ECONOMIST IMPACT

Biopharma's evolution: learnings from the pandemic for a revived regulatory landscape

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About this report

It took seven months from clinical trials commencing for the first covid-19 vaccine to be made available for public use. Pre-pandemic, the median time to market for a biotherapeutic treatment was nine years and four months, and the fastest had been four years for mumps in the 1960s.[1,2]

These ground-breaking reductions were executed in extraordinary circumstances. Now industry stakeholders are reflecting on what had happened—and assessing what tools and learnings can be carried forward to advance the future development of other therapies.

To capture those insights in this report, we spoke with stakeholders across the globe, representing industry, regulators and academics. We would like to thank the following participants for their time and insights (in alphabetical order):

- **Dr Peggy Hamburg**, former commissioner, Food and Drug Administration (FDA), US
- **Dr Ali Hansford**, head of regulatory strategy policy, The Association of the British Pharmaceutical Industry (ABPI), UK
- **Dr Jennifer Harris**, director of research policy, The ABPI, UK
- **Steve Hoare**, directory of quality, regulatory science and safety policy, The ABPI, UK
- **Hugo Hurts**, board of directors, Lygature Foundation; former executive director, Medicines Evaluation Board, The Netherlands
- **Dr Marianthi Ierapetritou**, Bob and Jane Gore centennial chair of chemical and biomolecular engineering, University of Delaware, US
- **Richard Johnson**, president and CEO, Parenteral Drug Association, US
- **Norihiko Kagawa**, senior director, regulatory affairs, Gilead, Japan
- **Professor Kenneth Kaitin**, senior fellow, Tufts University School of Medicine, Tufts Center for the Study of Drug Development, Tufts, US
- **Professor John Lim**, executive director, Centre of Regulatory Excellence, Duke-National University of Singapore Medical School, Singapore
- **Craig H Lipset**, founder, Clinical Innovation Partners; former head of clinical innovation, Pfizer, US
- **Heidi Marchand**, executive director, regulatory affairs, PharmD, Gilead, Japan
- **Nathalie Moll**, director-general, European Federation of Pharmaceutical Industries and Association (EFPIA), EU

[1] The IQVIA Institute for Human Data Science, "Lessons learned from COVID-19 vaccine trials", 2022, https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/lesson-learned-from-covid-19-vaccine-trials/lessons-learned-from-covid-19-vaccine-trials-forweb.pdf

[2] Philip Ball, "The lightning-fast quest for COVID vaccines — and what it means for other diseases", *Nature*, 589 (16-18), 2021, https://doi.org/10.1038/d41586-020-03626-1

- **Dr Richard Moscicki**, chief medical officer and executive vice president, science and regulatory advocacy, Pharmaceutical Research and Manufacturers of America (PhRMA), US
- **Anju Murayama**, student researcher, Medical Governance Research Institute (MGRI), Japan
- **Dr Akihiko Ozaki**, surgical oncologist, MGRI, Japan
- **Dame June Raine**, chief executive, Medicines and Healthcare Products Regulatory Agency (MHRA), UK
- **Jerry Stewart**, vice president and head of global regulatory policy and intelligence, Pfizer, US
- **Dr Tetsuya Tanimoto**, MGRI, Japan

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Executive summary

By December 2020, several potential covid-19 vaccines were showing promise in clinical trials. And by the middle of 2021, a vaccine was available to the public. Very few people had been optimistic that such a feat could be achieved.

In many ways, it was a perfect storm. The fast development of covid-19 vaccines benefited from years of previous research on related viruses and vaccine trials that used mRNA. It's said the research matured at just the right time, and that mRNA technology would not have been ready even five years ago.[3]

But the time-consuming part of bringing a vaccine to market is not necessarily the initial research, but everything that follows, including rigorous clinical trial testing, regulatory application approval, manufacturing and communication. On average, this takes just shy of a decade. But advanced digital tools and regulatory levers for faster approvals were at the ready, giving stakeholders the means to move at—relatively—lightspeed.

The process was a whirlwind that is likely to affect regulatory practices for years to come, prompting new mindsets and applications of tools to the wider biotherapeutic landscape.

We asked experts in regions with advanced regulatory systems—the UK, the US, the EU and Japan—what happened and what changes are likely to stick. The most significant takeaways are highlighted in this report.

Notable findings include:

- **Co-operation and collaboration between the industry, regulators, governments, clinical investigators, academic scientists and non-government organisations (NGOs) has been unprecedented.** For many, this was seen as the most effective tool in bringing the covid-19 vaccine to market so quickly. This could set the stage for further alignment in decision-making, de-risking for research and development (R&D), and establishing plans for programmes and standards across the biotherapeutic regulatory landscape. But for this to carry forward successfully, elements of nationalism and competition need to be revisited.
- **Rolling reviews and Emergency Use Authorisation (EUA) were essential tools for speed**. Coupled with an all-hands-on-deck mindset from industry and regulators, processes that typically took years instead

[3] *Nature*, "The lightning-fast quest for COVID vaccines — and what it means for other diseases", December 18th 2020. https://www.nature.com/articles/d41586-020-03626-1

took months, and those that took months accelerated into weeks. Post-pandemic, our experts think a middle ground can be found. Where the balance lies, of course, may be conditional for years to come. Some believe that such measures may be best for crisis situations, but others feel that these efficiencies can trickle down to the wider pool of biotherapeutic therapies.

- **Digital tools—onwards and upwards.** Digital tools adopted in the pharmaceutical sector have soared. Decentralised and remote clinical trials, remote inspections, digital submissions to regulators, and more data-driven discovery were always likely to be part of the future, but the pandemic sped up that eventuality. Many of these tools were already there for the taking but underutilised due to concerns about introducing risk to process and regulatory approval. There's little turning back now. Many regulators have been quick to offer guidance in these areas and show willingness to engage with industry to expand on them as needed.
- **Too often, manufacturing is an afterthought.** The high demand for drug manufacturing, and general shortfall of manufacturers available to produce new or additional drugs, means that, even if the rest of the pharmaceutical ecosystem sped up drug development and approvals, a bottleneck could slow time to market. Covid-19 put a spotlight on the issue, as well as supply-chain challenges, and the need for flexible manufacturing procedures to allow for more parallel planning with drug development. These needs may help speed the adoption of continuous manufacturing processes, which offer more flexibility than batch manufacturing and faster delivery times.
- **Global standards are in the pipeline.** Operating in multiple jurisdictions often introduces all manner of complications from a compliance and regulatory perspective, as well as data standards. Consortiums of global regulators and industry bodies have long tried to harmonise standards to ease the increasing number of global R&D initiatives and streamline applications for marketing approval. Progress was slow, but it helped lay the groundwork for the global collaborations that came to light during the pandemic. This momentum, stakeholders say, has continued, helping them carry on developing for the future benefit of global efficiencies.

Section 1: What happened? Covid-19 as a tipping point

The pharmaceutical industry has long complained about slow approval processes. According to an early 2019 IFPMA report, it takes around 10-15 years to develop a novel vaccine, as well as establish its quality, safety and efficacy.[4]

Over the years, regulators have introduced or permitted new mechanisms or adaptive processes to make the drug approval process faster while ensuring safety.[5] Still, slow and steady was the norm. But covid-19 vaccines were authorised for use by drug regulators at unprecedented speed. What happened?

