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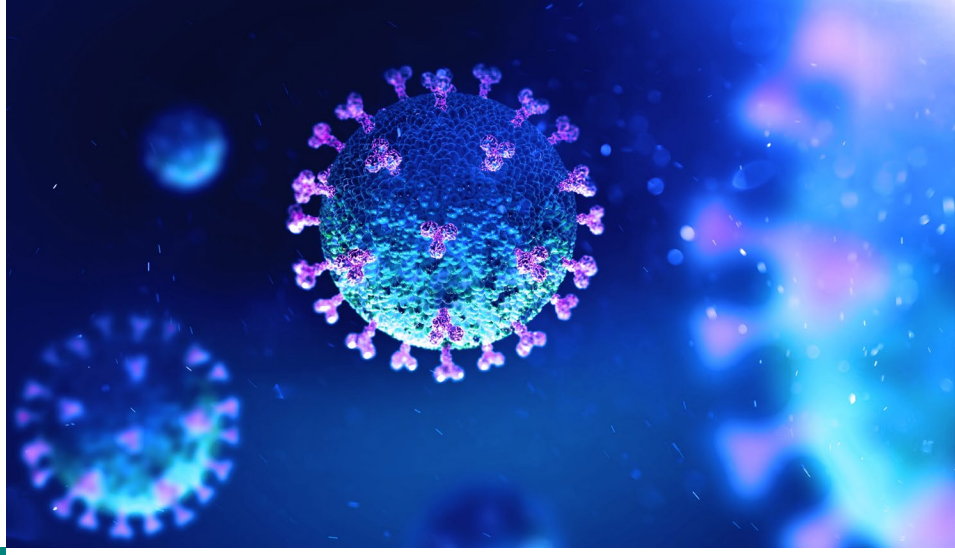

COVID-19 Global Regulatory Agilities

Multi-Stakeholder Virtual Workshop

February 7, 2022

Summary

Workshop hosted by MSD and Avalere Health

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I. Introduction

The COVID-19 pandemic led regulatory authorities around the world to develop and deploy innovative ways of working to speed the development and delivery of vaccines, therapeutics, and diagnostics targeting the virus without compromising their quality, safety, or efficacy. As policymakers shift their focus beyond the immediate public health emergency, there is a window of opportunity for stakeholders to consider the value in continuing, expanding, or stopping the regulatory flexibilities, policies, and procedures used during the pandemic.

As many organizations, including regulators, began issuing "lessons learned" assessments from their experiences working in the COVID-19 pandemic, MSD recognized a knowledge gap forming – that these regulatory agility assessments focused on the perspectives of regulators and the regulated industry and had not yet included additional stakeholder voices. In response, MSD, partnering with an external consultant Avalere Health (Avalere), embarked on an initiative to contribute to closing this gap, elucidate the perspectives of a diverse set of stakeholders, and identify the impacts specific regulatory agilities had (or would have) on these groups.

For the purposes of this initiative, we defined "regulatory agilities" or "agilities" as:

Actions taken by a regulatory agency (as part of broader health authorities) driven by and in the context of the COVID-19 public health emergency that depart from that regulatory agency's pre-pandemic actions, procedures, and approaches. Note, this may include actions with both positive or negative consequences across stakeholders.

Through a set of blinded interviews with 22 global stakeholders representing regulators (current or recent), life sciences and biotechnology manufacturers, patient advocacy groups, multilateral organizations, and academic thought leaders from 4 continents (North America, South America, Europe, and Africa), Avalere identified 10 high-impact agilities and outlined case studies that exemplify each agility and allowed more detailed review of process and outcomes of each agility.* See **Appendix A** for detail on each of the 10 agilities and case studies.

On February 7, 2022, Avalere and MSD hosted a half-day, invite-only, interactive multi-stakeholder workshop with the following objectives:

- To elucidate stakeholder views of select COVID-19 regulatory agilities that agencies could retain beyond the pandemic to strengthen routine regulatory practice, prepare for the next pandemic, and build a more coordinated global regulatory system to build out a "360° view" of each agility
- To discuss the (current and/or potential) impacts of these regulatory agilities on stakeholders across the healthcare ecosystem

Further, the workshop aimed to discuss opportunities, challenges, and strategies to sustain agilities beyond the end of the pandemic. See **Appendix B** for workshop agenda. Recognizing time limitations, we selected the following five (out of the 10 identified by Avalere) agilities to focus on during the workshop:

- Reliance & Mutual Recognition
- Convergence & Harmonization
- Decentralized Trials
- Data Expectations for Market Entry
- Advances in Use of Pre-Market Real-World Evidence

*Agilities related to devices and diagnostics were excluded as out of scope of this work. In addition, we do not mean to suggest that agilities not included in the 10 chosen are not impactful or should not be prioritized for action.

These five agilities were selected because the research concluded that these topics had relatively more outstanding questions and need for discussion. The remaining five capabilities are also greatly valued but also more substantially explored in other settings and publications.

Over 50 global experts participated in the workshop, including individuals from the pharmaceutical and biotech industry (companies, trade associations), clinical trialists (academics, CROs), patient advocacy organizations, payers/HTAs, data/technology companies, finance/multilateral organizations, and providers (trade associations). See **Appendix C** for a list of workshop participants.

This summary outlines what we heard at the workshop and highlights key insights that emerged from the discussion. As such, this document is not meant to be a chronological, comprehensive transcript of the event. We want to thank Avalere for its organization and facilitation of the event and partnership throughout this initiative, the global experts who spoke at the workshop for sharing their expertise and experience, and all participants for contributing their insights and unique views on the global regulatory agilities seen during the COVID-19 pandemic.

II. Stakeholder Insights on Selected Regulatory Agilities

During the workshop, participants joined a breakout group of their choice to discuss one of the five regulatory agilities. After the breakout sessions, each group presented its top insights followed by a full group discussion. The highlights captured below come primarily from those discussions, but also include participant comments made throughout the workshop.

A. Reliance & Mutual Recognition

For purposes of this work, we defined reliance and mutual recognition as "processes whereby a regulatory authority in one jurisdiction partially or wholly relies on evaluations of another regulatory authority or trusted institution. Mutual recognition signals that two or more regulatory authorities recognize comparability of assessment results."

Stakeholders recognized the benefit of reliance to reduce individual regulator workload and facilitate faster licensing of new products, which may be particularly valuable in less-resourced settings, but also acknowledged that using reliance to approve products does not necessarily guarantee access.

EMA's OPEN initiative, FDA's Project Orbis, and the new process for the African Union, African CDC, and WHO to evaluate EUA vaccines were cited as successful examples of work sharing and collaboration. For example, participants noted that EMA included WHO and LMIC regulators early in the OPEN initiative process, allowing their input and creating a sense of joint ownership in decision-making, which led to more comfort when using reliance. In addition, others mentioned that opportunities exist to use Project Orbis in therapeutic areas beyond cancer.

Stakeholders reported that the use of virtual technology has fundamentally changed the dynamic for reliance, and the group expressed hope that the use of these technologies (eg, for networking, joint assessments, meetings) will continue past the pandemic. For example, use of virtual technology was crucial to the success of AVEREF's implementation of its revised process for emergency joint assessment of clinical trials. Benefits included allowing meetings to happen quickly (days vs months) and simultaneous translation, which allowed regulators to work in the language they felt comfortable with.

Virtual technology fundamentally changed the dynamic for reliance, especially for LMICs. The hope is that these technologies for networking, joint assessments, and meetings continue, and we don't go back to always in-person meetings.

Participants recommended thinking of reliance in terms of the whole product life cycle, and not just for initial approvals. Variations require a huge commitment of resources, and delays in approval of post-approval changes have negative downstream impacts (eg, stockouts). As such, impacts of the use of reliance for this purpose may, in fact, be more significant than the use of reliance for initial product registration.

The use of reliance for product life cycle updates (variations) can be more impactful than reliance for initial product registration because delays can lead to stockouts and other negative downstream impacts. Variations currently require a huge commitment of resources.

Stakeholders recognized that every entity has finite resources, and that robust participation in reliance requires creation of efficiencies for all parties. Simply put, parties that only see burden and not benefit will not be incentivized to participate. In addition, participants noted that HICs who are leading the charge on reliance (and harmonization) need to (more fully) include LMICs in those discussions (rather than expect them to sign on to a process without being included in the conversations). Similarly, participants acknowledged the resource trade-offs for this work and that resource constraints and costs are magnified in LMICs settings because of capacity and capability realities.

Transparency and information sharing are foundational for successful use of reliance approaches. Reliance approaches require quick access to helpful documentation from regulators (how "helpful" the documentation is related, in part, to how redacted it is). Participants suggested that a rethinking of confidentiality provisions and agreements was needed, noting that treating regulators as the "public" does not make sense and, in fact, impedes a coordinated global regulatory system. Further, participants noted that current confidentiality laws place burdens both on regulatory agencies to protect data while also meeting disclosure requirements, and on industry to submit multiple and different data packages across markets. Having to submit the same dossier to separate countries is very onerous, particularly for a smaller company. Participants noted that use of electronic common technical document (eCTD) creates opportunities for streamlined, transparent data sharing, thereby reducing burden on industry and regulators. In addition, developing secure platforms so regulator-to-regulator communication could become routine was discussed and many participants expressed interest in developing a database to share data variations, citing ongoing work in Europe.

Participants explained that pharmacovigilance is an area of great challenge in LMICs, mentioning that the work MHRA is doing with joint assessment of adverse event reports with LMICs allows this work to happen much closer to "real time." Further, stakeholders noted that a significant challenge to reliance is that LMICs were not getting the same* version of products that the stringent regulatory authority had approved. Therefore, LMIC regulators had to spend limited resources determining if the product was the same or if not, how did it differ from the approved version, and therefore, whether they could use reliance or not.

*The WHO Good reliance guideline has the following definition on product sameness: Sameness of product. For the purpose of this document, sameness of product means that two products have identical essential characteristics (ie, the product being submitted to the relying authority and the product approved by the reference regulatory authority should be essentially the same). All relevant aspects of drugs, medical devices and in vitro diagnostics, including those related to the quality of the product and its components, should be considered to confirm that the product is the same or sufficiently similar (eg, same qualitative and quantitative composition, same strength, same pharmaceutical form, same intended use, same manufacturing process, same suppliers of active pharmaceutical ingredients, same quality of all excipients). Additionally, the results of supporting studies of safety, efficacy and quality, indications and conditions of use should be the same. The impact of potential, justified differences should be assessed by the manufacturer (for the purpose of this document, manufacturer also means marketing authorization holder) and the relying national regulatory authority (NRA) in determining the possibility of using foreign regulatory assessments or decisions.

B. Convergence & Harmonization

For purposes of this work, we defined convergence and harmonization as "regulatory requirements across countries or regions becoming more 'aligned' over time by adopting common, internationally recognized technical guidance documents, standards and scientific principles, or similar practices and procedures."

Participants mentioned a number of examples of successful initiatives that brought regulators together, including the Access Consortium, COVAX (eg, cluster meetings), and ICMRA. However, it was noted that convergence and harmonization are not as global as we think. For one thing, regulatory authorities differ in their awareness of convergence opportunities and access to groups like ICMRA, affecting their ability to participate. Increasing convergence and harmonization requires a significant amount of effort and awareness raising, and right now it is not reaching all regulators. Furthermore, language barriers can hinder harmonization.

Convergence and harmonization are not as global as we think.

Participants acknowledged the costs of these interactions among regulators (eg, at ICMRA), including the exponential workload increase that affects not just those participating, but others around them (eg, inspectors). Further, participants noted that complete harmonization or convergence is not ideal because a good reason (eg, patient interest, healthcare system priorities) may warrant some differences in policies and procedures. Therefore, we should aim for a balance of convergence or harmonization and some flexibility to allow tailored approaches.

