utilized during the early phases of the pandemic alongside related experiences, challenges, and lessons learned, to explore how regulatory processes might be further enhanced in the future in both non-emergency and emergency situations.

As part of this mission, IFPMA co-authored a peer-reviewed manuscript entitled "*Medicinal Product Development and Regulatory Agilities Implemented During the Early Phases of the COVID-19 Pandemic: Experiences and Implications for the Future-An Industry View*" and issued a series of position papers and recommendations on regulatory agilities (available via the following pages: regulatory agilities, clinical trials, quality assurance). Insights included in the manuscript and position papers were gathered via primary and secondary research, consisting of interviews with members of the pharmaceutical industry. The perspective of members of the pharmaceutical industry on regulatory agilities has previously been examined in greater detail by IFPMA, compared to the perspective of NRA members.

This report aims to explore the perspective of members of NRAs on the use of regulatory agilities which emerged during the COVID-19 pandemic and describe lessons learnt from this experience. Insights were collected via interviews with members of NRAs from Brazil, Ghana, and Japan, thus gathering views from different regions. Understanding the views of NRA members on regulatory agilities can help to develop realistic approaches to strengthen both non-emergency and emergency regulatory frameworks moving forward. The insights included in this report reflect the personal views of the individuals interviewed and are not representative of the position of any specific NRA.

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Methodology

IFPMA partnered with Clarivate on this project. On behalf of IFPMA, Clarivate conducted three interviews with members of different NRAs, or individuals who were affiliated with NRAs, between July and August 2023:

- **Dr. Delese Mimi Darko**, Chief Executive Officer of the Food and Drugs Authority (FDA) of Ghana. Interviewed on 04/07/2023.
- **Dr. Junko Sato**, Ex-Office Director of the Office of International Cooperation (Currently Associate Executive Director for Compliance) at Pharmaceuticals and Medical Devices Agency (PMDA) of Japan. Interviewed on 07/07/2023, together with Mr. Naoyuki Yasuda.
- **Mr. Naoyuki Yasuda**, Ex-Director of the Office of International Regulatory Affairs (Ministry of Health, Labour, and Welfare (MHLW)) of Japan (Currently Associate Executive Director for International Programs at PMDA). Interviewed on 07/07/2023, together with Dr. Junko Sato.
- **Dr. Varley Dias Sousa**, Directorate Advisor of the Brazilian Health Regulatory Agency (ANVISA), of Brazil. Interviewed on 04/08/2023.

All individuals interviewed reviewed this report and agreed to the publication of its content.

Results

Overall perspective and successes from the COVID-19 pandemic

All members of NRAs interviewed agreed that the COVID-19 pandemic highlighted the importance of agilities in regulatory processes, with. Dr. Sousa (ANVISA, Brazil) stating that, following the COVID-19 pandemic, **regulatory flexibility is seen as a strength rather than a weakness.**

According to Dr. Darko (FDA, Ghana), increased **collaboration** with NRAs, reference NRAs and the whole scientific community, and the use of **reliance in decision-making processes** were the biggest successes during the pandemic. Dr. Darko stressed that reliance continues to be relevant and used now that the COVID-19 emergency is over. When receiving a new marketing authorization application (MAA), the Ghana FDA can check whether the medicinal product has already been approved by another NRA, and if so, consider whether it would be appropriate to use regulatory reliance. Moreover, by relying on the approval decision of another trusted NRA, NRAs can dedicate more resources to other value-added activities, such as pharmacovigilance. According to Dr. Darko, risk-based approaches could be used in specific cases in non-emergency situations, leading to an efficient use of regulatory resources.

According to Mr. Yasuda (MHLW, Japan) the pandemic highlighted the **feasibility of agile approaches in regulatory processes which might not have been previously thought feasible.** In his opinion, two key agile approaches utilized during the pandemic were the conduct of decentralized clinical trials (DCTs) and remote inspections.

