International Federation of Pharmaceutical Manufacturers & Associations

IFPMA policy briefing on:

Regulatory agilities applied to clinical trials

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 clinical trials processes have been key to allow **rapid research and development of 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 in clinical trials** observed since the start of the pandemic, **reported challenges** to their implementation and **forward looking recommendations**, whether to prepare for the next pandemic or to modernize standard normative processes to accelerate patient access to safe and effective medicines.

Introduction

The COVID-19 pandemic has posed unprecedented challenges to all healthcare stakeholders and society at large. The implementation of a variety of agilities related to clinical trials were key to protect participant safety and ensure the continuity of clinical research, ultimately facilitating the development and approval of safe and effective COVID-19 and non-COVID-19 related pharmaceutical products.

In some instances, the pandemic led to the emergence of new practices and ways of working whilst in others, it accelerated the use of existing tools such as the digitalization of clinical trials conduct.

The experience of the pandemic offered unprecedented learnings on which the biopharmaceutical industry and NRAs can build to enhance the conduct of clinical trials in both standard normative regulatory process as well as to improve pandemic preparedness.

The pharmaceutical industry is committed to engaging in continuous efforts to improve the conduct of clinical trials. With this paper, IFPMA aims to outline important trends in reported experiences in clinical trial agilities that emerged during the COVID-19 pandemic, reported 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 without compromising the safety of participants and clinical trial data of products under development.

The main themes of this paper are grouped under three categories centered on maximizing efficiency, increasing collaboration and improving practicalities.

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 clinical trials*

Digitalization

Trends: The increase in **virtualization of working practices** and the **use of virtual tools** were key trends that allowed continuity of clinical trials during the pandemic. Examples included: electronic communication and exchange of information between the NRA and applicants, temporary use of telemedicine, use of remote written or non-written informed consent and use of e-signatures.

In the **European Union**, common trends included remote SDV (source data verification) and electronic informed consent. In **Japan**, meetings of the Institutional Review Board were held exceptionally via email or virtually to enable the quick start of clinical trials for COVID-19 products. Many clinical trial databases were made accessible via the Internet and the National Institute for Public Health of Japan database allowed cross-searching of clinical research information stored in four registries in both Japanese and English.

Challenges: **Lack of access** to appropriate **technology infrastructure,** such as internet accessibility, in settings with scarce resources, limited the implementation of agilities. Local language of clinical trial databases was also identified as a challenge, preventing non-speakers from accessing information.

Ways of working, Decision-Making, Reliance

Trends: During the pandemic, **innovative ways of working and flexible approaches** were key to allow the execution of clinical trials and sustaining patient participation. These agilities also aimed at minimizing the risk of COVID-19 infections by reducing the need for physical interactions, ensuring the availability of the trial product for participants and reducing the need for personnel at clinical trial sites. **Agilities and innovative clinical trial approaches, in both design and execution**, included:

- Conducting decentralized clinical trials; remote monitoring; utilizing e-consent; and waiving the requirement for wet-ink signatures.
- Temporarily pausing enrollment to clinical trials and restarting them without submission to NRAs; broadening criteria of healthcare professionals carrying out investigation duties, including at remote sites; reducing notification requirements for non-significant changes to authorized trials; allowing for shorter timelines to initiate clinical trials; allowing for justified protocol deviations without notifying the authority; rescheduling or postponing clinical visits by authorities with risk-based justification.
- Allowing for alternative means of drug delivery, such as direct to patient delivery at home; using alternative trial or lab sites.

There were also efforts to strengthen global collaboration on COVID-19 **real-world evidence (RWE) and observational studies**; for instance a workshop convened under ICMRA (the International Coalition of Medicines Regulatory Authorities) and co-chaired by Health Canada and the European Medicines Agency (EMA) which took place in October 2020, allowed NRAs to discuss their experiences with supporting and assessing RWE to facilitate regulatory decision-making on COVID-19 treatments and vaccines.

Risk-based approaches to decision making were taken to accelerate clinical trial processes. Commonly reported experiences included prioritizing the review and authorization of actionable studies or allowing some justified protocol deviations without notification (with sponsors still required to maintain the documentation to enable appropriate evaluation of trials).

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

The **Asia** region was characterized by a high level of agilities for clinical trial conduct during COVID-19. In **Japan**, alternative measures for sponsors or clinical trial sites were allowed if process in study protocol was no longer feasible (e.g. in cases where trial participants cannot visit the clinical trial site to receive study drugs), as well as shorter clinical trial notification timelines for COVID-19 products.