Successful convergence and harmonization requires a balance between complete harmonization or convergence, which is not ideal, and flexibility to tailor appropriately to the situation.

Participants discussed the risks associated with collaboration and the exchange of information among regulators (eg, risk of information "leaking"). However, participants acknowledged that these risks are not new and were present prior to the COVID-19 pandemic, with some suggesting that we must not always use the security risks/data privacy risks to block advancement, noting the increase of technology (eg, cloud computing) solutions to mitigate these risks. Others added that it is important to have positive messaging surrounding the means to address these risks and highlight that there are safeguards currently in place to help minimize them (eg, data and confidentiality agreements).

We heard that clinical research is an area ripe for more robust harmonization discussion. Participants noted that creating global alignment and convergence on master protocols would significantly ease the burden on regulators but would require effort to achieve. Another need mentioned was for harmonization of ethics committee review. Participants explained that in Africa, as regulatory authorities become more efficient, newly established ethics committees and requirements are surfacing as the new roadblock for product development.

C. Decentralized Trials

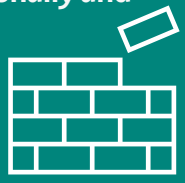
For purposes of this work, we defined decentralized trials as "clinical trials executed using a combination of digital technology and new processes to facilitate patient-centric trial participation, characterized by utilizing digital tools to conduct trial activities with fewer clinical visits."

Participants viewed decentralized trials as a spectrum, with each trial using elements in a context-specific way based on disease state, type of therapy, population of study participants, and individual participant needs.

Decentralized trials should be viewed on a spectrum – each using DCT elements in a context-specific way based on disease state, type of therapy, population of study participants, and tailored to individual participant needs and desires.

We heard that greater decentralization is both trial- and participant-dependent. Stakeholders noted that some degree of flexibility can alleviate some obstacles to trial participation (eg, finding childcare, getting time off work, sending drug directly to study participants, certain ancillary services done at local sites), but we need to understand the impact more clearly – did these things make participation in trials more manageable for individuals – because these challenges are trial- and participant-specific. As such, greater decentralization is not a panacea for all historical barriers to participation in clinical trials, and, in fact, it introduces new barriers for some.

Greater decentralization is not a panacea for historical barriers for participation in clinical trials for all individuals, and, in fact introduces new barriers. It is situationally and participant-dependent and requires a culture shift for the entire enterprise.



Participants explained that we cannot simply assume, as some do, that every study participant will find DCT elements better, easier, or more convenient. One participant offered an analogy to the challenges we have seen around remote learning – ie, remote learning sounded like a good way of dealing with the situation, but experience revealed different individual challenges (eg, household experience, technology, differences in learning style) leading to some kids thriving and others falling behind.

To this point, EveryLife Foundation for Rare Disease's 2020 workshop on COVID-19 lessons learned* was mentioned. We heard that during that workshop patients and families shared their unique experiences with decentralized trials and remote data capture. Importantly, they found that study participant experiences varied and depended on the individual's comfort in using the technology themselves. We need to ensure the study participant and family are confident in what we are asking them to do (eg, that they knew what to do, that they knew they were doing it right, that their data and time were going to be used). Furthermore, companies raised unexpected challenges, such as licensing to allow nurses to handle the drug in a participant's home. It was clear that for some individuals, the use of decentralized tools

*Rare Disease Scientific Workshop 2020

would be beneficial, but not for all. As such, ongoing patient engagement is needed to understand these differences and will be critical to ensuring the long-term success of decentralized trials.

We cannot simply assume all DCT elements benefit all trial participants. Trade-offs exist between benefits (eg, don't have to go to study site) and burden (eg, participants now have to do these things themselves). Understanding individual perspectives and ongoing patient engagement will be critical to the long-term success of greater decentralization of trials.

In addition, participants noted that the vast heterogeneity of patient experience with COVID-19 was a challenge to understanding the patient perspective, including uncertainty in how to define who are COVID-19 "patients" (ie, we are all patients) and the lack of a national COVID-19 patient organization to engage.

Data privacy and data protection frameworks were mentioned, noting that data protection laws vary by country and need to be addressed as barriers. Stakeholders explained that concerns exist regarding where study participant data goes first (eg, a sponsor's data system), how protected it is, and how much responsibility and accountability there is to ensure protection. More education is needed to inform potential study participants of data privacy rights, and this education can increase trust in decentralized trials, ensuring easier recruitment for new trials. Legal barriers such as anti-kickback statutes and state licensing (including the equivalent in other countries) also pose issues.

Participants mentioned ACRO's work during the last 3 years on the use of decentralized trial modalities and the creation of a toolkit for decentralized trials.[†] Stakeholders noted that further sharing of data and lessons learned for the use of decentralized trials is needed, including contributing both successes and challenges (eg, wearable data not accepted by regulators), and that we need to continue to improve data collection over longer periods of time.

[†]ACRO Releases Toolkit to Help Advance Decentralized Clinical Trials – ACRO (acrohealth.org)

In addition, the group noted that greater trial decentralization will entail a culture shift for the entire enterprise, including regulators, study participants, principal investigators, sponsors, and even funders. Further, increased use of decentralization will require some degree of infrastructure change and participants recommended considering downstream needs (eg, making sure trial sites have all the equipment and expertise to collect remote data) and non-traditional ways of thinking about completeness and confidence in data (eg, adverse events reported by each individual study participant instead of all reported by the same reporter).

D. Data Expectations for Market Entry

For purposes of this work, we defined data expectations for market entry as "additional flexibilities around timepoints and different types of data that are required before market approval. May also include flexibilities around the appropriate amount of data required for submission to regulatory authorities."

Participants acknowledged that tailoring market entry requirements to only the data necessary to make an approval decision (eg, some data could be postponed to post-marketing) has sped product time-to-market during the pandemic. However, they agreed that we must consider the potential impact on the public's perception of the safety, efficacy, and quality of the product (and appropriateness of the approval decision). And, further, the risk to population health if the uncertainty of reduced data requirements decreases public trust in the products, and especially if a safety signal was missed.

Trade-off for benefit of faster access with reduced data burden is the potential for a decrease in public trust in the product, leading to negative impacts on population health.

As such, stakeholders agreed that the sustainability of this agility requires more trust and confidence from, and communication with the public. Specifically, participants felt it was important to explain the overall features of uncertainty (eg, the fact that it is found at some level in every decision) and put it in context for the public, and set realistic expectations based on the risk to patients. We need transparent conversations around the level of evidence required, and how the benefit-risk calculus differs among patient populations and therefore demands different levels of evidence to enable speedy access. We need to define and clearly communicate the roles of regulators and public health agencies, and explain the state of the science and how it is constantly evolving (which reflects not a lack of understanding but rather a continuous process of clarification). Participants recommended that communications with the public be balanced with humility – of what we know today and what we will learn in the future. Participants mentioned that establishing post-marketing plans to address residual uncertainty and communicating those plans can help with public perception.

We also heard that this balance between uncertainty and public perception applies equally to understanding the data environments these data are coming from. In the pandemic speed mattered, and we needed to take risks regarding data interpretation. Moving forward, we need to work more efficiently, use pre-developed data transfer processes to allow us to work with parties not partnered with before, and be better prepared to roll up data (eg, from pharmacies).

Further, participants noted that these considerations don't just apply to pre-approval data, but it is also important to simplify the life cycle management of products on the market, reducing more burdensome and less valuable procedures to free up resources. The EU HMA working group was cited with reference to a review of Type 1A variations (minimal or no impact on safety, quality and efficacy) because the number of these variations is increasing and requiring significant regulator and industry resources.

Stakeholders highlighted that engagement of the patient community (both experts and lay patients) in this work has been missing, noting that it will add value and ultimately deliver higher trust in the process and the product. However, using the patient only for communication (as opposed to ongoing meaningful engagement) would only increase the level of noise without improving trust.

Engagement of the patient community (experts and lay) is critical and currently missing. Using the patient only for communication (versus ongoing meaningful engagement) will only increase the level of noise without improving trust in the process and product.

Finally, participants voiced hope that we will reach a stage where we might have platforms (eg, that apply across pathogens) that can ease requirements, and mentioned adaptive licensing as one approach to the continuous reduction of uncertainty and the broadening of indication based on iterative evidence production. And that long-term, there needs to be collaboration across stakeholders to enable alternative data collection methods to gain acceptance outside of COVID-19 and become sustainable.

E. Advances in Use of Pre-Market Real-World Evidence

For purposes of this work, we defined advances in use of pre-market real-world evidence (RWE) as "use of healthcare information derived from multiple sources outside of typical clinical research settings including EMRs, claims data, product and disease registries, and data gathered by personal devices and apps."

Stakeholders noted the greater utilization of RWE in COVID-19 trials, based on the need to make quick decisions, and recognized that the pandemic aligned key stakeholders' interests in accelerating the use of RWE to promote public health. However, they acknowledged the limitations of RWE data collection and lack of quality standards. It was also mentioned that having a neutral third party with data was very helpful to build trust (ie, rather than only using data from product sponsors).

The group mentioned the need to build incentives to drive the data collection required to support RWE adoption, and wondered who has the responsibility to do this and where in the timeline of collection of data would this fit. Participants noted that RWD consists of numerous data sources and collection methods. As such, RWD driving RWE in clinical trials is a tool to be used in conjunction with traditional clinical data.

Participants explained that expanding RWE to new disease classes post-pandemic will require new strategies to incentivize data collection and information sharing. While this might be easier for certain therapeutic areas, the group noted that we also need to tie together better data collection throughout the broader healthcare system and better define the need that would drive that work.

While setting clear, transparent limitations on the uses of RWD may build trust, it also may open RWE to unproductive public scrutiny.

We heard that while setting clear, transparent limitations on the uses of RWD may build trust, it also may open RWE to unproductive public scrutiny. We need to understand the potential broader impact of regulatory guidance clearly defining RWD uses and limitations (eg, consider whether transparency would be increased or decreased). Public scrutiny around RWE deployed during the COVID-19 pandemic may have been unique, but participants agreed that public trust in RWE will impact adoption going forward.

F. Comments on Other Regulatory Agilities

While the workshop focused on the five selected regulatory agilities above, participants commented on other agilities and successes and challenges during the pandemic.

Participants hoped that what was seen with trials getting into clinic quicker, for example by relying on some preclinical studies done in parallel with first in human studies and the use of seamless phases for trials would continue post-pandemic. In addition, countries creating new emergency use legislation (eg, UK amended legislation) to provide flexible pathways for these situations was seen as a positive advancement.

Participants mentioned regulator communications as a positive, both that regulators published (and updated) guidance very rapidly, and that they used "real time" communications with sponsors. EMA's emergency task force for triaging scientific advice was mentioned as important, as well as rolling reviews (important for both regulators and product sponsors). One participant felt that rolling review was the single most effective action (although resource intensive) used to accelerate review, noting that it led to a much more multi-discipline approach with the regulatory agency and regulators knowing the product better. Other agilities mentioned as beneficial were parallel testing/batch release, remote inspections, relying on other regulatory agency inspection reports, and desk audits.

Manufacturing and the ability of developers to perform tech transfers and source critical materials for manufacturing were mentioned as challenges, especially early on in the COVID-19 pandemic.

III. Foundational Stakeholder Insights

Interestingly, no participant mentioned a regulatory agility that should outright be stopped or not be used either in the next pandemic or in routine practice in some form. However, as discussed briefly below, there are many considerations stakeholders must assess when integrating agilities into routine practice or planning for the next pandemic.