The answer is multifaceted but can be broken into a few main buckets that we will explore in this chapter:

- Funding
- Application of regulation tools, including rolling reviews, EUAs, digital
- Remote clinical trials
- Collaboration
- An all-hands-on-deck approach

Funding

Vaccine R&D is costly, but governments, as well as NGOs, private companies and philanthropists, provided large sums to pharma companies for the purpose of rapid development.

Through the resources and financial de-risking, companies were able to run multiple clinical trials in parallel.[6,7] It also helped companies take the commercial risk of manufacturing vaccine stocks even before knowing they had an approved, successful product. And billions were spent on manufacturing capacity, including converting labs and factories.[8,9]

[4] International Federation of Pharmaceutical Manufacturers & Associations, "The Complex Journey of a Vaccine: The Steps Behind Developing a New Vaccine", July 2019,
https://www.ifpma.org/resource-centre/the-complex-journey-of-a-vaccine-final/

[5] Di Giorgio C, Adami S, Provenzani A, Bianchi S, D'Alessandro N, Polidori P, "The evolution of European Medicines Agency drug approval: the adaptive licensing", *Eur J Hosp Pharm*, 2016;23(1):1-2, doi:10.1136/ejhpharm-2015-000740

[6] "Accelerating vaccine trials", *Bulletin of the World Health Organization*, vol. 99,7 (2021): 482-483. doi:10.2471/BLT.21.020721, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8243025/

[7] WHO, "Coronavirus disease (COVID-19): Vaccine research and development ", August 10th 2021, https://www.who.int/news-room/questions-and-answers/item/coronavirus-disease-(covid-19)-vaccine-research-and-development

[8] *The Washington Post*, "Biden administration will invest billions to expand coronavirus vaccine manufacturing", November 17th 2021, https://www.washingtonpost.com/us-policy/2021/11/17/biden-covid-vaccine-manufacturing/

[9] McKinsey & Company, "Fast-forward: Will the speed of COVID-19 vaccine development reset industry norms?", May 13th 2021, https://www.mckinsey.com/industries/life-sciences/our-insights/fast-forward-will-the-speed-of-covid-19-vaccine-development-reset-industry-norms

In many ways, the accelerated covid-19 vaccines would not be possible without this bankrolling.

In the US, the government stimulus package, Operation Warp Speed, directed nearly US$10bn of investment towards covid-19 vaccines.[10] This played a significant role in Moderna's vaccine development, and although Pfizer largely self-funded its vaccine development and manufacturing,[11] the programme helped remove some of the financial risk and Pfizer struck a US$1.95bn deal for the government to buy 100m doses once approved.[12]

The European Commission also spent over US$470m on 105 covid-19 research projects, including four vaccine projects in 2020.[13] In the UK, the Vaccine Taskforce contributed to vaccine research, which ultimately helped in the development of the AstraZeneca vaccine.[14,15]

Tools

During the pandemic, mechanisms in the regulator toolbox to speed approvals along were used in a significant way. Prior to this, the appetite to take on perceived risk by doing things

[10] US Department of Health and Human Services, "Explaining Operation Warp Speed", https://www.nihb.org/covid-19/wp-content/uploads/2020/08/Fact-sheet-operation-warp-speed.pdf

[11] Scientific American, "For Billion-Dollar COVID Vaccines, Basic Government-Funded Science Laid the Groundwork", November 18th 2020, https://www.scientificamerican.com/article/for-billion-dollar-covid-vaccines-basic-government-funded-science-laid-the-groundwork/#

[12] US Department of Health and Human Services, "Explaining Operation Warp Speed", https://www.nihb.org/covid-19/wp-content/uploads/2020/08/Fact-sheet-operation-warp-speed.pdf

[13] European Commission, "EU research and innovation in action against the coronavirus: funding, results and impact", January 2021, https://ec.europa.eu/info/sites/default/files/research_and_innovation/research_by_area/documents/ec_rtd_eu-research-innovation-against-covid.pdf

[14] Department for Business, Energy & International Strategy, "UK Vaccine Taskforce 2020 Achievements and Future Strategy End of year report", https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1027646/vtf-interim-report.pdf

[15] Bingham K, " The UK Government's Vaccine Taskforce: strategy for protecting the UK and the world", *The Lancet*, Volume 397, Issue 10268, P68-70, January 2nd 2021, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7833709/

"This was a time to use many of the tools that were at our disposal that perhaps we had neglected or failed to embrace in a meaningful way."

Craig Lipset, founder of Clinical Innovation Partners and former head of clinical innovation at Pfizer in the US

differently made some stakeholders uneasy. But with the death count rising, speed became a necessity, and risk appetites altered.

"I would describe the last two years as one of adoption, rather than necessarily radical innovation," says Craig Lipset, founder of Clinical Innovation Partners and former head of clinical innovation at Pfizer in the US. "This was a time to use many of the tools that were at our disposal that perhaps we had neglected or failed to embrace in a meaningful way."

Emergency use

EUA was among one of the most impactful tools used during vaccine development.

In the US, EUA allows a drug to be available to the market before it is fully approved by the Food and Drug Administration (FDA). It is a tool to expedite the availability of medical products during public health emergencies when there is no adequate, approved, available alternative, and when the known and potential benefits outweigh the potential risks.[16]

Since the start of the pandemic, the FDA has granted numerous covid-related EUAs. Two vaccines (Pfizer-BioNTech and Moderna) and one treatment (Gilead Science's remdesivir) went on to receive full FDA approval.[17,18,19] An EUA can also be revised or revoked. For example, when it became clear that hydroxychloroquine posed a risk without significant benefit, the FDA retracted the treatment's EUA.[20,21]

The authorisation, coupled with rolling reviews (more on that later) and unheard levels of collaboration (more on that later, too) with the FDA led to several time-saving efficiencies. For example, the FDA required the covid-19 clinical trial participants be followed for a median of at least two months after vaccination.[22] For full approval, participants are followed for at least six months.[23,24]

Jerry Stewart, the vice president and head of global regulatory policy and intelligence at Pfizer in the US, reflects that EUA was a "critical" tool in the US during vaccine development.

Under the expedited process, Mr Stewart says that labelling for the vaccine was provided electronically in place of physical packaging and paperwork, meaning anyone—patients,

[16] FDA, "Emergency Use Authorization for Vaccines Explained", https://www.fda.gov/vaccines-blood-biologics/vaccines/emergency-use-authorization-vaccines-explained

[17] Pfizer; https://www.fda.gov/news-events/press-announcements/fda-approves-first-covid-19-vaccine#:~:text=Today%2C%20the%20U.S.%20Food%20and,-years%20of%20age%20and%20older.