Accelerated/emergency authorizations and approvals

The existence of clear emergency regulatory frameworks and guidelines is of paramount importance during a health emergency to allow all stakeholders to promptly take action to address the crisis. As outlined by Dr. Darko, **guidelines on emergency use authorization (EUA),** including defined timelines for the evaluation of EUAs, were already in place in Ghana since the Ebola crisis, and they proved very helpful during the outbreak of the COVID-19 pandemic.

A considerable **increase in communication between the Ghana FDA and other reference NRAs also helped to address the COVID-19 emergency**. For instance, the Ghana FDA communicated closely with the Medicines and Healthcare products Regulatory Agency (MHRA) of the United Kingdom to discuss the observed real-world effects of the recently authorized vaccines. According to Dr. Darko, the regulatory evaluation of COVID-19 vaccines was not particularly challenging, given reliance was used in decision-making processes and the existence of defined pathways for emergency authorizations. On the other hand, **safety monitoring of vaccines proved quite difficult** in Ghana. In today's closely interconnected world, countries were at times highlighting safety concerns related to vaccines that had not been witnessed among the Ghanaian population. **Assessing and managing the flow of safety information** from other countries, including the impact of these announcements on the overall Ghanaian population, proved challenging. To increase awareness on vaccines among the population, the Ghana FDA, like many other NRAs, increased communication with the public, issuing recurrent statements on the amount of vaccine doses administered as well as on local safety-related concerns.

Managing news and information around vaccines during the COVID-19 emergency was challenging for many other NRAs around the world. Dr. Sousa stated that one of the largest challenges in Brazil was the **dissemination of false information around COVID-19 vaccines**. Despite regulatory authorizations in Brazil resulting in government purchases of vaccines, uptake among the Brazilian population was relatively low due to general vaccine hesitancy. ANVISA worked hard to improve direct communication with the Brazilian population and, according to Dr. Sousa, the authority was ultimately able to communicate with the public in a successful and transparent way. Like other NRAs globally, ANVISA tried to clearly communicate to the public the reasons for approving certain vaccines versus others, which data was available at time of authorization, as well as the risk-benefit profile of COVID-19 vaccines.

Dr. Sousa also noted that extensive resources were dedicated to addressing the COVID-19 emergency which ultimately led to **some regulatory backlogs**, the effect of which is still felt today. Acknowledging this backlog is important when discussing which agilities, especially among those that are particularly resource-intensive for NRAs, should be further implemented moving forward.

Dr. Sato (PMDA, Japan) and Mr. Yasuda noted that the Government of Japan had a mechanism for "special approval for emergency" pharmaceutical products, rather than "emergency use authorizations" which were allowed in many other countries, such as in the United States. According to both interviewees, this **"special approval for emergency" pathway** proved very effective during the COVID-19 pandemic and could also be implemented in the future for other emergency circumstances.

According to Dr. Sato and Mr. Yasuda, the **initial lack of vaccine safety data related to Japanese people**, or Asian people more generally, represented a barrier to faster approval of COVID-19 vaccines. Despite the political and social pressures to approve vaccines as fast as possible, the PMDA made sure that necessary safety data was available before approving the COVID-19 vaccines. These "delays" in vaccine approvals compared to other NRAs globally were at times politically criticized in Japan. However, the approval time was considered necessary from an NRA standpoint to prioritize the safety of the Japanese population.

Similarly, Dr. Sousa stressed how employees of ANVISA were working under considerable **public pressure** when evaluating potential medicinal products to fight the pandemic. Employees of ANVISA felt highly accountable to the Brazilian population. Some members of the population wanted certain vaccines authorized, whilst others hoped for the opposite. According to Dr. Sousa, **the greatest success of the pandemic was that NRAs were able to provide answers to the society in a timely manner, without sacrificing technical science and data robustness.**

Increased digitalization

All interviewees agreed that the **digitalization of ways of working, processes, and methods was crucial** in allowing continuity of clinical research and regulatory processes during the pandemic, given the restrictions placed upon movement and in-person interactions to limit the coronavirus transmission.