Further, this is not the first emergency we have faced, and we should look to previous situations (eg, HIV, H1N1 flu) to see how regulatory changes were integrated into practice, what challenges were faced, and how they were overcome.

A. Trade-offs Inform Integration of Regulatory Agilities into Routine Practice

As mentioned throughout the workshop, the use of regulatory agilities is rarely, if ever, "one size fits all" and it will be critical to consider the trade-offs for each regulatory agility as it is implemented into routine use or planned for the next pandemic. Further, some regulatory agilities come with significant resource costs, the challenges of financing of which are magnified in LMICs.

First, most, if not all, regulatory agilities can create both beneficial and costly consequences on different stakeholders. For example, increased communication between regulators and industry shortened time-to-access for patients but was human resource intensive, leading to burnout and backlogs for non-priority work. Similarly, while virtual tools increased real-time interaction, stakeholders cited ensuring security and lack of face-to-face interactions as challenging. Further, increased transparency is critical to building trust, however, use of shared data challenged existing data infrastructure and required a paradigm shift for regulators and sponsors.

Second, the urgency of the COVID-19 pandemic necessitated an expediency and single purpose that rapidly and widely rolled out regulatory agilities for COVID-19 vaccines, therapeutics, and diagnostics, but the use of these agilities in routine practice will be situationally dependent. Determining guardrails and appropriate criteria for implementation will be crucial, including considering cultural differences, differences in healthcare systems, and the perspectives of patients. Agilities will need to be tailored to what is needed, which is not necessarily what was needed in the pandemic.

Ensuring all stakeholder voices are included and considering the nuanced trade-offs and balance of benefit and burden (to whom) inherent in all agilities is crucial.

Overall, ensuring all stakeholder voices are included in discussions and considering the nuanced trade-offs and balance of benefit and burden (to whom) inherent in all agilities will be crucial moving forward.

B. The Critical Importance of Trust and Communication with the Public & Meaningful Patient Engagement

The group discussed how rapid the pace of data output was during the COVID-19 pandemic. Unfortunately, sometimes new data contradicted previous data, and the way it was disseminated via press release confused regulators and the public. Without peer-reviewed papers, shared dossiers, or regulators explaining what the public was seeing in the press, it was extremely difficult to understand what was going on (especially in LICs). Participants agreed that this (confusion based on "science by press release") is one of the legacies we will have to deal with moving forward. Further, the large number of uninformative trials complicated the challenge of explaining to the public what was going on, in particular why what they were seeing in the press was not right.

During the COVID-19 pandemic, we had to live in a world of science by press release, confusing regulators and the public. This confusion is one of the legacies from the pandemic we will have to deal with moving forward.

Participants explained that during the pandemic, regulators needed to greatly enhance their communication with the public to explain their every step, and not just what they did with the product, but to explain their role and describe the benefit-risk assessment. And myth-busting sometimes required so much detail that it ran into commercially confidential information. This was challenging in part because of the dichotomy of public perception – on the one hand the public had great fear of COVID-19 and demanded a quick response, but at the same time they equated "fast" with "unsafe." Participants noted that we saw this same challenge in relation to HIV in the US, although with a smaller, more focused (not global) community.

Participants discussed the importance of having trusted people (people see industry and regulators as biased messengers) educate the public and continue the dialogue (especially for vaccine uptake) because the public forgets very quickly. People want to hear from someone who they think sees it from their same perspective, so we need to find advocates across communities. Stakeholders explained that this “advocates in the community” strategy is key and an important lesson, and it doesn't create an alternative to the educational role of healthcare professionals but was a great assist during the pandemic. Participants agreed that a real public relations approach to health regulation is indeed beneficial, including a network of ambassadors to support building trust in regulators and minimizing suspicion, but noted the challenges to make this work on a global level (ie, ensure citizens trust in regulators and products from other parts of the world).

Participants lamented that the patient community (advocates and experts) was completely absent from discussions about communication and could have helped address many of the issues outlined above. However, participants made it clear that good communication would be one of the outcomes of a good collaboration with the patient community across the life cycle of products, not just a one-off discussion about communication strategies.

Ongoing, meaningful patient engagement is key to informing agilities, understanding impacts, and ensuring successful implementation of agilities.

In addition, as mentioned throughout the workshop and this summary, but it bears repeating, stakeholders agreed that meaningful patient engagement is critical throughout the life cycle of a product, and patient perspectives are key to informing agilities, understanding impacts of agilities, and ensuring successful implementation of agilities. We have not done a good job of engaging patients during the pandemic, and as such, the patient voice has been missing during the last 2 years.

C. Moving Forward

Even though we are still in the pandemic and still learning about the ramifications of the regulatory agilities, participants agreed that the time is now to do these assessments and advance conversations about which regulatory agilities to retain after the pandemic and how to successfully incorporate them into routine regulatory practice globally. As one stakeholder noted, it's always the right time to have a dialogue. Participants explained that we can practice for the next pandemic by using regulatory agilities for other unmet medical needs between pandemics and we should use the opportunity we have now to experiment and iterate. In that way we can benefit people during the next pandemic, but also people living now and not "wait" until the next pandemic hits. In addition, participants noted that many of the regulatory agilities are set forth in guidance that will expire at the end of the public health emergency, so we should be planning now and not wait until after they expire.

It's always the right time to have a dialogue.
The time to do this is now.

Participants noted that all stakeholders need to work together to avoid everyone reaching out to regulators in a fragmented way, to minimize the risk that regulators might not adopt any recommendations. To this end, the group recognized the importance of having a broader conversation with all healthcare parties, engaging voices not fully included at this time. In addition, all regulators, but in particular those that serve as reference authorities, have an additional role in considering the impacts on the rest of the world of their decisions on how they choose to implement (or not) regulatory agilities. As the global regulatory system is so interconnected, divergent independent decisions by regulators will impact the system as a whole, and we do not want to inadvertently end up with a less harmonized, less efficient, and/or more burdensome system.

It is also important to talk about resources and funding and how resource needs will shift with implementation of regulatory agilities. For example, NIH trials are underfunded now, so as we expand trial sites, funding, technology, and personnel needs will increase. And this is true for RWE as well; it is a misperception that RWE means you "push a button and you get immediate access to information," because a good RWE trial requires the same level of planning and expertise as other trials.

Participants anticipated that every regulator and country will look at their legislation and regulation to make sure all the tools are there (eg, conditional approval, rolling review, reliance models). However, the group noted that while legislation is very important, putting approaches into practice to ensure they work is critical (eg, EULs after H1N1 didn't work quite the way they expected them to in other situations).

In addition, participants discussed the opportunity costs and risks of introducing bias into decisions on prioritizing products. Specifically, prioritizing certain products results in opportunity costs for regulatory attention for non-prioritized products, and may introduce a bias that might not result in a good outcome to healthcare as a whole or align with cultural and local priorities (vs global priorities).

All stakeholders want to ensure the lessons learned from the COVID-19 pandemic are not lost, but rather used to advance the global regulatory system for the benefit of patients. Time is limited before the public health emergency expires, so we need to advance this work quickly. And we must consider how limited the bandwidth is at regulatory agencies right now, as regulators continue to work with pandemic-driven urgency (and deal with the associated burnout) and will soon be faced with a backlog of their usual duties. Therefore, stakeholders need to be as practical as possible when suggesting new projects for regulatory agencies to take on.

We need to work together to move from a general discussion to a focused effort with concrete asks that align with regulatory priorities and practical realities, reflect the current legislative opportunities, have a clear global message, are feasible, and that would make a real difference for patients and the global regulatory system as a whole.

IV. Conclusion

The pandemic has clearly challenged the world in many ways – rapid pace of (sometimes contradictory) science, urgent decisions made on best available data, innovation in process and regulatory science. Regulators did (and are still doing) a herculean job. We recognize, however, that the significant burden on regulators to work at pandemic speed is not sustainable past the pandemic, and we cannot ask regulators to continue everything they have done during the pandemic and use every beneficial agility in every situation moving forward.

There is considerable interest in regulatory agilities, including the five discussed at the workshop, and regulators want to know whether and how each flexibility worked or not – data on impacts to stakeholders – to help them determine how to best implement (or not) moving forward. With this work we aimed to bring additional voices to the table to add more diverse perspectives to the conversation. But there is more to be done, and we have a path before us to achieve our goals.

MSD looks forward to continuing to work with those who attended the workshop and other stakeholders to build a more robust and diverse understanding of stakeholder perspectives on these agilities and specific impacts, develop and advocate for concrete asks for policymakers so that the global regulatory system, and most importantly patients, benefit now from the regulatory lessons learned during COVID-19.

V. Abbreviations

ACRO – Association of Clinical Research Organizations

AVEREF – African Vaccine Regulatory Forum

CDC – US Centers for Disease Control and Prevention

COVAX – COVID-19 Vaccines Global Access

COVID-19 - Coronavirus Disease 2019

DCT – Decentralized Trials

EMA – European Medicines Agency

EMR – Electronic Medical Record

EU – European Union

EUA – Emergency Use Authorization

EUL – Emergency Use Listing

FDA – US Food and Drug Administration

H1N1 – Virus causing swine flu (2009)

HMA – Heads of Medicines Agencies

HIC – High Income Country

HIV – Human Immunodeficiency Virus

ICMRA – International Coalition of Medicines Regulatory Authorities

LIC – Low income Country

LMIC – Low- and Middle-income Countries

MHRA – Medicines and Healthcare products Regulatory Agency

NIH – US National Institutes of Health

RWD – Real-World Data

RWE – Real-World Evidence

US – United States

WHO – World Health Organization

VI. Appendices

A. Avalere pre-read materials

B. Workshop agenda

C. List of workshop participants

D. Avalere workshop summary slides

Global Regulatory Agilities During the COVID-19 Pandemic: *Workshop Pre-Read*

Prepared by Avalere Health

January 2022

Executive Summary

Workshop Purpose & Objectives

Background: The COVID-19 pandemic has altered regulatory systems and prompted regulators to establish new ways of working. Through interviews with global regulators, industry representatives, and other organizations, MSD and Avalere explored how regulatory authorities deployed innovative approaches during the COVID-19 pandemic and the potential impacts of these agilities to a diverse set of stakeholders.

Purpose: This workshop provides a forum for candid conversations to pressure test learnings from the interviews; solicit perspectives from a diverse set of stakeholders; discuss the impact of selected regulatory agilities; and consider opportunities and strategies to sustain agilities beyond the end of the pandemic.

Workshop Objectives:

1. To explore stakeholder views of select COVID-19 regulatory agilities that agencies could retain beyond the pandemic to strengthen routine regulatory practice, prepare for the next pandemic, and build a more coordinated global regulatory system to build out a “360 view” of each
2. To discuss the (current and/or potential) impacts of these regulatory agilities on stakeholders across the healthcare ecosystem

Avalere Interviewed Global Stakeholders To Identify 10 Regulatory Agilities Exhibited During the COVID-19 Pandemic

Working Definition of "Agility" /

Avalere worked in partnership with the project Steering Committee to define the terms **"regulatory agilities"** or **"agilities"** as the following:

> *Actions taken by a regulatory agency (as part of broader health authorities) driven by and in the context of the COVID-19 public health emergency that depart from that regulatory agency's pre-pandemic actions, procedures, and approaches. Note, this may include actions with both positive or negative consequences across stakeholders.*

Selection of Agilities /

Agilities" were grouped based on the regulatory activity to which they applied (e.g., trial design, rolling submissions)

- Topics raised by multiple types of stakeholders were considered for inclusion or exclusion in the context of regulatory action taken that differed from business as usual.