[18] Moderna: https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/spikevax-and-moderna-covid-19-vaccine

[19] Remdesivir: https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-covid-19

[20] FDA, "Frequently Asked Questions on the Emergency Use Authorisation", June 15th 2020, https://www.fda.gov/media/136784/download

[21] FDA, "FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems", https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or

[22] FDA, "Emergency Use Authorization for Vaccines to Prevent COVID-19", 2022, https://www.fda.gov/media/142749/download

[23] Mayo Clinic News Network, "FDA gives full approval to Pfizer COVID-19 vaccine", August 23rd 2021, https://newsnetwork.mayoclinic.org/discussion/fda-gives-full-approval-to-pfizer-covid-19-vaccine/

[24] Abbas, N., Babar, ZUD., "Marketing authorization of COVID-19 vaccines across UK, EU, and the US: fact-checking and the implications for future research", *J of Pharm Policy and Pract* 14, 110 (2021), https://doi.org/10.1186/s40545-021-00400-0

physicians, caregivers—could go to websites to access up-to-date labelling electronically. "There was no need to develop packaged labelling per the usual process, which takes time and resources," he says. "This is an area that needs to be carried forward. Asia and parts of Europe have more experience than the US in progressing e-labelling processes."

EUA played out differently across the world. The UK's Medicines and Healthcare products Regulatory Agency (MHRA) (which is outside the EU regulatory system), enacted its national equivalent, temporary use authorisation.[25,26,27]

According to Ali Hansford, head of regulatory strategy policy at the Association of the British Pharmaceutical Industry (ABPI), many processes were expedited for those working on covid-19. "There was expedited scientific advice and reviews of applications for manufacturers and researchers that were looking into covid-19 therapeutics and vaccines."

"The MHRA also brought in a whole raft of flexibilities. The main ones were the use of electronic signatures, or basically electronic ways of doing things rather than pen on paper. People have been asking for that for absolutely years, and suddenly it was possible."

When the pandemic struck, EUA was only available at EU member state level, explains Nathalie Moll, director-general of the European Federation of Pharmaceutical Industries and Association (EFPIA).

Therefore, other levers were put in place to expedite EU approvals such as activating the EMA Pandemic Task Force, accelerated scientific advice, and international alignment through the International Coalition of Medicines Regulatory Authorities (ICMRA) (see Section 2).

Ms Moll says clarifications were made by the European Medicines Agency (EMA) and the European Commission, which granted flexibilities (eg, on remote good manufacturing practice inspections, and waiving bringing import testing), the use of rolling reviews and expedited Commission decisions. "This led to the first vaccine receiving conditional marketing authorisation 76 days after the start of the rolling review."

And in Japan, Norihiko Kagawa, senior director of regulatory affairs at Gilead, and Heidi Marchand, executive director of regulatory policy and intelligence at Gilead, explain that the Pharmaceutical and Medical Device Agency (PMDA) demonstrated its flexibility through its reliance on the Exceptional Approval pathway. This option in Japan provides a full approval when the product has already received marketing authorisation from a major health authority such as the FDA or the EMA.

"While this system is not new, this pathway had limited use and was last relied upon over ten years ago when there was an outbreak of a new type of influenza," explains Dr Marchand. Veklury (remdesivir) and other products such as Moderna's mRNA vaccine, Pfizer/BioNTech's coronavirus vaccine, molnupiravir and baricitinib were approved through this pathway. In the case of Veklury, the Exceptional Approval in Japan relied on reference to the corresponding EUA in the US.[28]

Dr Tetsuya Tanimoto of the Medical Governance Research Institute (MGRI) in Japan, explains why

[25] EMA, "COVID-19 guidance: evaluation and marketing authorisation", https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/guidance-developers-companies/covid-19-guidance-evaluation-marketing-authorisation

[26] Mahase E, "Vaccinating the UK: how the covid vaccine was approved, and other questions answered", BMJ, 2020; 371:m4759 doi:10.1136/bmj.m4759

[27] Abbas, N., Babar, ZUD., "Marketing authorization of COVID-19 vaccines across UK, EU, and the US: fact-checking and the implications for future research", *J of Pharm Policy and Pract* 14, 110 (2021), https://doi.org/10.1186/s40545-021-00400-0

[28] Gilead, "Gilead Announces Approval of Veklury® (remdesivir) in Japan for Patients With Severe COVID-19", May 7th 2020, https://www.gilead.com/news-and-press/press-room/press-releases/2020/5/gilead-announces-approval-of-veklury-remdesivir-in-japan-for-patients-with-severe-covid19

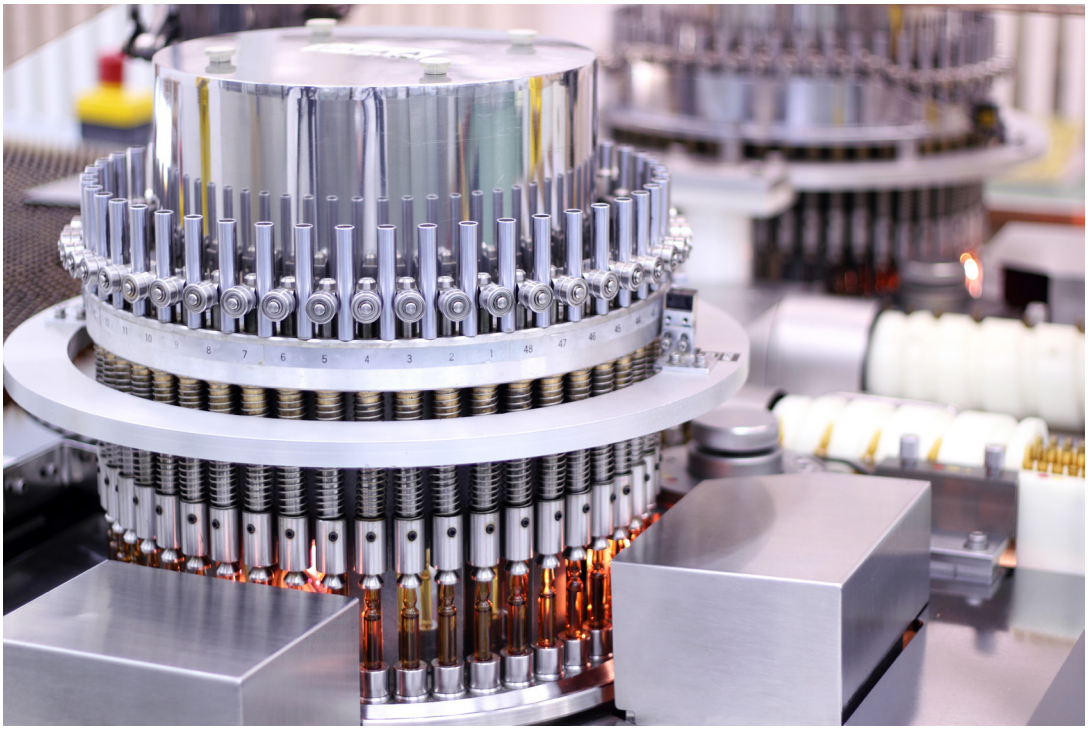
this approval is so extraordinary: normally, when approving therapies in Japan, clinical trials must include Japanese populations.[29] "It is mandatory, so even if a drug is already approved in the US or Europe, or pending approval, that is not enough to be approved in Japan. This usually means there is about a one-year interval between Japanese approval and Europe or US approval."