In the **United States**, the Food and Drug Administration (FDA) created the CTAP (Coronavirus Treatment Acceleration Program), emergency program supporting clinical trial testing of new COVID-19 treatments, as well as the ACTIV (Accelerating COVID-19 Therapeutic Interventions and Vaccines) partnership. ACTIV involves government and industry partners, including FDA, working to prioritize vaccine and therapeutic candidates, streamline clinical trials, and rapidly expand clinical research resources to develop COVID-19 therapies. CTAP provided subject matter expertise for ACTIV initiatives, including clinical trial design and conduct and regulatory standards. The FDA could then facilitate prioritized review and increased efficiency in evaluating proposed pre-clinical and clinical studies.

In the **European Union**, additional risk-based approaches were utilized to ensure prioritization and resource availability. Examples of risk-based approaches included GMO (Genetically Modified Organism) derogation, highly valued by developers of COVID-19 therapeutics as it provided consistency and shortened review times, as well as remote SDV.

Generally, **Japan and the Asia region** showed a high level of agilities for clinical trials conducted during the pandemic.

In the **United Kingdom**, trends included: use of e-signatures; remote monitoring of clinical trials; temporarily halting recruitment of ongoing clinical trials (more frequently utilized at the beginning of the pandemic); temporarily waiving the requirement to report increases in protocol deviations to the MHRA (Medicines and Healthcare products Regulatory Agency); expedited scientific advice and rapid reviews of clinical trial applications. Overall, the UK experienced a reduction in use of agilities over time, as clinical trials resumed following the first wave of the pandemic.

Challenges: In some cases, **prioritization** of COVID-19 related clinical trials led to a temporary pause of clinical trials for non-COVID-19 related products, creating an important backlog and delays in development of products.

The pandemic also caused severe **disruptions to clinical trial recruitment**, due to the efforts needed to minimize risks of transmission of COVID-19 among participants and healthcare providers and several other existing **individual and systemic barriers to participation** such as lack of trust in the medical and biopharmaceutical industry, lack of awareness of clinical trial options, time and financial costs of participation, lack of supportive infrastructure.

Finally, despite the benefits of digitalization in conducting clinical trials, getting **traceable and auditable data** from non-traditional sources into the Electronic Data Capture system remained a challenge.

In the **European Union**, burdensome administrative requirements negatively impacted the pace at which sponsors, personnel in trial sites and NRAs conducted their activities; national requirements and approaches of member states as well as allowance for remote SDV were also problems flagged by the industry. With regards to clinical trial applications in **Africa**, industry highlighted challenges related to the legalization of documents and provision of hard copy / CD ROM files (in the absence of e-portal) as well as delayed inspections of products.

Harmonization

In the **European Union**, harmonized guidance and agilities for amendments, direct to patient delivery, remote assessment and alternative trial/lab sites were useful agilities for the industry. Attempts to harmonize requirements among different regions also involved **joint procedural information** for sponsors for submitting PIPs (Paediatric investigation plans) to the EMA and iPSP (Initial Pediatric Study Plan) to the US FDA. The EMA provided scientific recommendations on how compassionate use medicines should be used to support a harmonized EU-wide approach.

Challenges: As NRAs around the globe took different approaches to clinical trial processes, patients' continued access to treatment in ongoing trials was easier in some countries compared to others. This is also due to the fact that different regulatory approaches may be needed in different countries or regions.

In the **European Union**, the harmonization guidance was still limited by Member States' national requirements and approaches.

Early-dialogue, Transparency

Trends: During the COVID-19 emergency, **increased collaboration** among sponsors and NRAs facilitated clinical trials and the continuity of research for innovative medicines. NRAs provided guidelines as well as technical communications for sponsors and researchers on clinical trial requirements and, generally, the industry considered NRAs' support in addressing challenges around the execution of clinical trials very helpful.

In the **United States**, the FDA quickly published **guidance for industry** on developing COVID-19-related treatments, including how to efficiently engage with FDA and expedite clinical trial initiation. The FDA gave **recommendations on data generation** to support an EUA for monoclonal antibody products targeting SARS-CoV-2. Additionally, the CTAP dashboard provided a snapshot of the development of potential COVID-19 therapeutics, with the number of companies and researchers developing COVID-19 related therapies, updated monthly. **For patients and consumers**, the FDA provided **clear explanations** of key technical terms and answers to frequently asked questions about COVID-19 therapies. CDER (Center for Drug Evaluation and Research) and CBER (Center for Biologics Evaluation and Research) promoted EUA transparency to increase public confidence in FDA's scientific review process and in products by disclosing information from scientific review documents, in alignment with legal processes for the appropriate redaction of commercially confidential/trade secret information.

In the **European Union**, **guidance** to facilitate protocol amendments and for initiation of new trials was provided, as well as a dedicated early point of contact at EMA and the provision of rapid scientific advice to further accelerate mechanisms.