Avalere identified 10 regulatory agilities implemented by regulators through interviews with stakeholders representing a cross-section of global regulatory agency representatives; life sciences and biotechnology manufacturers; and global health agencies.

Reliance & Mutual Recognition	Convergence & Harmonization	Decentralized Trials	**Data Expectations Prior To Market Entry**	Advances in Use of Pre-Market RWE
Active Real-World Data Exchange & Use	Rolling Submissions	Virtual Inspections	Regulator & Industry Interactions	Novel Clinical Trial Designs

** Agilities related to devices and diagnostics were excluded. Several activities met the inclusion criteria for an agility but are not featured in the case studies because they are one-off deployments, were already well-utilized prior to the pandemic, or are likely to become routine without external advocacy or intervention.*

RWE: Real World Evidence

These Cases Showcase Agilities Deployed by Regulators During the COVID-19 Pandemic and Identify Agilities That May Be Sustained or Augmented

Featured Cases /

"Case Studies" are intended to be exemplars that can elucidate process and outcome details about featured agilities

Avalere researched explicit mention of cases or examples from interviewees and determined the level of flexibility exhibited by regulatory authorities; those that did not involve regulator actions were excluded from consideration

How to use this pre-read /

The workshop spotlights 5 of the 10 originally identified cases and aims to foster discussion about how each of them impacts patients, the development and review of products, and the broader healthcare system.

This pre-read provides background information on the cases that will be discussed during the workshop. As you read through it, please consider whether you have experienced any of these agilities in your work, how it impacted your workflow or your target outcomes, and if and how these regulatory agilities may be sustained or augmented.

Agility	**Reliance & Mutual Recognition**	**Convergence & Harmonization**	**Decentralized Trials**	**Data Expectations Prior to Market Entry**	**Advances in Use of Pre-Market Real World Evidence**
Case Study	AVAREF Emergency Joint Reviews to Support Reliance on WHO's EUL Process	ICMRA Workshops to Facilitate Regulator Dialogue and Alignment	FDA Flexibility in Regulation of Cancer Clinical Trials	FDA and Data Expectations for EUAs	FDA and Aetion's Development of RWE on COVID-19

AVAREF: African Vaccine Regulatory Forum; ICMRA; International Coalition of Medicines Regulatory Authority; FDA: Food and Drug Administration; EUAs: Emergency Use Authorization; RWE: Real World Evidence; WHO: World Health Organization

Featured Agilities

Reliance Practices Across Authorities Reduce Regulatory Burden and Facilitate Rapid Authorization of COVID-19 Countermeasures

Situational Analysis /

- Resource and time constraints can delay regulatory agency action, leading to backlogs in conducting key functions and delaying access to critical medical products. Further, duplication of regulatory activities creates burden for manufacturers who need to respond to regulator requests.
- The need to rapidly review and authorize COVID-19 countermeasures, coupled with pandemic-related travel restrictions, increased the number and intensity of reliance schemes among regulatory authorities.

Case Study: AVAREF COVID-19 Vaccine Joint Review /

- AVAREF has convened 6 joint review workshops to facilitate authorization of COVID-19 vaccines in participating countries following WHO's issuance of an emergency-use listing.
- Participating RAs access and review the full dossiers and WHO assessment reports through a WHO portal prior to the workshops. During workshops, WHO leads present their assessments and key considerations and participating RAs have an opportunity to ask questions.
- Following the joint review, RAs may issue full authorizations, import licenses, or other regulatory approvals to enable national registration, depending on their statutory frameworks.
- Workshops enable regulators to rely on WHO EUL without having to undertake independent reviews.

Perceived Impact /

PUBLIC HEALTH	+	The ability to significantly cut down on individual jurisdiction review time can help bring needed product to market faster
MANUFACTURERS	+	May benefit from more efficient review clocks and less duplicative submission efforts; time to market may be reduced
REGULATORY AUTHORITIES	+	Recognition of work conducted in other jurisdictions not only mitigates individual review burden and better serves the public health, but establishes a cultural shift around a global regulatory competency

+ Positive ↔ Mixed - Negative

While some reliance practices were limited to the emergency context, stakeholders anticipate that processes and trust built during the pandemic may foster future reliance initiatives.

Sources: African Union, 2021. Guidance on Emergency Expedited Regulatory Authorisation and Access to COVID-19 Vaccines in Africa; Gates Foundation, 2021. Vaccine Access in Africa: Africa Medicines Agency Treaty Update; NASEM, 2020. Regulating Medicines in a Globalized World: The Need for Increased Reliance Among Regulators.
AVAREF: Africa Vaccine Regulatory Forum; CDC: Africa Centres for Disease Control and Prevention; EUL: Emergency Use Listing; RA: Regulatory Authority; WHO: World Health Organization

Expanding Reliance Practices Requires Transparency and Trust Among Regulatory Authorities

Lessons Learned

- **Data Requirements:** Alignment on data requirements is critical to maximize the value of reliance arrangements.
- **Impact on Timelines:** Reliance arrangements during COVID-19 created process efficiencies, but more evidence is needed on whether and how they would reduce approval timelines in a non-emergency scenario.
- **Proximity Matters:** Regional approaches have offered the most robust opportunities for reliance in the context of the pandemic, building on existing relationships and cooperation mechanisms (e.g., APEC RHSC, AVAREF, EU zero-day repeat us mutual recognition).

Enabling Factors

- **Existing Relationships:** Existing ways of working and relationships engendered trust among regulators that supports reliance.
- **Pre-existing Infrastructure:** Previously established confidentiality agreements and secure platforms facilitated document exchange and review.

What's Next?

- Widespread adoption of reliance has been inhibited by poor information sharing across regulatory authorities, lack of mutual recognition agreements, and low utilization of existing recognition agreements.
- Increased regulatory convergence and tools to facilitate transparency will facilitate more process alignment and trust between regulatory authorities.
- In order to move toward full reliance, processes need to be formalized through the development of internal standards, data management, and data security for electronic reviews.

Sources: Gates Foundation, 2021. Vaccine Access in Africa: Africa Medicines Agency Treaty Update; NASEM, 2020. Regulating Medicines in a Globalized World: The Need for Increased Reliance Among Regulators.
APEC: Asia-Pacific Economic Cooperation; AVAREF: Africa Vaccine Regulatory Forum; CTA: Clinical Trial Application; EUL: Emergency Use Listing; RHSC: Regulatory Harmonization Steering Committee

Global Collaboration and Exchange Enhanced Regulators' Pandemic Response and Accelerated Convergence

Situational Analysis /

- Differing requirements and expectations across regulatory authorities for novel vaccines and treatments create inefficiencies for manufacturers and may slow review processes.
- To streamline regulatory processes as much as possible and enable rapid approval of COVID-19 countermeasures, regulatory authorities are coordinating trial and submission expectations.

Case Study: ICMRA Engagement /

- ICMRA brings together leaders from 29 RAs to collaborate, improve communication, and develop joint approaches to common challenges. Experts agreed the COVID-19 pandemic represented a maturation point for the group's collaboration.
- Since the start of the pandemic, ICMRA has convened at least 45 times for topic-specific workshops and strategic alignment meetings and has published joint statements on regulatory expectations and agilities in the context of the pandemic.
- The workshops provided a "safe space" for regulators to be transparent with one another about their opinions and considerations, identify areas of non-alignment to provide better guidance for sponsors on how to address them, and build trust in each others' processes and assessments.
- As an example, following an ICMRA workshop on animal studies in which specific non-alignment was identified between FDA and EMA, both agencies quickly released guidance clarifying their expectations.

Perceived Impact /

PUBLIC HEALTH	+	Alignment among RAs supports more efficient development and approval of countermeasures
MANUFACTURERS/ SPONSORS	+	Convergence on RA expectations reduces burden from conflicting requirements and speeds access to markets
REGULATORY AUTHORITIES	+	Workshops provided RAs the opportunity to learn from their peers in a rapidly evolving context; building relationships and trust across RAs may enable new reliance and work sharing arrangements

+ Positive ↔ Mixed - Negative

ICMRA and other forums that promote dialogue and transparency among regulators, build relationships, and drive convergence around standards and principles, which could lead to progress towards regulatory reliance.

Sources: Center for Innovation in Regulatory Science, 2020. Re-Imagining Medicines Regulatory Models: Implementing Fit-For-Purpose Sustainable Activities for Patient Access; ICMRA, 2021. ICMRA Aims for International Alignment on Policy Approaches and Regulatory Flexibility During COVID-19; ICMRA, 2021. COVID-19.
ICMRA: International Coalition of Medicines Regulatory Authorities; RA: Regulatory Authority

ICMRA Leveraged Pre-existing Relationships Between Regulators To Promote Collaboration Beyond Policy

Lessons Learned

- **Alignment on Clinal Trial Processes and Post-Market Data Dossier Requirements:** supported faster development timelines and delivery of COVID-19 countermeasures.
- **Transparency and Alignment:** communication among regulatory authorities can create resource efficiencies for regulators and generate greater opportunities for reliance in the future.
- **Upfront Investment in Information Sharing:** Substantial resource investment may be required for information sharing and alignment, can save greater resources in the long term.

Enabling Factors

- **Pre-existing Relationships Among Key Member Regulatory Authorities:** many participants were acquainted through participation in regional conversations; existing relations provided a basis of trust to support open dialogue and willingness to engage.
- **Timely Information Sharing and Collaboration:** frequent contact points enabled RA and WHO regulatory decisions, requirements, communications, and plans for COVID-19 products.

What's Next?

- While increased convergence and harmonization was driven by the pandemic, continued future global regulatory collaboration will enable a more efficient and effective response to future pandemics and enable broad access to medicines and diagnostics.
- In non-emergency situations, bodies like ICMRA can help regulators communicate consensus and divergence as it relates to issues relating to drug development.
- While convergence is seen by many as a key step toward increased reliance among regulators, moving beyond information sharing and alignment on high-level principles will require implementation of tools to help RAs build trust in each others' processes and capabilities (e.g., WHO's Global Benchmarking Tool).

Sources: EMA, 2021. An Overview of Emergency Use Authorizations and Similar Authorities; Khadem Broojerdi A, Baran Sillo H, Ostad Ali Dehaghi R, Ward M, Refaat M, Parry J. The World Health Organization Global Benchmarking Tool an Instrument to Strengthen Medical Products Regulation and Promote Universal Health Coverage. Front Med (Lausanne). 2020 Aug 19;7:457. doi: 10.3389/fmed.2020.00457. PMID: 32974367; PMCID: PMC7466745.
ICMRA: International Coalition of Medicines Regulatory Authorities; RA: Regulatory Authority; WHO: World Health Organization

Disruptions to Clinical Trials during COVID-19 Created An Opportunity to Re-evaluate Long-standing Clinical Trial Processes

Situational Analysis /

- Overtime, in an interest to ensure data of sufficient quality and quantity while providing for upmost safety of patients, the required protocols for clinical trials have increased. New technological capabilities and novel approaches have not always been implemented rapidly.
- During the pandemic, regulators issued guidance permitting remote outcomes assessments, alternative administration practices, and home delivery of investigational products to ensure trials could continue throughout the PHE.

Case Study: NCI & FDA Regulation of Cancer Trials /

- COVID-19 related lockdowns and social distancing requirements disrupted cancer clinical trials, which have traditionally relied on in-person administration in traditional clinical trial locations
- In response, NCI and FDA created new regulations to facilitate decentralized trials that were responsive to public health concerns while simultaneously upholding high standards of efficacy and safety
- Decentralized trials use a combination of digital technology and new processes to facilitate patient-centric trial participation. These trials draw on digital tools to conduct trial activities with fewer clinical visits.
- While elements of decentralized trials existed pre-COVID-19, the pandemic accelerated remote surveillance and home-based services.