As there were no timely organisation for Japanese trials, the scheme allowed PDMA to consider drugs approved based on clinical trials in foreign countries. For Anju Murayama, a researcher at the MGRI in Japan, this is a significant event. "This is more than just a divergence from the norm, but evidence of a potential improvement in the Japanese regulatory system. The Japanese government generally hesitates to change their regulatory and healthcare system," he says.

Rolling reviews

The process by which drug regulators like the FDA and EMA approve applications for market authorisation usually take many months or even years, but rolling reviews helped pharma companies gain faster approval during covid-19.

Normally, all data on a medicine's effectiveness are delivered at once in a formal application at the end of exhaustive studies. With rolling reviews, agencies look at how a treatment is performing in real time as data emerge, offering feedback as needed until a formal application should be submitted—by which point, the regulator is deeply familiar with the data and can approve it in a much shorter timeframe.[30]



[29] Makoto Kosaka, Takanao Hashimoto, Akihiko Ozaki, Tetsuya Tanimoto, Masahiro Kami, "Delayed COVID-19 vaccine roll-out in Japan", *The Lancet*, Volume 397, Issue 10292, P2334-2335, June 19th 2021, https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)01220-4/fulltext

[30] EMA, "EMA starts first rolling review of a COVID-19 vaccine in the EU", October 1st 2020, https://www.ema.europa.eu/en/news/ema-starts-first-rolling-review-covid-19-vaccine-eu#:~:text=A%20rolling%20review%20is%20one,during%20a%20public%20health%20emergency.

"We completely broke the old paradigm, which was that you wait until you get every strand of regulation completed."

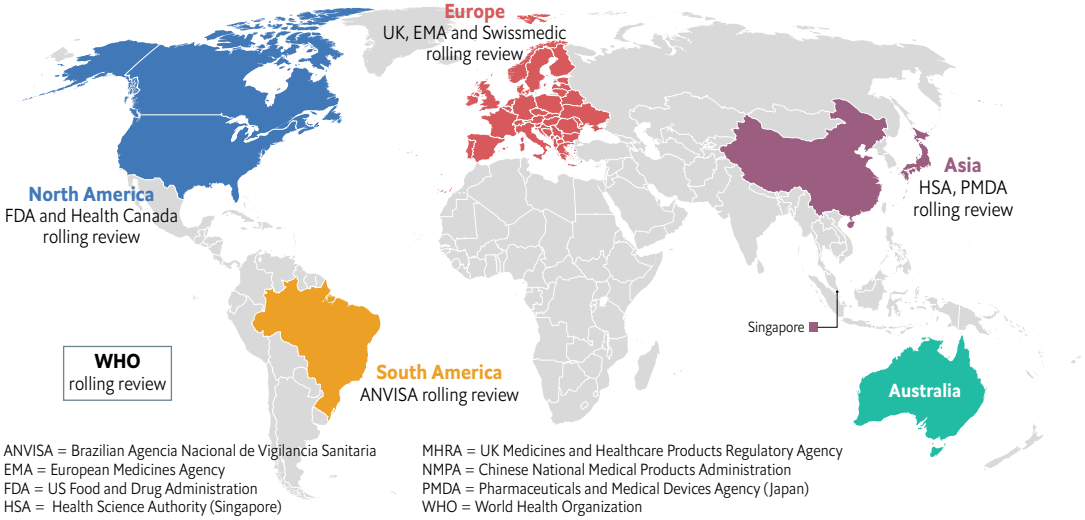
Dame June Raine, chief executive, Medicines and Healthcare Products Regulatory Agency (MHRA), UK

It is an underutilised regulatory tool, only really employed for a promising medicine or vaccine during a public health emergency.

In December 2020 the MHRA granted a temporary authorisation for emergency use for Pfizer's covid-19 mRNA vaccine based on a rolling submission, including data from the Phase 3 clinical study.[31] "We completely broke the old paradigm, which was that you wait until you get every strand of regulation completed," reflects Dame June Raine, chief executive of the MHRA. "We kept track of the different work streams from the clinical trials to the manufacturing batch release all in parallel and assessed packages of data as they came through. That rolling review was absolutely central to delivery."

And according to EU pharmaceutical legislation, the standard timeline for evaluating medicine is 210 working days. For context, there are about 250 working days in a year. However, the EMA applied rolling reviews for covid-19 treatments' marketing authorisation applications, reducing the review to under 150 working days. Approved vaccines went through 2-3 review cycles, ranging from 16-45 days per review cycle.[32]

Figure 1: Many regulatory agencies initiated some form of rolling review process for evaluating covid-19 treatments and vaccines



ANVISA = Brazilian Agencia Nacional de Vigilancia Sanitaria
EMA = European Medicines Agency
FDA = US Food and Drug Administration
HSA = Health Science Authority (Singapore)
MHRA = UK Medicines and Healthcare Products Regulatory Agency
NMPA = Chinese National Medical Products Administration
PMDA = Pharmaceuticals and Medical Devices Agency (Japan)
WHO = World Health Organization

Source: https://www.clinicaltherapeutics.com/article/S0149-2918(22)00005-4/fulltext#%20.

[31] Pfizer, "Pfizer and BioNTech Achieve First Authorization in the World for a Vaccine to Combat COVID-19", December 2nd 2020, https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-achieve-first-authorization-world

[32] Roelie Marinus, Sarah Mofid, Marya Mpandzou, Thomas C. Kühler, "Rolling Reviews During COVID-19: The European Union Experience in a Global Context", *Clinical Therapeutics*, Volume 44, Issue 3, 2022, Pages 352-363, https://doi.org/10.1016/j.clinthera.2022.01.001

The pandemic, however, activated digital processes that had been taking place in fragmented, unsystematic ways but suddenly became centre stage. Centralised and face-to-face turned to decentralised and remote.

In the US, there is a rolling review programme for "fast tracked" applications. Several covid-19 vaccines, like the ones from Moderna and Pfizer/BioNTech, received such designations.[33,34]

In Japan, while not explicitly a rolling review, Mr Murayama says an equivalent is in unofficial operation: "A lot of negotiation takes place between the government and the pharmaceutical company before the company submits an application for approval. In Japan, almost all drug applications have been approved due to this negotiation."

Digital adoption

Much can be said about the adoption of digital tools to help speed along the covid-19 vaccine. We focus on three areas that experts repeatedly raised as the most impactful and likely to see future application for other therapies.

Decentralised and remote clinical trials

According to IQVIA, a provider of technology solutions and clinical research services, clinical trial times for covid-19 vaccines were reduced by an average of 70% due to increased efficiencies.[35]

Clinical trials, the mainstay of testing the risk-benefit profile of medicines, have long been criticised by EMA experts. "The current environment for clinical trials is challenging," EU bodies wrote in their Accelerating Clinical Trials in the EU (ACT EU) proposal.[36] The pandemic, however, activated digital processes that had been taking place in fragmented, unsystematic ways but suddenly became centre stage. Centralised and face-to-face turned to decentralised and remote.

"In its basic term, it's telemedicine," says Mr Stewart. During lockdown and isolation, trial participants didn't have to travel to test sites, informed consent was handled electronically, and much data were self-reported. On the sponsor side, there were efficiencies in managing the clinical trial sites in a more centralised way and electronically.