All interviewees identified remote inspections as one of the key areas where digitalization of working practices proved particularly impactful. They all recommended that remote inspections should continue in the future as appropriate to gain efficiencies in regulatory processes, including in non emergency situations. Moreover, remote inspections should not replace physical inspections, but should rather be perceived as complementary. Dr. Sousa highlighted how remote inspections can allow large cost reductions and several inspectors to be present at the same time. However, he also stressed the need to have further discussions to decide which facilities should be assessed via a physical, hybrid, or remote inspection. For instance, remote inspections could be used when dealing with a facility which has been already assessed by another NRA or in case of low-risk products. Similarly, Mr. Yasuda noted that stakeholders in Japan are now considering in which non-emergency situations it may be beneficial to use remote versus physical inspections.

Another example of an effective method utilized in clinical research was **electronic consent (e-consent).** As highlighted by Dr. Sato, e-consent started to be extensively utilized in Japan during the pandemic. Now that the emergency is over, e-consent is considered as an efficient method in non-emergency situations which can contribute to further increasing the decentralization of clinical trials in the future.

Interviewees reported **different experiences with relation to e-labelling**, which is not surprising considering the different speeds at which e-labelling is being adopted around the world. Dr. Sato noted that e-labelling was already implemented in Japan before the COVID-19 pandemic. Dr. Sousa highlighted how in Brazil, due to the labels of some medicinal products being in English, barcodes were utilized so that information could be easily accessed in Portuguese during the pandemic. Following the pandemic, e-labelling was allowed for hospital products in Brazil; however, Dr. Sousa stressed that challenges related to the more widespread use of e-labeling remain. Brazil is a large country with considerable variation in internet accessibility. Similar challenges also exist in other countries which may have poor access to the internet and technology. Dr. Darko noted that, so far, e-labeling has not been utilized in Ghana. However, she believes its future adoption would be beneficial to facilitate updating product information and improve patient safety.

Telemedicine was mentioned as another important way to deliver healthcare services, enabled by increased digitalization. Dr. Sousa noted that telemedicine was widely used in Brazil during the pandemic, resulting in virtual prescriptions and virtual dispensing, and that a new Telehealth Act came into force in Brazil in December 2022 (Federal Law n. 14,510/2022).

Digitalization was also an important enabler of close collaboration among stakeholders based in different locations during the pandemic. As outlined by Dr. Darko, in Ghana, thirteen **COVID-19 clinical trial applications** were jointly reviewed among different NRAs (with reviews successfully held virtually). Before the pandemic, stakeholders from various NRAs would have normally met in person for such collaborative reviews.

Finally, as noted by Mr. Yasuda, the **pandemic further reinforced and accelerated a process of digitalization of ways of working which continues today.**

Decentralized clinical trials (DCTs)

The conduct of clinical trials was heavily impacted during the COVID-19 pandemic, and decentralized methods were implemented to mitigate the barriers aimed at minimizing risk of virus transmission. According to all interviewees, **DCTs can offer important benefits moving forward** in non-emergency situations, depending on the type of study and context. Dr. Sato and Mr. Yasuda noted how an increased level of decentralization of clinical trials might be particularly beneficial when study participants have limited mobility, for instance. On the other hand, if serious adverse events are feared or if certain daily activities of patients could affect the results of a trial, doctors should physically monitor and interact with patients. The two interviewees also stressed how **DCTs can make it easier for people to participate in trials and can thus increase the number of study participants.**

For instance, in disease areas where the patient population is small, such as rare diseases, DCTs can increase the chances of recruiting an acceptable number of patients by decreasing barriers to participation. Moreover, Dr. Darko stressed how DCTs have the potential to **increase diversity** by reducing geographical barriers and allowing more people to participate in trials. From the perspective of an NRA, a higher percentage of local population included in a trial is key to strengthening safety data, if appropriate digital data collection tools are used.

According to Dr. Sato, the industry appears interested in reaping the benefits of increased decentralization of clinical trials, but **companies are still in the process of weighing the benefits and limitations of DCTs.** In Japan, the PMDA is open to discussing this topic with the pharmaceutical industry but is currently not actively encouraging DCTs, as they believe that companies should decide the level of decentralization of clinical trials based upon the objectives and characteristics of each individual study.