Perceived Impact /

PUBLIC HEALTH	+	Allowed clinical trials to continue with minimized in-person contact.
MANUFACTURERS	+	Adopting remote administration and monitoring in a decentralized model drove efficiencies and harnessed technological advancements.
REGULATORY AUTHORITIES	↔	Increased burden on regulators due to the need for frequent guidance and reliance on stakeholder feedback to promulgate standards. Regulators had to exercise more flexibility than had been typical.

+ Positive ↔ Mixed - Negative

A survey of trial investigator sites showed **69%** of current clinical trials and **78%** of new trials were impacted by COVID-19 by April 2020.[1]

Source: JAMA, 2021. Cancer Clinical Trial Participation at the 1-Year Anniversary of the Outbreak of the COVID-19 Pandemic.
FDA: United States Food and Drug Administration, NCI: National Cancer Institute, OCE: Oncology Center for Excellence

NCI and FDA Cancer Trial Standards and Regulations Accelerated Digital Technology and Patient-Centered Designs in Clinical Trial Processes

Lessons Learned

- **More Patient Centered Clinical Trials**: In the past, clinical trials focused on the clinical trial site where patients had to be present for signed consent, product administration, collection of routine outcomes assessments, trial-specific imaging, and all follow up procedures. New regulations allowed for a patient centric model with many of the activities occurring at or near their home.
- **Efficiency:** Ability to integrate new technology and accommodate minor protocol deviations while retaining a valid trial protocol allowed for case-by-case efficiencies.
- **Access for Broader Patient Population**: In modifying the clinical trials programs to accommodate for COVID-19 lockdowns, participation by underserved and rural individuals become more accessible and less burdensome.

Enabling Factors

- **Previous Champions:** Prior to the pandemic, there had been strong advocates for more acceptance and use of the technologies implemented during COVID-19, including remote outcomes assessments with virtual visits and electronic informed consent.
- **Access to Technology:** The technology required to modify clinical trial processes were widely available. Open Code for MyStudies App, for example, had been released by FDA in 2018 as a secure approach to gather patient reported data for a decentralized clinical trial.

What's Next?

- Positive experiences with many of the policies developed to enable decentralized trials suggests that industry will continue to incorporate these practices in clinical trial protocols and regulators will continue to explore how expand best practices and regulations accordingly.
- The increased interest in advancing the diversity of clinical trials, ensuring maximum inclusion of subpopulations and creating a patient centric framework for clinical trials suggests momentum will continue and stakeholders will build upon lessons learned during the pandemic.
- Most recent draft FDA guidance on clinical trial procedures was updated in December 2021 but currently is "intended to remain in effect only for the duration of the public health emergency". CURES 2.0 and PREVENT pandemics Act each include provisions for an FDA guidance on formalizing decentralized clinical trials.

FDA: Food and Drug Administration, NCI: National Cancer Institute, OCE: Oncology Center for Excellence
Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency

Urgency for COVID-19 Vaccines and Therapeutics Enabled Flexibilities around Data Expectations Prior to Market Entry

Situational Analysis /

- During the pandemic, scientists and manufacturers had to determine the right amount of data needed within expedited timeframes to enable timely market access to COVID-19 products while continuing to meet high standards of efficacy and safety.
- Regulators around the world provided expanded guidance and modified their data expectations to facilitate making medicines, vaccines, and diagnostics available as rapidly as possible to address the emergency, while adhering to stringent criteria of safety, efficacy, and quality.

Case Study: FDA and Data Expectations for EUAs /

- Risk-based assessments prioritized obligations and identified the most critical data for submission prior to approval and directed the least critical data to post approval submission. This includes:
  - Reduced data package based on risk for process qualification/validation data
  - Leveraging of platform data, prior knowledge, and concurrent validation
  - Approval of post-approval changes in the absence of complete data sets with agreement to submit certain data later
  - Alternatives to real time data for stability assessments and determining shelf life

Perceived Impact /

PUBLIC HEALTH	+	Provides more rapid access to lifesaving drugs while maintaining stringent quality and safety measures
MANUFACTURERS	+	Quicker information access ensures timely market access and encourages optimization of domestic manufacturing capacity
REGULATORY AUTHORITIES	-	Increased burden assessing what data are most/least critical and aligning on timeline of modified expectations.

+ Positive ↔ Mixed - Negative

Adopting risk-based data requirements for EUAs enabled FDA and other regulators to shorten approval times for COVID-19 vaccines from an average of 5-10 years to under 12 months, but required a greater emphasis on post-approval oversight.

Sources: ; FDA, 2020. VRBPAC Briefing Document: Development, authorization and licensure of vaccines to prevent COVID-19; RAPS, 2020. Marks, Hahn confirm COVID vaccine EUA guidance coming
The Hill, 2021. Questions the FDA Must Ask Drug Makers as It Considers Full COVID-19 Vaccine Approval
EUA : Emergency Use Authorization; FDA: United States Food and Drug Administration

Pandemic Risk-Benefit Paradigm Modified Regulators' Data Expectations For Emergency Authorizations

Lessons Learned

- **Risk-Based Pre-market Expectations**: The high risk created by the PHE allowed both the regulators and industry to consider alternative approaches to allowing certain types of data to be submitted after market entrance.
- **Increased Burden to Modify Expectations:** Increased resources are needed to identify appropriate new expectations on a case-by-case basis.
- **Product and Process Knowledge**: Products and manufacturers with increased experience were able to leverage existing knowledge to decrease uncertainty for any change in data submission.

Enabling Factors

- **Supporting Data:** Ability to demonstrate scientific rigor was key to ensure gold standards continue to be met. This includes supporting data such as manufacturing experience or platform approaches.
- **Open Communication:** Ongoing communication between regulators and manufacturers through the public health emergency enabled real-time understanding of where data flexibility was possible.

What's Next?

- The increased flexibility demonstrated during the pandemic is correlated to the urgency of the PHE and the use of pathways such as EUAs by FDA and other regulators. Post-pandemic, lessons learned may collectively enable regulatory authorities to allow flexibilities in data expectations for areas such as post approval changes and stability.
- Regulators are likely to be hesitant to apply such risk-based measures widely outside of an emergency context. Case-by-case implementation may prove burdensome and challenging particularly for products new to the market. Certain product types, such as those built on platform technologies (e.g., mRNA vaccines), may be more likely to benefit from more durable policies of leveraging existing data sets.

Source: RAPS, 2020. FDA issues COVID-19 vaccine EUA guidance after clash with White House
CMC: Chemistry, Manufacturing and Controls; EUA : Emergency Use Authorization; FDA: United States Food and Drug Administration

Methodology and Good Practices for Use of RWE Were Advanced Due to Urgency of The COVID-19 Pandemic

Situational Analysis /

- The standards and practices of collecting and analyzing Real World Evidence (RWE) have been advancing rapidly in recent years beginning with 21st Century Cures and continuing through to recent guidance release from FDA.
- The urgency of the pandemic created additional attention and interest in the utilization of RWE to better characterize diseases, identify patient populations and assess potential benefit of treatments.

Case Study: Collaborating Data for Pre-Market RWE to Help Address Questions Regarding Covid-19 /

- In May 2020, FDA partnered with Aetion to develop RWE analytics to help answer questions related to Covid-19. This work focused on Aetion data sources such as electronic health records, insurance claims, patient registries and lab results to help inform the agency's understanding of COVID-19 treatment and response.
- The collaboration advanced the Agencies practices for assessing data fitness, optimizing methodology, identifying good practices for data analysis and creating a foundation for rapid cycle analytics.
- In tandem, FDA also collaborated on additional real-world sources of data such as the Sentinel initiative and the Reagan-Udall Foundation and Friends of Cancer Research COVID-19 Evidence Accelerator.

Perceived Impact /

PUBLIC HEALTH	+	Utilizing RWE can strengthen understanding of a disease or treatment in broader, more diverse population with long term outcomes
REGULATORY AUTHORITIES	↔	While the promise of RWE is immense, burden exists as regulators are still determining standards and expectations for proper use
INDUSTRY	+	Use of RWE remains a strategic priority; capabilities continue to grow with applications broadening from post market surveillance to pre-market regulatory submissions

+ Positive ↔ Mixed - Negative

The difficulty associated with analyzing and collecting RWE leads to burdens for both manufacturers and regulatory agencies.

Source: RAPS, 2020. FDA, Aetion partner on real-world data analytics for COVID-19 | RAPS
FDA: United States Food and Drug Administration; RWE: Real-World Evidence

The Partnership With Aetion Provided the FDA with Increased Access to RWE

Lessons Learned

- **Rapid and Meaningful Data:** The pandemic required rapidly up to date information in order for agencies to respond to the dynamic and evolving situation. RWE enabled an efficient and meaningful data set to be generated for actionable insights.
- **Integrated Approach:** The value and utility of any RWD is directly limited by the extent to which the data is standardized and integrated. By working directly with Aetion and their validated software (Aetion Evidence Platform®), verses a wide array of stakeholder with various data sources, agencies are able to access standardized and integrated data sets.

Enabling Factors

- **Previous Experience with RWE in Post-Market Surveillance:** RWE has been used for post market purposes for a long time. Experience gained can be leveraged to support use of RWE in broader purposes such as epidemiology and regulatory submissions for new indications.
- **History of RWE Policy Advancement:** Policies and tools for use of RWE were implemented prior to the COVID-19 pandemic. For example, in 2016, the 21st Century Cures Act first defined RWE and created expectations for FDA to develop a framework for further use of RWE to support the regulatory process.

What's Next?

- Aetion and FDA announced an expansion of their collaboration in Oct 2021 to begin assessing inpatient treatments for COVID-19 as well as develop a framework for evidence generation for future pandemics. Similarly in the same month, Aetion announced a partnership with NICE to explore use of RWE in clinical effectiveness. In December 2021, EMA selected Aetion to conduct RWE studies on the utilization, safety, and efficacy of products used in routine clinical practice.
- Agencies continues to take steps to advance use and expectations for RWE programs. FDA, for example, recently published three RWE guidance documents and released the PDUFA VII commitment letter which includes a pilot program to increase use of RWE for new indications and an increase in use of RWE in the Sentinel initiative.

Source: RAPS, 2020. FDA, Aetion partner on real-world data analytics for COVID-19 | RAPS
AEP: Aetion Evidence Platform; FDA: United States Food and Drug Administration; RWE: Real-World Evidence

Interviews Underscored Tradeoffs That Arise When Regulatory Agilities Are Implemented

Many agilities were underway prior to the pandemic, but COVID-19-related lockdowns and rapid R&D timelines amplified or accelerated efforts that were already underway. The rapid rollout revealed tradeoffs that will impact how and where these agilities are sustained.

Push and Pull Dynamics

Implementation of each regulatory agility can create both positive and negative consequences:

- Increased communication between regulators and industry shortened time-to-access for patients but was human resource intensive, leading to burnout and backlog
- Increased data sharing may partially compromise intellectual property and trade secret integrity

Situational Dependency

Interviewees observed that demand for expediency required processes to be widely and rapidly rolled out for COVID-19 products, whereas future applications may be situationally dependent:

- Determining guardrails and appropriate criteria for implementation will be crucial for many future applications
- Trusted manufacturers with an established track record may be allowed more flexibility (e.g., rolling submissions, virtual inspections) than a new manufacturer

Virtual Interactions

While virtual tools increased real-time interaction and were integral to many agilities, stakeholders cited ensuring security and lack of face-to-face interactions as challenges:

- Virtual meetings and other informal communications mechanisms are more effective when there are pre-existing relationships
- Increased transparency is critical to building trust, however use of shared data challenged existing data infrastructure and required a paradigm shift for regulators and sponsors

ICMRA: International Coalition of Medicines Regulatory Authorities; RA: Regulatory Authority

Thinking Ahead: Prioritization and Discussion to Inform Next Steps for Regulators

Questions /

As policymakers around the world shift their focus beyond the immediate public health emergency, there is a window of opportunity for global R&D stakeholders to advocate for continuing, expanding, or stopping the regulatory flexibilities, policies, and procedures used during the pandemic.