In **Japan**, the PMDA (Pharmaceuticals and Medical Devices Agency) allowed close interaction with sponsors to streamline product development and to deal with diversions from clinical trial protocols. Sponsors of candidate products for COVID-19 also had shorter CTN (clinical trial notifications) timelines to clinical trials initiation. Principles for the evaluation of efficacy and safety of COVID-19 vaccines were published and the PMDA offered free scientific advice for COVID-19 vaccines development to enhance the predictability of vaccine development and to facilitate early initiation of clinical trials.

Challenges: Among the several barriers in accessing clinical trials, the **lack of awareness around clinical trial options** for participants was identified, signaling the need for enhancements to public communications regarding clinical trials.

> In the US, the FDA held **advisory committee meetings for COVID-19 products that were open to the public** and that were available by webcast. That was a way to have **scientific debate independent of the regulatory authority and ensure transparency**."
>
> *Excerpt from interview with Janet Vessotskie, PhRMA*

Evidence

Trends: The COVID-19 pandemic highlighted health inequities globally, pushing the industry to adopt strategies to address those inequities, including addressing diversity in clinical trial participation.

In the **United States**, industry wide principles on clinical trial diversity were published to reduce barriers to clinical trial access and use real-world data to enhance information on diverse populations and information about diversity and inclusion in clinical trial participation.

> [to improve confidence in the accelerated development and approval process of products] people from different ethnicities and backgrounds could be included in the trial design, for instance people of African origins regardless of clinical trials setting.
>
> *Excerpt from interview with Philip Tagboto, AREPI*

Challenges:

In the **European Union**, ensuring data integrity was identified as a challenge together with protocol requirements and deviations. In **Latin America**, issues flagged included the translation of scientific evidence for decision-making purposes and for the understanding of health personnel, as well as lack of complete data for submissions for EUA.

Environment

Trends: The COVID-19 pandemic led to **increased levels of decentralization of clinical trials,** with the use of digital technologies and virtual consultations decreasing the need for movement and traveling for both personnel of clinical trial sites and clinical trials participants.

Recommendations

Efficiency

Digitalization

Ways of working, decision-making, reliance

Harmonization

Standard Normative Process	Pandemic Preparedness
• Adopt virtualization in ways of working and digital formats: decentralized clinical trials and using digital tools to capture endpoints. • Give the option to participate in decentralized or standard clinical trials.	• Use electronic methods such as digital tools to capture endpoints, technologies supporting decentralized clinical trials.
• Require actions from ICMRA and NRAs for protocol deviations, remote SDR (Source Data Review) and SDV, alternative method of consent and alternative means of drug delivery to study participants. • Improve health equity by increasing diversity and inclusion in design and recruitment. • Implement risk-based approaches to improve efficiency. • Plan future protocols to accommodate flexibility for in-clinic, home health, and/or telemedicine visits	• Lessen barriers to participation to clinical trials: increase communication, bring trials closer to patients, make office hours more accessible, direct to patient delivery, alternative trial/lab sites. • Explore use of clinical trials platforms to conduct emergency clinical trials. • Flexibility in regulations and processes such as accelerated assessment of clinical trial applications. • Support alternative clinical trials methods.
• Support international convergence (through ICMRA) on minimum data package	• Alignment of regulatory requirements (through ICMRA), support convergence on minimum data package in case of emergency & avoid multiple development plans during emergencies.

Collaboration

Early dialogue, transparency

Standard Normative Process	Pandemic Preparedness
• Increase dialogue among ICMRA and industry for NRA development of future approaches and alignment of regulatory requirements. • Embrace transparency and enable appropriate information sharing, compliant with international data protection rules, among regulatory bodies. • Introduce trusted data platforms, for global information sharing and collaboration.	• Sponsors to make contact as soon as possible to discuss strategies. • Transparent and accessible-to-all communication to increase public confidence.

Practicalities

Evidence

Standard Normative Process	Pandemic Preparedness
• Institutionalize the generation and use of RWD (Real-world data) and RWE (Real-world evidence).	• Adopt risk-based approaches to what is reasonable / enough data to be generated during clinical trials for emergency and conditional approval. • Avoid multiple development plans at time of public health emergency.

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

ACTIV (Accelerating COVID-19 Therapeutic Interventions and Vaccines).
CBER (Center for Biologics Evaluation and Research).
CDER (Center for Drug Evaluation and Research).
CTAP (Coronavirus treatment acceleration program).
EMA (European Medicines Agency).
EUA (Emergency use approval).
FDA (Food and Drug Administration).
GMO (Genetically modified organism).
MHRA (Medicines and healthcare products regulatory agency).
NRA (National regulatory authority).
PIPs (Paediatric investigation plans)
iPSP (Initial pediatric study plan).
RWD (Real world data).
RWE (Real world evidence).
SDR (Source data review).
SDV (Source data verification).

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