Dr. Sousa highlighted a lack of clear regulation and requirements for DCTs and a need to **further regulate DCTs**, stating that the industry and NRAs need to explore in which circumstances increased decentralization would be positive.

Remaining barriers and possible solutions moving forward

Interviewees were asked about perceived barriers and enablers for further adoption of regulatory agilities in the future. According to all interviewees, **global coordination, collaboration, and sharing of best practices** are critical to encourage appropriate adoption of regulatory agilities.

In case of future global emergency, such as a pandemic, Dr. Sato and Mr. Yasuda stressed it would be important for all countries to be able to implement regulatory agilities. Similarly, Dr. Sousa noted how, particularly in emergency situations, global decisions influence local decisions. According to Dr. Sousa, the **role of the World Health Organization (WHO) and other international agencies / fora** is fundamental to encourage the use of regulatory agilities. Moreover, recommending the use of certain regulatory agilities can be far more impactful than simply accepting their use. Dr. Sousa also noted that **maximizing transparency** in the decision-making processes of NRAs can be an enabler for successful use of reliance and for increased collaboration among NRAs to address the common emergency.

Dr. Darko pointed out the value of **initiatives aimed at sharing best practices** among NRAs, for instance in relation to guidelines development or strategies for implementing risk-based approaches in decision-making. **Capacity building programs** on emerging methods and processes, such as e labelling, would also be beneficial. Dr. Darko finally highlighted the importance of **multi stakeholder collaboration** during the COVID-19 pandemic and how such collaboration, including industry, NRAs, and academia, is increasing to help to drive innovation.

The **legal framework and political environment** can be important enablers for NRAs to implement regulatory agilities. As opposed to many other NRAs, the Ghana FDA was able to issue enforceable guidelines on reliance which proved helpful during the pandemic. However, as noted by Dr. Darko, the **establishment of Memorandums of Understanding** is helping many African countries, such as Rwanda, to approve medicinal products in an agile way, relying on the approval of products by other NRAs, such as the Ghana FDA. Dr. Darko also stressed how **NRAs globally are continuing to become more agile**, adapting their ways of working to benefit patients.

Finally, Mr. Yasuda stressed how the COVID-19 pandemic experience helped NRAs to **gain more confidence in the implementation of regulatory agilities**. Dr. Sato agreed with this, but also noted that despite the critical role of global coordination, collaboration, and sharing of best practices, due to the different local contexts, ultimately some **NRAs will be able to implement certain agilities that other NRAs will not be able to apply.** Similarly, Dr. Darko suggested that for some countries, the level of available resources may influence their ability to advance regulation or implement certain agilities.

Conclusion

All members of NRAs interviewed believed that the COVID-19 pandemic highlighted the importance of implementing regulatory agilities to allow the rapid development and approval of safe and effective medicinal products during a health emergency. Maximizing cooperation at a global level, ensuring emergency guidelines are in place, and the ability to grant emergency or accelerated authorization (or approvals), were recognized as important factors to address future emergencies, such as a pandemic. However, interviewees also saw significant benefits in utilizing certain regulatory agilities, depending on the context, in non-emergency situations, to increase efficiencies in regulatory processes. For instance, increased decentralization in clinical trials can facilitate patient recruitment, improve the patient experience, and increase diversity; remote or hybrid inspections can allow for savings in financial and human resources; e-labelling can facilitate the update of product information and enhance patient safety; and using reliance in decision-making can allow for efficient use of regulatory resources. Interviewees also acknowledged that the adoption of some agilities is ultimately likely to differ among NRAs, depending on different local contexts, laws, regulations, and country resources. Finally, according to NRA members, further discussions and potentially further regulation on regulatory agilities would be beneficial to determine in which circumstances agilities should be applied, and to what degree. Such discussions would be beneficial within NRAs, at the global level via organizations such as the WHO or the International Coalition of Medicines Regulatory Authorities (ICRMA), respecting the guidelines from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) as a global technical framework, and among NRAs and the pharmaceutical industry.