In preparation for the workshop, please consider:

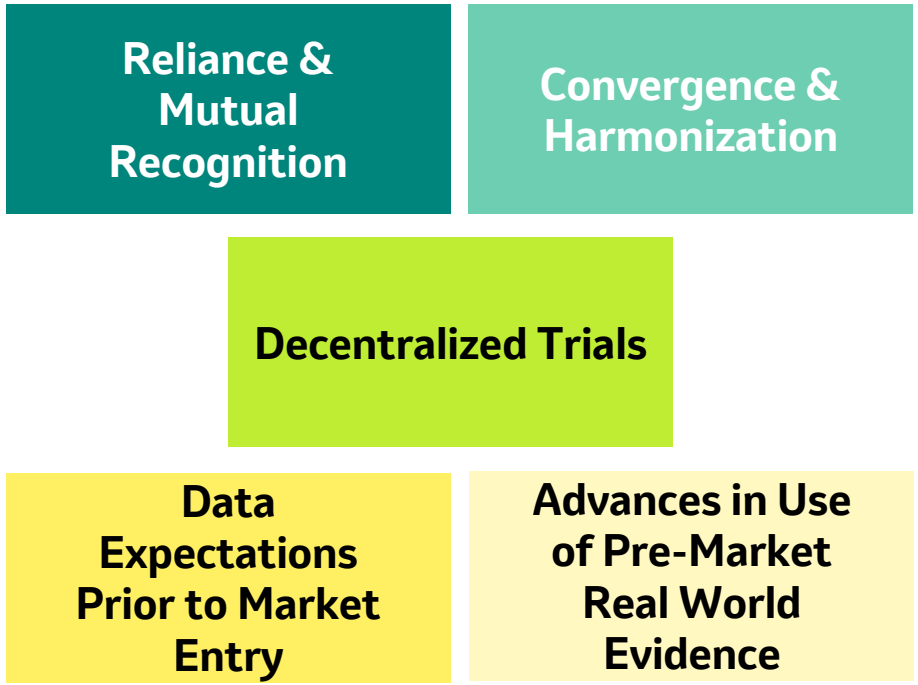
Have these agilities affected your work and your target outcomes? How?

Which agilities do you think will become naturally self-sustaining?

Why?

Which agilities do you think should be stopped or time-limited for the duration of the pandemic?

Why?



MSD

Thank you

MSD/Avalere | Global Regulatory Agilities During COVID-19
Monday, February 7, 2022
Workshop Agenda: 7:30am-12:45pm US ET

Time (Eastern)	Mins.	Session
7:30am-7:45am	15	• Welcome from MSD and Avalere • Opening poll question
7:45am-8:30am	45	Panel Discussion on What Next for COVID-19 Regulatory Flexibilities: What Have We Learned? Where Do We Go From Here? • Murray (Mac) Lumpkin, Bill & Melinda Gates Foundation • Deb Yeskey, Coalition for Epidemic Preparedness Innovations • Christian Schneider, Pharmalex
8:30am-9:00am	30	Research Readout • Overview of Avalere's research • Preview Case Studies • Clarifying Q&A
9:00am-9:30am	30	Discussion: Impact, Priority, and What is Missing? • Is anything missing? • What has had the biggest impact on your work or global systems? • What doesn't fit your experience? What do we not know yet?
9:30am-9:45am	15	Break
9:45am-10:00am	15	Spotlight interview: Jeff Allen, Friends of Cancer Research
10:00am-10:30am	30	Breakout Session For each of these agilities (or others): • When will this work, and when will it *not* work? • How are/would you/your stakeholder group impacted/be impacted if this agility became routine practice? • How can we make it sustainable? • Are there ways to quantify or dig into those impacts? Who should we talk to? What data sources exist?
10:30am-11:15am	45	Breakout Debrief and Discussion with Full Group
11:15am-11:30pm	15	Break
11:30pm-12:00pm	30	Discussion: What Next? • Challenges to embedding these things in routine regulatory authority practice globally • Best practices for embedding and making culture changes, as needed • If we did nothing, what would happen – do these agilities have enough momentum for keeping them?
12:00pm-12:30pm	30	Keynote Address reflecting themes from the day and where we go from here Mark McClellan, Duke Margolis Center for Health Policy
12:30pm-12:45pm	15	• Wrap-up • Closing remarks from MSD and Avalere

Roughly 50 Participants Joined the Workshop Throughout the Day; 90% Stayed For More Than 3 Hours *

Adam Hacker, Coalition for Epidemic Preparedness Innovations
Anina Adelfio, Association of Clinical Research Organizations
Annetta Beauregard, Janssen
Annie Kennedy, Everylife Foundation
Awo Osei-Anto, FasterCures, a Center of the Milken Institute
Camilla Gomes, Roche, Epfia (Latam Network)
Carlos Garner, Lilly
Christian Schneider, Pharmalex
Debra Yeskey, Coalition for Epidemic Preparedness Innovations
Eric Gascho, National Health Council
Fabio Bisordi, Roche
Gillian Woollett, Samsung Bioepis
Ginny Beakes Read, Amgen
Ian Hudson, Bill & Melinda Gates Foundation
Ilisa Bernstein, American Pharmacist Association
Jamie Sullivan, Everylife Foundation
Janis Bernat, International Federation of Pharmaceutical Manufacturers and Associations
Jeff Allen, Friends of Cancer Research
Jennifer Dudinak, Bristol-Myers Squibb
Jerry Stewart, Pfizer
John Lim, Duke-NUS Center for Regulatory Excellence
Karen Noonan, Association of Clinical Research Organizations
Kay Larholt, MIT Center for Biomedical Innovation
Khyati Roberts, Abbvie
Kristin Schneeman, FasterCures, a Center of the Milken Institute
Lauren Silvis, Tempus
Lina Aljuburi, Sanofi
Linda Peters, Google Health
Linda Aljuburi, Sanofi
Lowell Schiller, Aetion
Louise Gill, GlaxoSmithKline
Lucy Vereshchagina, PhRMA
Mark Cziraky, HealthCore
Mark McClellan, Duke Margolis Center for Health Policy
Mark Taisey, Amgen
Max Wegner, Bayer
Michelle Rohrer, Roche
Mike Ward, ex-World Health Organization
Morgan Romine, Duke Margolis Center for Health Policy
Murray Lumpkin, Bill & Melinda Gates Foundation
Murray Ross, Kaiser
Neil McAuslane, Centre for Innovation in Regulatory Science
Nicholas Brooke, Patient Focused Medicines Development
Nick Sykes, Pfizer
Sarah Emond, Institute for Clinical and Economic Review
Sarah Montagne, Bayer
Sergio Cavalheiro Filho, International Federation of Pharmaceutical Manufacturers and Associations
Stacey Holdsworth, Lilly
Susan Berger, Bristol-Myers Squibb
Yuan Fang, Google

Additional colleagues joined throughout the day.

* Not all participants are noted on this slide. The slide excludes the Avalere and MSD teams.

GLOBAL REGULATORY AGILITIES DURING COVID-19 *WORKSHOP SUMMARY*

February 18, 2022

Global Customer Insights

Executive Summary

Overview: Avalere and MSD brought together a cross functional group of stakeholders to discuss the impact of regulatory agilities precipitated or accelerated by the COVID-19 pandemic. This workshop contributed to an ongoing collaborative and participatory process of assessing impact of global regulatory agilities on diverse stakeholders and working to embed those that are beneficial in routine practice moving forward.

Takeaways

- These agilities have significant tradeoffs. Maximizing efficiencies will be key to sustain this work moving forward.
- Time is limited. Stakeholders need to develop a response plan before the PHE ends.
- Clinical trial infrastructure should be modernized.
- Data requirements should be re-organized to focus on clear, transparent, and efficient data measures.
- Global harmonization and convergence is a strong goal but not achievable with current information sharing systems and exclusion of LMIC voices.

Next Steps: MSD will lead development of a publication to widely disseminate insights from the workshop and work with partners (e.g., regulatory agencies, policymakers, industry, patient and provider groups) to sustain agilities introduced during the COVID-19 pandemic.

LMIC: Low- and Middle-Income Countries; PHE: Public Health Emergency

OBJECTIVES & PARTICIPATION

MSD

Avalere Health Organized a Workshop on Behalf of MSD to Build a 360 View of Regulatory Agilities Agencies Can Retain Beyond the Pandemic

Background: The COVID-19 pandemic has altered regulatory systems and prompted regulators to establish new ways of working. Through interviews with global regulators, industry representatives, and other organizations, MSD and Avalere explored how regulatory authorities deployed innovative approaches during the COVID-19 pandemic and the potential impacts of these agilities to a diverse set of stakeholders.

Purpose: This workshop provided a forum for candid conversations to pressure test learnings from the interviews; solicit perspectives from a diverse set of stakeholders; discuss the impact of selected regulatory agilities; and consider opportunities and strategies to sustain agilities beyond the end of the pandemic.

Workshop Objectives:

1. To explore stakeholder views of select COVID-19 regulatory agilities that agencies could retain beyond the pandemic to strengthen routine regulatory practice, prepare for the next pandemic, and build a more coordinated global regulatory system to build out a “360 view” of each
2. To discuss the (current and/or potential) impacts of these regulatory agilities on stakeholders across the healthcare ecosystem

Case Studies Identified Through Interviews Informed the Agenda for The Stakeholder Workshop to Test Results and Identify Impacts

Development of Cases

- Avalere identified 10 regulatory agilities implemented by regulators in prioritized markets and develop brief case studies exemplifying the agilities
- Cases were surfaced through interviews with stakeholders representing a cross-section of global regulatory agency representatives; life sciences and biotechnology manufacturers; and global health agencies

Stakeholder Workshop

- Avalere convened an interactive workshop with key stakeholders and opinion leaders, during which participants pressure tested the cases, identified additional potential cases and data, surfaced perspectives from a diverse set of stakeholders and dug into the impacts of selected agilities

Impact Assessment Plans

- Avalere will develop a plan to assess the impact of up to 5 of the identified cases
- Assessments will focus on impact to product development and review, broader healthcare system (e.g., HTA assessment), and patients.