It should also be said that most clinical trials conducted during the pandemic weren't just for covid-19 therapeutics. Clinical trials for other diseases were already under way. "The rest of our medicine pipeline was placed in jeopardy. We had no choice without adopting these approaches," says Richard Moscicki, chief medical officer and executive vice president of science and regulatory advocacy at Pharmaceutical Research and Manufacturers of America (PhRMA) in the US.

Before the pandemic, there was a lack of frameworks for managing decentralised trials across jurisdictions,[37] and questions were flying between industry and regulators. But regulators quickly became engaged and were ready to help.

[33] Venn Life Sciences, "Rolling reviews: a useful tool to speed up the regulatory review process", https://www.vennlifesciences.com/wp-content/uploads/2021/04/Speder-Bruno-Rolling-Reviews-Feature-May-2021.pdf

[34] European Pharmaceutical Review, "FDA grants Fast Track Designation to Moderna's COVID-19 vaccine", May 14th 2020, https://www.europeanpharmaceutical-review.com/news/119464/fda-grants-fast-track-designation-to-modernas-covid-19-vaccine/

[35] IQVIA, "Lessons learned from COVID-19 Vaccine Trials: A CRO perspective on accelerating clinical development", April 2022, https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/lesson-learned-from-covid-19-vaccine-trials/lessons-learned-from-covid-19-vaccine-trials-forweb.pdf

[36] EMA, "Accelerating Clinical Trials in the EU (ACT EU)", https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/accelerating-clinical-trials-eu-act-eu-delivering-eu-clinical-trials-transformation-initiative_en.pdf

[37] Outsourcing Pharma, "Decentralized trial transformations are here to stay", July 6th 2022, https://www.outsourcing-pharma.com/Article/2022/07/06/decentralized-trial-transformations-are-here-to-stay-icon

The EMA provided clarity when it published the "Guidance on the management of clinical trials during the COVID-19 (Coronavirus) pandemic" in 2021 (it has been updated several times since).[38] It allowed physical visits to be converted into phone or video visits, and for clinical laboratory tests, imaging or other diagnostic tests to be performed in a local certified laboratory.

The regulatory response was similar in the US: the FDA updated the guidance document for industry, investigators and institutions, which lays out similar simplification measures (virtual engagement with participants, remote visits and monitoring).[39]

For all the change and adoption during covid-19, Mr Lipset reminds us that this technology was always there for the taking: "We did the first fully remote clinical trial when I was at Pfizer, 17 years ago. These tools are not new. They were simply necessary for running studies during the last few years, because the risk in the external environment was so high that the perceived risk of adoption was lowered."

Digital submissions

"Digital was a huge factor that allowed countries to approve Paxlovid and Comirnaty faster," says Mr Stewart. "Normally, many countries require a paper submission, even responses to agency questions about the data are delivered in person in written format. But during the pandemic, for both products, regulators accepted email and electronic filing."

[38] EMA, "Guidance on the management of clinical trails during the COVID-19 (Coronavirus) pandemic", 2022, https://ec.europa.eu/health/system/files/2022-02/guidanceclinicaltrials_covid19_en_1.pdf

[39] FDA, "Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency: Guidance for Industry, Investigators, and Institutional Review Boards", August 2020, https://www.fda.gov/media/136238/download

Additionally, Mr Stewart says, several countries created a secure website for Pfizer to upload documents. "There are a lot of certifications that regulators require to approve products, for example, inspection and manufacturing certificates. In this circumstance, they were very quick to accept them electronically."

Remote inspections and approvals

"Getting your manufacturing sites inspected during the pandemic turned out to be a nightmare," says Dr Moscicki. The FDA wasn't allowed to travel and couldn't send inspectors to many of the manufacturing sites around the world.

An alternative was found. Remote inspections via secure video conferencing allowed inspectors to tour facilities, interview personnel, review procedures and validate data virtually. According to a published summary of learnings by Mr Stewart, this created efficiencies for regulators and industry by eliminating travel, using document management systems and fostering discipline and focused communications.[40]

"The development of abilities to do remote assessment using digital tools is an important learning to come out of the pandemic. I think this will be increasingly used in the future," says Dr Moscicki.

Collaborations

Drug regulators were not working in a vacuum. An extensive network of stakeholders played their part to drastically reduce regulatory review times. Industry was also moving quickly and making new partnerships.

"International crisis situations really help to co-operate internationally," reflects Hugo Hurts, former executive director of the Medicines Evaluation Board, in the Netherlands. "That's the time when networks really accelerate their development."

We asked the experts for examples of how collaboration during the pandemic helped speed up efforts to bring vaccines to market. Here are their replies:

Public-public: trust and team-players

- **Reliance between regulators**: "During the pandemic many global regulators engaged in 'reliance', a pathway where a given regulator will rely on the review of another regulatory agency instead of conducting their own review, or they'll agree to an abridged version of the review. There has been a lot of effort over many years to try to develop greater mutual reliance between the regulators from different countries, and I think this particular situation accelerated it. Not only was it successful, but it saved resources and demonstrated high levels of trust. I believe reliance is likely to stay in some capacity, even in the future, which

[40] RAPS, "Convergence: FDA officials on future COVID vaccine updates, remote inspections and hiring", September 14th 2022, https://www.raps.org/news-and-articles/news-articles/2022/9/convergence-fda-officials-on-future-covid-vaccine

will translate into faster approvals."—**Richard Johnson, president and CEO, Parenteral Drug Association, US**

- **Regulators helping regulators.** "The ICMRA was set up in 2012, but its global value and impact was really demonstrated during the first year of the pandemic, because then it was not just the members who were sharing information to facilitate and expedite the decisions, but they were opening up their virtual workshops to any other regulator around the world who would want to be part of that. This meant they were able to have scientific, technical discussions to facilitate decision-making on a more evidence-based approach to help regulators looking at products that they had not dealt with before. And I think that helped many regulators, especially in low- and middle-income countries, to have access to information that otherwise they would not have, and gain confidence in moving ahead with EUA procedures."—**Professor John Lim, executive director, Centre of Regulatory Excellence, Duke-National University of Singapore Medical School, Singapore**
- **Globalised efforts.** "Part of what was successful from a regulatory perspective was that regulatory agencies had started to work together in new ways. It mattered that the FDA and the EMA had established a stronger global presence. EMA has always worked across nations in the EU but one of my core priorities at the FDA, a domestic agency, was globalisation of the agency. It didn't happen overnight; it took time to set up trust for regulatory harmonisation and enhanced reliance, including the establishment of the ICMRA to strengthen co-ordination, communication and collaboration including the development of shared standards and approaches even before the covid vaccine efforts were significantly under way."—**Dr Peggy Hamburg, former commissioner, Food and Drug Administration (FDA), US**