HTA: Health Technology Assessment; SOW: Scope of Work

Avalere Identified 10 Regulatory Agilities and Used Case Studies to Explore Enabling Factors, Lessons Learned, and Next Steps

The project defines **"regulatory agilities"** or **"agilities"** as the following: *Actions taken by a regulatory agency (as part of broader health authorities) driven by and in the context of the COVID-19 public health emergency that depart from that regulatory agency's pre-pandemic actions, procedures, and approaches. Note, this may include actions with both positive or negative consequences across stakeholders.*

Agility	**Reliance & Mutual Recognition**	**Convergence & Harmonization**	**Novel Clinical Trial Designs**	**Decentralized Trials**	**Regulator & Industry Interactions**
Case Study	AVAREF Emergency Joint Reviews to Support Reliance on WHO's EUL Process	ICMRA Workshops to Facilitate Regulator Dialogue and Alignment	UK RECOVERY Trial	FDA Flexibility in Regulation of Cancer Clinical Trials	Frequent FDA Guidance Release to Communicate Evolution in Thinking
Agility	**Data Expectations for Market Entry**	**Advances in Use of Pre-Market Real World Evidence**	**Active Real-World Data Exchange & Use**	**Rolling Submissions**	**Virtual Inspections**
Case Study	FDA and Data Expectations for EUAs	FDA and Aetion's Development of RWE on COVID-19	Epidemiological Evidence Collaboration Agreement between Pfizer and Israeli MoH	MHRA's Rolling Submissions and Ongoing Feedback	EMA Virtual Pharmacovigilance Inspections

AVAREF: African Vaccine Regulatory Forum; ICMRA; International Coalition of Medicines Regulatory Authority; FDA: Food and Drug Administration; EUS: Emergency Use Authorization; MoH: Ministry of Health; MHRA: Medicines and healthcare Products Regulatory Agency; EMA: European Medicines Agency; RWE: Real World Evidence

The Workshop Aimed to Foster Discussion About 5 Regulatory Agilities

Agility	Reliance & Mutual Recognition	Convergence & Harmonization	Decentralized Trials	Data Expectations for Market Entry	Advances in Use of Pre-Market Real World Evidence
Definitions	Processes whereby a regulatory authority in one jurisdiction partially or wholly relies on evaluations of another regulatory authority or trusted institution. Mutual recognition signals that two or more regulatory authorities recognize comparability of assessment results.	Regulatory requirements across countries or regions becoming more "aligned" over time by adopting common, internationally recognized technical guidance documents, standards and scientific principles, or similar practices and procedures	Clinical trials executed using a combination of digital technology and new processes to facilitate patient-centric trial participation; characterized utilizing digital tools to conduct trial activities with fewer clinical visits	Additional flexibilities around timepoints and different types of data that are required before market approval. May also include flexibilities around the appropriate amount of data required for submission to regulatory authorities	Use of healthcare information derived from multiple sources outside of typical clinical research settings including EMRs, claims data, product and disease registries, and data gathered by personal devices and apps
Case Study	AVAREF Emergency Joint Reviews to Support Reliance on WHO's EUL Process	ICMRA Workshops to Facilitate Regulator Dialogue and Alignment	FDA Flexibility in Regulation of Cancer Clinical Trials	FDA and Data Expectations for EUAs	FDA and Aetion's Development of RWE on COVID-19

AVAREF: African Vaccine Regulatory Forum; ICMRA; International Coalition of Medicines Regulatory Authority; FDA: Food and Drug Administration; EUAs: Emergency Use Authorization; RWE: Real World Evidence

MSD

The Agenda Was Structured To Maximize Participant Engagement Using a Mix of Facilitated Conversations, Discussion, and Breakout Sessions

Time (*ET*)	Topic
7:30am – 7:45am	Welcome from MSD and Avalere
7:45am – 8:30am	Panel Discussion: What Have We Learned? Where Do We Go From Here?
8:30am – 9:00am	Research Readout: Case Studies on COVID-19 Regulatory Agilities
9:00am – 9:30am	Discussion and Prioritization
9:30am – 9:45am	Break
9:45am – 10:00am	Agility Spotlight: Decentralized Trials (Jeff Allen, Friends of Cancer Research)
10:00am – 10:30am	Breakout Session
10:30am – 11:15am	Breakout Debrief
11:15am – 11:40am	Discussion: What's Next?
11:40am-12:00pm	Break
12:00pm – 12:30pm	Keynote: Themes from the Day and Where We Go from Here (Mark McClellan, Duke-Margolis Center for Health Policy)
12:30pm – 12:45pm	Wrap-up and Closing Remarks

Roughly 50 Participants Joined the Workshop Throughout the Day; 90% Stayed For More Than 3 Hours *

Adam Hacker, Coalition for Epidemic Preparedness Innovations
Anina Adelfio, Association of Clinical Research Organizations
Annetta Beauregard, Janssen
Annie Kennedy, Everylife Foundation
Awo Osei-Anto, FasterCures, a Center of the Milken Institute
Camilla Gomes, Roche, Epfia (Latam Network)
Carlos Garner, Lilly
Christian Schneider, Pharmalex
Debra Yeskey, Coalition for Epidemic Preparedness Innovations
Eric Gascho, National Health Council
Fabio Bisordi, Roche
Gillian Woollett, Samsung Bioepis
Ginny Beakes Read, Amgen
Ian Hudson, Bill & Melinda Gates Foundation
Ilisa Bernstein, American Pharmacist Association
Jamie Sullivan, Everylife Foundation
Janis Bernat, International Federation of Pharmaceutical Manufacturers and Associations
Jeff Allen, Friends of Cancer Research
Jennifer Dudinak, Bristol-Myers Squibb
Jerry Stewart, Pfizer
John Lim, Duke-NUS Center for Regulatory Excellence
Karen Noonan, Association of Clinical Research Organizations
Kay Larholt, MIT Center for Biomedical Innovation
Khyati Roberts, Abbvie
Kristin Schneeman, FasterCures, a Center of the Milken Institute
Lauren Silvis, Tempus
Lina Aljuburi, Sanofi
Linda Peters, Google Health
Linda Aljuburi, Sanofi
Lowell Schiller, Aetion
Louise Gill, GlaxoSmithKline
Lucy Vereshchagina, PhRMA
Mark Cziraky, HealthCore
Mark McClellan, Duke Margolis Center for Health Policy
Mark Taisey, Amgen
Max Wegner, Bayer
Michelle Rohrer, Roche
Mike Ward, ex-World Health Organization
Morgan Romine, Duke Margolis Center for Health Policy
Murray Lumpkin, Bill & Melinda Gates Foundation
Murray Ross, Kaiser
Neil McAuslane, Centre for Innovation in Regulatory Science
Nicholas Brooke, Patient Focused Medicines Development
Nick Sykes, Pfizer
Sarah Emond, Institute for Clinical and Economic Review
Sarah Montagne, Bayer
Sergio Cavalheiro Filho, International Federation of Pharmaceutical Manufacturers and Associations
Stacey Holdsworth, Lilly
Susan Berger, Bristol-Myers Squibb
Yuan Fang, Google

Additional colleagues joined throughout the day.

* Not all participants are noted on this slide. The slide excludes the Avalere and MSD teams.

TAKEAWAYS FROM PLENARY DISCUSSIONS

The Opening Panel Explored the Topic of "*What Have We Learned? Where Do We Go From Here?*"

Panelists /

Murray Lumpkin
Bill and Melinda Gates Foundation
Lead for Global Regulatory Systems Initiatives

Christian Schneider
Pharmalex
Head of Biopharma Excellence and Chief Medical Officer (Biopharma)

Debra Yeskey
Coalition for Epidemic Preparedness Innovations
Head of Regulatory Policy and Intelligence

Key Takeaways /

Most Valuable Developments During the Pandemic

- Manufacturers produced countermeasures rapidly while still meeting stringent quality and safety requirements.
- Regulators took strides towards greater reliance, including harmonized trial requirements, reliance-based decision-making for approvals, and increased formal and informal communication.
- Public health systems improved adverse event reporting and management.

Costs (to Regulators, Industry, and Systems)

- Burden on regulators and industry to work at pandemic speed is not sustainable.
- Costs of the pandemic were magnified in LMICs, with delayed access to innovative products. Lack of regulatory resources caused greater burden on WHO PQ.

Bottlenecks and Challenges During the Pandemic

- There were many uninformative trials with poor designs.
- Data was disseminated via press release, which confused regulators and the public.
- Small and inexperienced manufacturers struggled with tech transfers and supplies.
- Equality of access and convergence of requirements for international use is needed.

WHO PQ: World Health Organization Prequalification Programme; LMICs: Low- and Middle-Income Countries

The First Plenary Discussion Session Focused on the *Impact and Priorities of Featured Agilities*

Key Takeaways /

Patient Engagement is Crucial

- Participants commented on the advantages of increasing patient engagement for future success of agilities.
- Participants noted that engaging patient groups contributes to increased trust in the process and product.
- An HTA participant noted that the heterogeneity of the COVID-19 patient experience made engaging patients challenging.

Pandemic Preparedness Remains a Priority

- Participants discussed the importance of pharmacovigilance and safety of products through adequate data expectations prior to market entry.
- Regulators need to think about how the FDA can be prepared for the next pandemic.

Data Sharing Necessitates Global Coordination

- There was a gap in coordination globally, including the WHO.
- The transfer of data globally can hopefully be more efficient in the future.

Post-Market Trials Need Reconsideration

- Manufacturers are allocating resources to post-market trials to provide data on vaccines that are already well researched due to regulatory requirements.
- As we move forward, there is an opportunity to consider how much data is enough, and whether we are asking manufacturers to provide more data than necessary.

HTA: Health Technology Assessment; FDA: Food and Drug Administration; WHO: World Health Organization

The Second Plenary Discussion Explored *What Needs to Happen to Sustain the Featured Agilities*

Key Takeaways /

Lessons Learned Can Drive Future Change

- There have been several disparate efforts to identify lessons learned from COVID-19 and support regulators to build these into future practice, particularly for clinical trials and medical models.
- It's important to remember that regulators should never reserve learning just for a pandemic.

Accelerated Approvals Pathways Should Remain

- Regulatory agilities like accelerated approvals and rolling reviews have proven to be successful at expediting patient access.
- As such, regulators should be motivated to incorporate similar practices in the future – but with a targeted scope given the resources required to achieve expedited reviews.

Continued Data Sharing and Learning Must Continue

- Participants noted that there needs to be a collaborative effort with effective data sharing capabilities among stakeholders.

TAKEAWAYS ON SPECIFIC AGILITIES

Participants Joined 30-Minute Breakout Sessions to Discuss the Impact and Sustainability of Specific Agilities

Overview: Participants will self-select into breakout rooms to discuss the impact of specific regulatory agilities

Room 1: **Reliance & Mutual Recognition**	Room 2: **Convergence & Harmonization**	Room 3: **Decentralized Trials**	Room 4: **Data Expectations Prior to Market Entry**	Room 5: **Advances in Use of Pre-Market Real World Evidence**

Objective: To gather input from diverse stakeholders in order to understand the impact and durability of the selected agilities

Discussion Questions:

1. When will this work?
2. When will this not work?
3. How are/would you/your stakeholder group impacted/be impacted if this agility became routine practice?
4. How can we make it sustainable?
5. Are there ways to quantify or dig into the impact? Who should we talk to? What data sources exist?

Takeaways from Breakout Room #1: Reliance & Mutual Recognition

What are the 3 most important points you would like to share in the debrief?

1. **Transparency and information sharing are the foundation for reliance. Advancing reliance may require rethinking confidentiality provisions and agreements and developing secure platforms, among other efforts to improve transparency.**
   - Current confidentiality laws place burden on regulatory agencies to protect data while also meeting disclosure requirements and burden on industry to submit multiple and different data packages across markets. ECTD creates opportunity for streamlined, transparent data sharing, thereby reducing burden on industry and regulators.
   - Cross-section of participants expressed interest in developing a database to share data variations, citing ongoing work in Europe to achieve this.
2. **Everybody has finite resources. Robust participation demands creation of efficiencies for all parties.**
   - Stakeholders across the enterprise are interested in finding efficiencies through work sharing, centralized procedures, and unified standards.
   - HICs are leading the charge on convergence and reliance, using fora like ICMRA. These countries advance conversations on minimum data requirements and clinical trial protocols but do not share their thoughts out with LMICs, which are expected to sign on to the process without partaking in the conversation.
3. **We need to think of the whole product life cycle. Delays in life cycle updates have negative downstream impacts (e.g., stockouts). Reliance throughout the life cycle may be as or more pressing than initial product registration.**

ECTDs: Electronic Common Technical Document; ICMRA: International Coalition of Medicines Regulatory Authorities; HICs: High Income Countries; LMICs: Low- and Middle-Income Countries

Stakeholders Shared Diverse Perspectives on Reliance & Mutual Recognition

	PERSPECTIVES	VIEWS AND TRADE-OFFS
REGULATORY AUTHORITIES	Recognition of work conducted in other jurisdictions not only mitigates individual review burden and better serves the public health but also establishes a cultural shift around a global regulatory competency.	• Reliance can reduce the workload borne by individual regulators, which may be particularly valuable in less-resourced settings. • Investing time in reliance activities can be challenging without guarantees that participating countries will gain access to products assessed through them. • Confidentiality agreements that allow ready information and data sharing are essential to facilitate reliance, and their absence can be a critical barrier.
MANUFACTURERS	May benefit from more efficient review clocks and less duplicative submission efforts; time to market may be reduced.	• Industry is burdened by duplicative submission and inspection processes and would like to see greater use of reliance. • It would be helpful for reliance schemes to extend beyond initial authorizations to also include post-approval changes. • Manufacturers may face risk in allowing sharing of full dossiers due to concerns about IP and data protection, but there are solutions.
OTHER (PATIENT GROUPS, MULTILATERALS, ETC.)	Ability to significantly cut down on individual jurisdiction review time can help bring needed product to market faster.	• Reliance can facilitate faster access to new technologies, particularly in less-resourced settings that may typically wait longer. • Regulatory approval is only 1 step and may not automatically result in immediate availability and access.

IP: Intellectual Property

Takeaways from Breakout Room #2: Convergence & Harmonization

What are the 3 most important points you would like to share in the debrief?

1. **Convergence and harmonization are not as global as we think.**
   - Regulatory authorities have differing awareness of convergence opportunities, affecting their ability to participate. For example, regulators should not assume that every regulator has access to groups like ICMRA.
   - Language barriers can also hinder harmonization.
2. **There are areas where convergence and harmonization can be achieved.**
   - This will require significant effort among regulators. For example, creating global alignment and convergence on master protocols would significantly ease the burden on regulators but would require effort to achieve.
3. **While there are risks associated with convergence and harmonization, there are clear solutions.**
   - IP threats are a significant risk associated with convergence and harmonization. However, participants noted that these risks are not new and were present prior to the COVID-19 pandemic.
   - Its important to have positive messaging surrounding these risks and highlight that the safeguards currently in place to help minimize them (e.g., data and confidentiality agreements).

ICMRA: International Coalition of Medicines Regulatory Authorities; IP: Intellectual Property

Stakeholders Shared Diverse Perspectives on Convergence & Harmonization

	PERSPECTIVES	VIEWS AND TRADE-OFFS
REGULATORY AUTHORITIES	ICMRA workshops provided RAs the opportunity to learn from their peers in a rapidly evolving context; building relationships and trust across RAs may enable new reliance and work sharing arrangements	• ICMRA pilots on post-approval change management and hybrid inspections may help surface areas of misalignment that make some countries slower than others. • Language barriers can inhibit participation in harmonization efforts.
MANUFACTURERS	Convergence on RA expectations reduces burden from conflicting requirements and speeds access to markets	• Alignment achieved through ICMRA, or other mechanisms only extends to participating countries; RAs that do not participate may be unaware of or unaligned with ICMRA statements. • Manufacturers have a strong interest in streamlined expectations around data variations, CTAs, and approval of master protocols. WHO has a strong role to play here.
OTHER (PATIENT GROUPS, MULTILATERALS, ETC.)	Alignment among RAs supports more efficient development and approval of countermeasures	• Many convergence and harmonization efforts (e.g., ICMRA, ICH, IMDRF) focus on HICs rather than LMICs, leading to a perception that LMICs are being left behind. • Greater harmonization of patient engagement paradigms across regions would be helpful.

RA: Regulatory Authority; ICMRA: International Coalition of Medicines Regulatory Authorities; WHO: World Health Organization; CTA: Clinical Trial Application; ICH: International Council for Harmonization; IMDRF: International Medical Device Regulators Forum; HIC: High Income Countries: LMIC: Low- and Middle-Income Countries

Takeaways from Breakout Room #3: Decentralized Trials

What are the 3 most important points you would like to share in the debrief?

1. **Context-specific need to consider patient input prevails.**
   - We need a hybridized approach to decentralized trials that tailors to patients' individual needs.
   - More education is needed to inform patients of data privacy rights. This education can increase patient trust in decentralized trials, ensuring easier patient recruitment for new trials.
2. **Data protection and product regulatory frameworks are barriers that differ by country and need to be addressed.**
   - There is concern on where patient data goes first (e.g., a sponsor system), how protected it is, and how much responsibility and accountability there is to ensure protection.
   - Legal barriers such as anti-kickback statues and state licensing (including the equivalent in other countries) pose issues.
3. **Stakeholders need to share data with each other and improve data collection over longer periods of time.**
   - Consistent clinical measurements are needed to compare trials.
   - Interoperability is needed to streamline data sharing across stakeholders and countries.
   - ACRO has been working on surveillance of modalities for the last 3 years, using data to create a tool-kit for decentralized trials. This type of long-term data collection can help stakeholders ensure decentralized trials continue effectively.

ACRO: Association of Clinical Research Organizations

Stakeholders Shared Diverse Perspectives on Decentralized Trials

	PERSPECTIVES	VIEWS AND TRADE-OFFS
REGULATORY AUTHORITIES	Increased burden on regulators due to the need for frequent guidance and reliance on stakeholder feedback to communicate standards. Regulators had to exercise more flexibility than had been typical.	• New technology and data collection methods create potential for more complete data sets • Yet, this also generates increased burden for regulators to review and validate data those methods
MANUFACTURERS	Adopting remote administration and monitoring in a decentralized model drove efficiencies and leveraged advancements in technology.	• Ability to conduct trials with more remote activities may allow for quicker enrollment, fewer dropout patients and more efficient use of resources • Yet, designing protocols which rely primarily on use of novel technology may require additional effort and flexibility
OTHER (PATIENT GROUPS, MULTILATERALS, ETC.)	Allowed clinical trials to continue with minimized in-person contact.	• Possibilities for broader inclusion in trials, better data on diverse patient populations, and more patient-centric trial designs • Yet, for this to come to fruition, community will need to ensure that patients and patient groups are consulted to ensure patient voice is well understood and needs of more diverse population are addressed as protocols become more standardized

Takeaways from Breakout Room #4: Data Expectations Prior to Market Entry

What are the 3 most important points you would like to share in the debrief?

1. **Uncertainty is a universal concept, and therefore a need exists to set expectations with numerous types of stakeholders on what uncertainty means and how to form perceptions and operations within uncertain parameters.**
   - From a regulatory perspective, the feasibility of rigorous and rapid real-world data collection remains uncertain and lacks adequate precedents or standardization.
   - From a regulator or developer standpoint, few doubt the success that a transition in data expectations to heightened post-market surveillance has had to speed product time-to-market. However, an on-going need exists to establish post-marketing plans that address residual uncertainty.
2. **Long-term, there needs to be collaboration across stakeholders to enable these data collection methods to gain acceptance outside of COVID-19 and become sustainable.**
   - Sustainability for altered data expectations requires more trust, confidence, and communication by regulators, developers, and the public. Regulators must communicate with humility while still accommodating skepticism or apprehension by the public. It is critical to underscore the dynamic nature of science and how information shifts are not a result of lack of understanding, but rather continuously clarified understanding.
3. **Driving expectations based on risks to patients (e.g., for certain populations).**
   - Need transparent conversations around the level of evidence required and how the risk-benefit for certain patient populations is greater and demands differing levels of evidence to enable speedy access.

Stakeholders Shared Diverse Perspectives on Data Expectations Prior to Market Entry

	PERSPECTIVES	VIEWS AND TRADE-OFFS
REGULATORY AUTHORITIES	Increased burden assessing what data are most/least critical and aligning on timeline of modified expectations.	• Increased experience reassessing previous expectations may allow for efficiencies going forward • Yet, modified expectations may increase number of requests to act accordingly in cases where risk does not necessitate such flexibility
MANUFACTURERS	Quicker access to information ensures timely market entrance and encourages optimization of domestic manufacturing capacity.	• Sponsors of products built on platform technology or with existing data sets may continue to see advantages, given experience with product • Yet, Sponsors will need to balance between the regulatory certainty of traditional strategies and potential efficiencies gained through the PHE
OTHER (PATIENT GROUPS, MULTILATERALS, ETC.)	Provides more rapid access to lifesaving drugs while maintaining stringent quality and safety measures.	• Broad public appreciation for the speed to market, safety and efficacy of COVID countermeasures • Yet, these experiences may have also altered opinion, trust, and hesitancy for certain populations

Takeaways from Breakout Room #5: Advances in Use of RWE

What are the 3 most important points you would like to share in the debrief?

1. **Building incentives to drive data collection required to support RWE adoption.**
   - The COVID-19 pandemic aligned key stakeholders' interests in accelerating use of RWE to promote public health.
   - Expanding RWE to new disease classes post-pandemic will require new strategies to incentivize the data collection and information sharing required for continued growth.
2. **Establishing transparency by tying together artificial clinical data and RWD.***
   - RWD consists of numerous data sources and collection methods. As such, RWD driving RWE in clinical trials is a tool to be used in conjunction with traditional clinical data.
3. **Understanding potential broader impact of regulatory guidance clearly defining RWD uses and limitations.**
   - Public scrutiny around RWE deployed during the COVID-19 pandemic may have been unique, but public trust in RWE will impact adoption going forward.
   - While setting clear limitations and uses of RWD may build trust through transparency, it also may open RWE to unnecessary public scrutiny.

*RWE is derived from RWD
RWE: Real-World Evidence; RWD: Real-World Data

Stakeholders Shared Diverse Perspectives on Advances in Use of RWE

	PERSPECTIVES	VIEWS AND TRADE-OFFS
REGULATORY AUTHORITIES	Use of RWE remains a strategic priority; capabilities continue to grow, with applications for post market surveillance and pre-market regulatory submissions involving RWE	• RA gained valuable experience working with, assessing, and making regulatory decisions based on RWE • Yet, increased attention on RWE may increase regulatory burden at a time when expectations are still being formed
MANUFACTURERS	While the promise of RWE is immense, burden exists as regulators are still determining standards and expectations for proper use	• Increased appreciation for the value that RWE can contribute to an evidence generation strategy may allow for more advanced and targeted approaches • Yet, uncertainty remains about the likelihood of studies based on RWE being accepted by RAs, as well as how payers will view this data
OTHER (PATIENT GROUPS, MULTILATERALS, ETC.)	Utilizing RWE can strengthen understanding of a disease or treatment in broader, more diverse population with long-term outcomes	• The ability to bridge the clinical understanding of products from efficacy to effectiveness can prove vital for populations less commonly represented in clinical trials • Yet, data security and public trust may need to be continually addressed

RA: Regulatory Authorities; RWE: Real World Evidence

WHAT'S NEXT?

MSD

MSD Will Broadly Disseminate Findings from the Workshop and Continue to Engage With Partners to Sustain Beneficial Regulatory Agilities

MSD will continue to provide thought leadership on COVID-19 regulatory agility flexibilities that agencies can retain beyond the pandemic to strengthen routine regulatory practice and will work with partners to build a more coordinated global regulatory system.

Next Steps /

Avalere will develop an impact assessment plan related to the agilities highlighted during the workshop.

MSD will develop a publication to widely disseminate insights from the workshop.

MSD will identify and work with partners (e.g., policymakers, industry, patient and provider groups) to develop and advance strategies to sustain agilities introduced during the COVID-19 pandemic.

THANK YOU