Public-private: dialogue and information flows

- **A shared purpose creates green lanes. "**In crisis mode, there was no fear of hidden agendas, or questions about whether proposals were necessary. The facts spoke for themselves, and it was just a case of 'of course, let me help you'. We were all on the same side helping patients and that was amazing."—**Nathalie Moll, director-general, EFPIA, EU**
- **Reaching out.** "One major change that I saw over the course of the first few months of the pandemic was an unprecedented level of collaboration at the global level among clinical researchers, academic scientists, both large and small pharma, regulators, non-profit organisations

and government institutions. We've never seen anything like that. I think in large part that can be credited with the discovery, testing and public availability of vaccines within a staggeringly short period of ten months."**—Professor Kenneth Kaitin, professor of medicine, Tufts University School of Medicine, and senior fellow, Tufts Center for the Study of Drug Development, Tufts, US**

- **Rapid replies, constant dialogue.** "One of the biggest tools was the early discussion and the constant dialogue between the sponsor company, Pfizer, and the regulator. When the regulator asked for something, or if Pfizer asked for something by way of scientific guidance, for example, that guidance came within weeks. Normally that could take months. If the FDA asked for some data or clarification, Pfizer turned that around in days, and the FDA would respond in days. There was even collaboration communication that took place in days, which under normal circumstances, even under an expedited pathway sometimes can take months. There were tremendous savings right there."—**Jerry Stewart, vice president and head of global regulatory policy and intelligence, Pfizer, US**
- **Early advice and dialogue.** "My reflection is that we engaged with developers at the very earliest stage and we made it clear that they didn't need to hold back, that we would offer advice on clinical trial design, we would look at manufacturing, and any other aspect they needed like advice on risk assessment and acceptable methods for remote trial delivery. We also encouraged ongoing dialogue during development, so no longer do we just give advice, which is one way in its definition."—**Dame June Raine, chief executive, MHRA, UK**
- **Early dialogue between pharma and regulators across the globe.** **"**Pfizer sought approval internationally and I can say that with Brazil, Japan, the EU, there was early dialogue as far as 'here's the development programme, here's what we're trying to accomplish.' Everybody weighed in, and all those factors were accounted for in order to try to avoid surprises or misunderstandings down the road. We know that the FDA and the EMA collaborated with one another on everything from sharing data to understanding that there could only really be one programme. In other words, you know, Pfizer wasn't going to work with the EU on a development programme, and then have a different programme in the US. So that was another advantage of having early dialogue with these two key agencies to ensure alignment and moving quicker." —**Jerry Stewart, vice president and head of global regulatory policy and Intelligence, Pfizer, US**

- **Willingness to share information.** "I was personally involved in setting up a dialogue between the heads of R&D in our industry, on both vaccines and therapeutics, with the commissioner of FDA. And the commissioner was quite willing to listen to what the heads of R&D thought could speed up development. There was a lot of dialogue. And that's not a dialogue that normally occurs, because people don't have time and there are often firewalls. But those came down. We had information sharing in a way that really was going to put aside many trade secret issues or confidential information from clinical trials. I think during the pandemic, with everybody trying to expedite solutions, such as the vaccines or therapeutic agents, the same spirit was felt across the board."—**Dr Richard Moscicki, chief medical officer and executive vice president of science and regulatory advocacy, PhRMA, US**

- **Open exchange of views**. "What was unprecedented is how the MHRA approached us with their thoughts on some draft regulatory flexibilities. They came to us and said, 'can you discuss with your members and see which ones may be more useful than others, so we can direct our efforts towards generating guidance in that area'. That was new to my experience. They have done other things in the past, but less significant. It was clear everyone was in this together, and they wanted to try and solve this for us. And it just went on from there. It was a really good, frank exchange of views."—**Steve Hoare, directory of quality, regulatory science and safety policy, The ABPI, UK**

- **Clinical trials up and running.** "From a clinical trials perspective, following the WHO [World Health Organization] declaring covid-19 as a global pandemic, UK government, regulators and research bodies in the UK came together and agreed on expedited way of working to get covid-19 clinical trials not only approved quickly but set up quickly. It's all well and good approving studies quickly, but if you can't get the clinical trial set up and recruited quickly, you will end up delaying evidence generation. This was not only a collaborative way of working across government, but also with pharmaceutical companies and across the entire clinical research ecosystem."—**Dr Jennifer Harris, director of research policy, The ABPI, UK**

Private-private: teaming up for a common enemy

- **Scaling up for good.** "We saw unprecedented collaborations in terms of scaling up because as vaccines were being developed, and other companies fell further behind, they stopped their activities and joined forces to scale up. One company had something like 200 collaborations with other companies to get a vaccine manufacturing

process transferred globally and scaled out to meet demand."—**Dr Steve Hoare, directory of quality, regulatory science and safety policy, The ABPI, UK**

- **How can we help?** "IMI—the Innovative Medicines Initiative—is the biggest public-private partnership on health in the world, and it's between the European Commission and the European pharmaceutical industry. It's a way of doing pre-competitive research together and overcoming bottlenecks to R&D that no one organisation can solve alone. Usually, it takes a year or two to get a call for research in a given area published. During covid it took just two months. We had companies and research centres scanning their databases for anything that would be useful—in any way—whether for a diagnostic or therapeutic or vaccines. The level and speed of exchange of information was phenomenal, like never before."—**Nathalie Moll, director-general, EFPIA, EU**

All hands on deck

"So much of the success was really driven not just by innovation in technology and in processes, but by highly motivated people putting in extraordinary amounts of effort and time," says Mr Lipset.

Regulators and industry rallied

Regulators had their world turned upside down by covid-19. Not only were they expected to find a solution to the health crisis, but they also had to deal with internal upheaval. "Suddenly, the whole team was working from home," recalls Ms Moll. Between elderly parents and kids of different ages, regulators experienced the same work and personal challenges as people across industries.

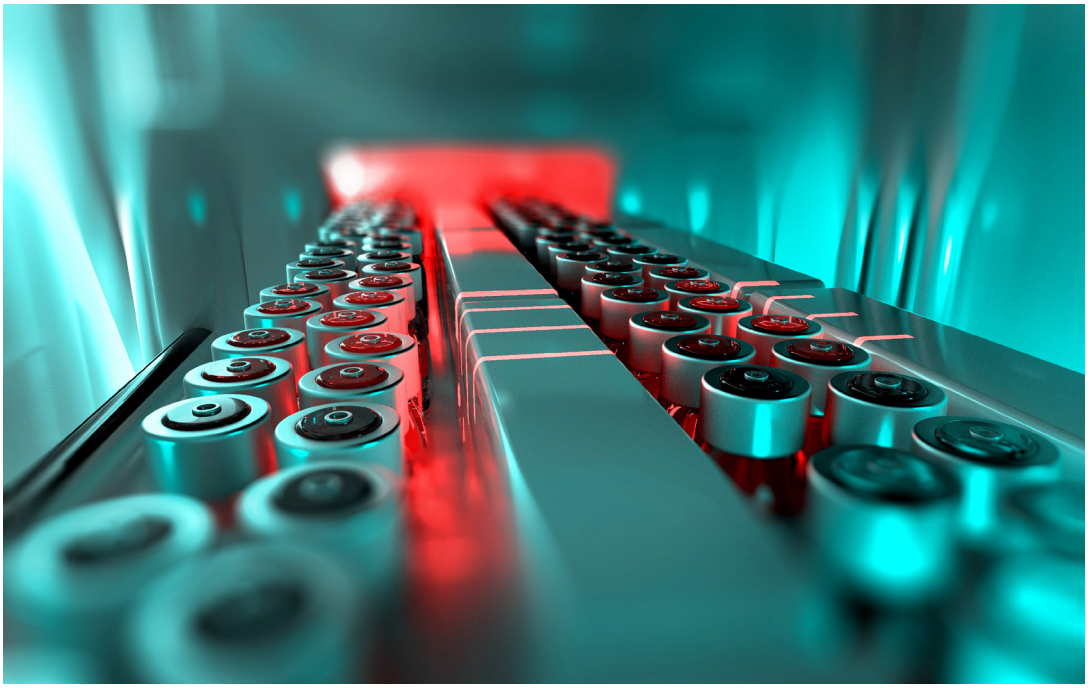
And the rest of the medical world didn't halt in its tracks, so regulators were undertaking their normal responsibilities in addition to covid-related work, all the while learning to deal with more people in new ways. "We were working double, but very grateful to be able to make a difference," says Ms Moll.

Industry also rose to the occasion. The scope of work was profound. "There was enormous enthusiasm amongst everyone involved," adds Mr Hurts. "They worked day and night. But there's a limit to what you can ask of people and if this lasts for a long, long time, you really run into the limitations of what is possible."

Swell of public support

Patient recruitment is one of the biggest challenges and rate-limiting steps to running clinical trials, explains Steve Hoare, directory of quality, regulatory science and safety policy at ABPI. "But with covid, everyone came forward to volunteer."

The public knew lives were at stake and many were eager to help where possible. For many, that meant funding vaccine efforts, but mostly it manifested in participating in clinical trials. This also meant a chance at early vaccination and reintegrating safely with family and friends.



Consequentially, tens of thousands volunteered. For example, Pfizer reports over 46,000 people participating in their covid-19 vaccine clinical trial.[41] It was an incredible feat that would normally take months or even years, according to an IQVIA report, which says that the enrolment stage for vaccine trials with over 10,000 participants takes an average of 12.5 months. Because covid-19 trials were enrolled in six months, this was 52% faster than the benchmark. The report adds that "this is particularly noteworthy as the average covid-19 trial is also nearly 80% larger than the benchmark cohort."[42]

Safety was never compromised

Amid all the speed and uptake of underutilised technology, no regulatory bars appeared to be lowered, and no standards were relaxed in terms of safety and data integrity. This is an important point to raise considering the rise in anti-vaccine sentiment.[43] We spoke to many stakeholders across the globe, and all echoed the same certainty of the approved covid-19 vaccines' safety.

In Europe, declarations were made that no corners were cut. "If you take it all together, EU's

[41] Covid Vaccine Study, "The Pfizer & BioNTech COVID-19 Vaccine Studies", https://www.covidvaccinestudy.com/

[42] IQVIA, "Lessons learned from COVID-19 Vaccine Trials: A CRO perspective on accelerating clinical development", April 2022, https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/lesson-learned-from-covid-19-vaccine-trials/lessons-learned-from-covid-19-vaccine-trials-forweb.pdf

[43] WHO, "Statement for healthcare professionals: How COVID-19 vaccines are regulated for safety and effectiveness", June 2021, https://www.who.int/news/item/11-06-2021-statement-for-healthcare-professionals-how-covid-19-vaccines-are-regulated-for-safety-and-effectiveness

"Speed did not mean that there was less rigor in the review process of the vaccines that were granted EUA. In fact, I think there probably haven't been too many products that are being studied as extensively as these products ."

Richard Johnson, president and CEO of the Parenteral Drug Association in the US

approvals didn't take that much more time than they took in the US. But it was done properly, without EUAs. Nothing has been missed. And we really felt safe to say we've looked at all the important issues at stake, but we did it a lot quicker than usual," says Mr Hurts, the former head of the Dutch agency.

Asked about the risk-benefits and speed, Dame Raine, who is adamant about the safety of the vaccines, said "one of my perpetual reflections was to be able to justify to the public how we've made a decision… we clearly wanted the public to understand our decisions."

Independent reviews of the vaccine and side effects also backed safety claims.[44, 45, 46] According to a statement by the ICMRA and WHO, the speed of development "has been unprecedented… but the safety and efficacy requirements for vaccines have not been compromised."[47]

"The only thing different was people actually went through the effort to adopt tools that were always available," recaps Mr Lipset. "There were some policies that may have been adjusted in some countries to stabilise healthcare delivery during this time, like modifying some rules related to telehealth and telemedicine. But when it came to the clinical trials that we had under way, the bars didn't change."

Affirmations of safety are echoed across the industry. Richard Johnson, president and CEO of the Parenteral Drug Association in the US, says: "Speed did not mean that there was less rigor in the review process of the vaccines that were granted EUA. In fact, I think there probably haven't been too many products that are being studied as extensively as these products."

Mr Stewart adds: "We were on solid ground, moving expeditiously did not change that. Safety was always at the forefront. These were blinded clinical studies, and in terms of benefit-risk and drug development, there wasn't a compromise. It all just happened faster, with earlier planning."

[44] Noam Barda, MD, et al, "Safety of the BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting", *N Engl J Med*, 2021; 385:1078-1090, doi: 10.1056/NEJMoa2110475, https://www.nejm.org/doi/full/10.1056/NEJMoa2110475?query=featured_home

[45] Wu, Qianhui et al, "Evaluation of the safety profile of COVID-19 vaccines: a rapid review", *BMC Medicine* vol. 19,1 173. 28 Jul. 2021, doi:10.1186/s12916-021-02059-5https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8315897/

[46] Medeiros KS, Costa APF, Sarmento ACA, et al, "Side effects of COVID-19 vaccines: a systematic review and meta-analysis protocol of randomised trials", *BMJ Open*, 2022;12:e050278. doi: 10.1136/bmjopen-2021-050278 https://bmjopen.bmj.com/content/12/2/e050278

[47] WHO, "Statement for healthcare professionals: How COVID-19 vaccines are regulated for safety and effectiveness", June 2021, https://www.who.int/news/item/11-06-2021-statement-for-healthcare-professionals-how-covid-19-vaccines-are-regulated-for-safety-and-effectiveness

Section 2: Now what? The future of regulatory pathways

In reflection, almost every step of developing and delivering the covid-19 vaccine diverged from the norm. And the world was watching. After seeing what is possible, few will accept pre-covid norms going forwards.

But not all of it is repeatable. According to the EMA in a written response, "it is clear that some of the flexibilities applied during covid-19 are only suitable for use in an emergency context, while some others (eg, rolling review) require considerable additional efforts and resources, and therefore could only be applied in future based on strong prioritisation of the products deemed to bring the biggest benefits."

So where will we land? What lessons can we take from covid-19 that have inspired change? We asked experts how and where they see the biotherapeutic landscape evolving.

Responses fall into two broad categories:

- **Environmental and people powered enablers.** We saw unprecedented levels of efficiencies through collaboration, dialogue, information sharing, trust and a common enemy. But the experts think we should lower our expectations if we expect this will continue outside of a global pandemic. Simply put, stakeholders are burned out by the experience, and our experts say people and nations are too competitive to maintain such free flows of information. This chapter will explore why some of these enablers are difficult to maintain—and why there's optimism, nevertheless.
- **Digital evolution will bring the most change.** Digital—namely remote clinical trials, the use of RWE and digital platforms—saw rapid innovation and adoption during the pandemic, and this is an area that is most likely to progress. This chapter will dive into areas most shaken up by this trend.

A new world for collaborations

Unsustainable momentum

The experts we interviewed believe that the pandemic provided a unique set of circumstances and the speed to market of the covid-19 vaccines could not necessarily be applied to other biotherapeutics.

Capturing a sentiment shared by many of the experts we spoke to about the future of the regulatory landscape, one interviewee said:

"Sometimes I think we all did it a bit too well and too fast. The expectations have gone up incredibly."

The human element—time, speed and the highest possible levels of motivation—that went into the rapid delivery of the covid-19 vaccine is simply not sustainable. "At the end of the day, regulators are just like everybody else. You can't maintain that kind of a pace forever," says Mr Johnson.

"The levels of turnover... I continue to see the comments from people that tell me you can't go lightspeed forever," says Mr Lipset.

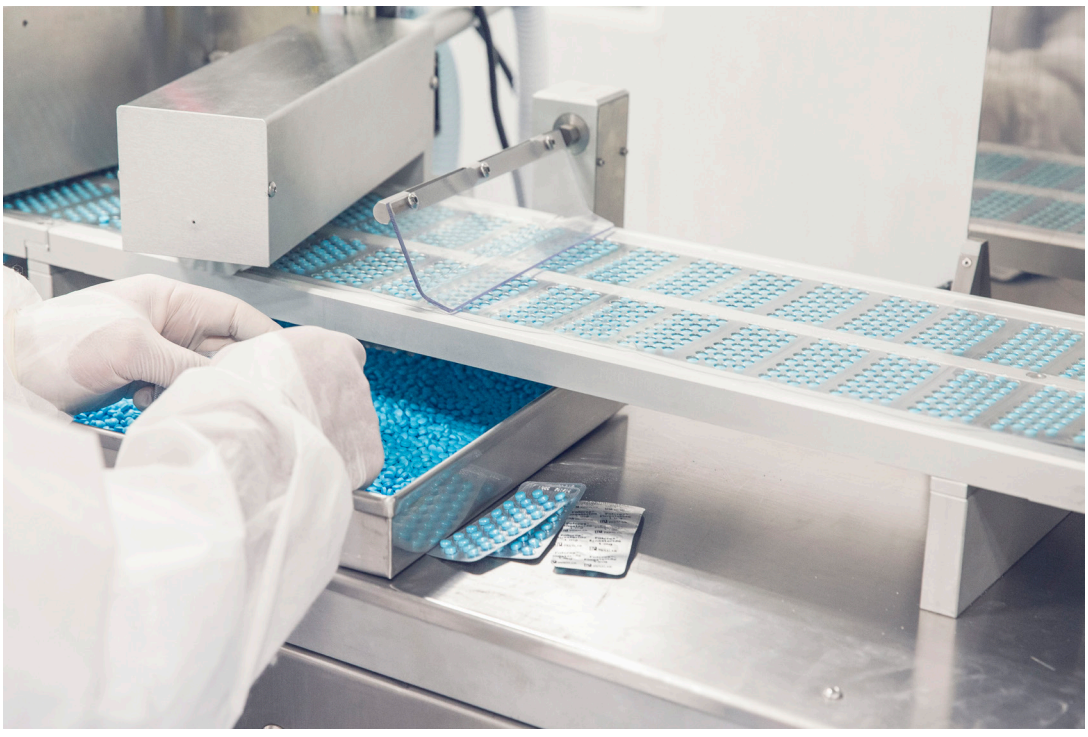
Supporting private collaborations

Private collaborations may be the hardest to sustain. Stakeholders were all fighting a common enemy, and funding was widely available to take risks, so people were more willing to exchange research and team up. But at the end of the day, industry and academic institutions are deeply competitive bodies. "They all want to be the first to find new results," says Kenneth Kaitin, professor at Tufts University School of Medicine, and senior fellow at the Tufts Center for the Study of Drug Development.

Experts we spoke with say one of the most efficient things that can be done now is make it easier for stakeholders to engage in future collaborations and data-sharing efficiencies, so that individuals and organisations designing therapeutics around the world can do more with less.

As a priority for the industry: sharing data for the goal of repurposing drugs.

"Before starting to develop a therapy from scratch, it's better to look and see if there's anything else out there that would work. New links between drug compounds and diseases are often being discovered," explains Professor Kaitin.



"If a drug gets approved, the data gets published. If a drug doesn't get approved, they have no obligation to share that data, and many don't. But we need to recognise that failures are an intrinsic part of science and development. The R&D community needs to be able to learn from negative results as well as positive outcomes ."

Dr Peggy Hamburg, former commissioner of the FDA

"There's a real market for this, but we don't see much of it yet. I expect we'll start to in the years ahead." It's not unfeasible, he adds, that the next treatment for Alzheimer's is sitting in a company's compound library somewhere and was developed for something completely different.

Dr Peggy Hamburg, former commissioner of the FDA, would also like to see pharma companies share more data on unsuccessful drug development. "If a drug gets approved, the data gets published. If a drug doesn't get approved, they have no obligation to share that data, and many don't. But we need to recognise that failures are an intrinsic part of science and development. The R&D community needs to be able to learn from negative results as well as positive outcomes."

Collaborative efforts are under way, such as the TransCelerate BioPharma—a non-profit global biopharmaceutical consortia with a mission to collaborate on research for new medicines—but the engagement levels and success in enabling sponsors to build on prior and emerging knowledge are not yet clear.[48]

Regulatory collaborations show promise

During covid-19, regulators across the world demonstrated higher levels of collaboration with industry and each other, and it had an incredible impact on time to market. Many say there's no need to see this regress to pre-pandemic norms.

"We need to recognise that not every regulatory authority in every country in the world can be fully mature and elaborated," says Dr Hamburg. "However, all countries and their citizens really do need the benefits of robust regulatory systems. Enhanced collaboration at a regional and international level, as well as technical assistance and capacity-building at a national level, can all make a difference." She hopes that the pandemic helped demonstrate the huge value of greater regulatory collaboration and will stimulate greater activity and support for this work.

Mr Johnson hopes so too: he believes the biggest impact could be ongoing mutual reliance between regulators around the world. "It's a complicated process to get a product approved, and you have to repeat that with each regulatory authority. So the extent to which they will start to co-operate and use any reviews and information that they have from other agencies around the world that is going to speed up the availability of these products, more than any other single effort that I could think of."

This is easier said than done, of course. Nations are bound by sovereign laws and often limited by existing systems and practices. For various reasons, there can be restrictions on the ability to share information with other trusted regulators, explains Dr Hamburg. "It's problematic. We also run into commercial confidentiality, even when

[48] TransCelerate BioPharma, https://www.transceleratebiopharmainc.com/

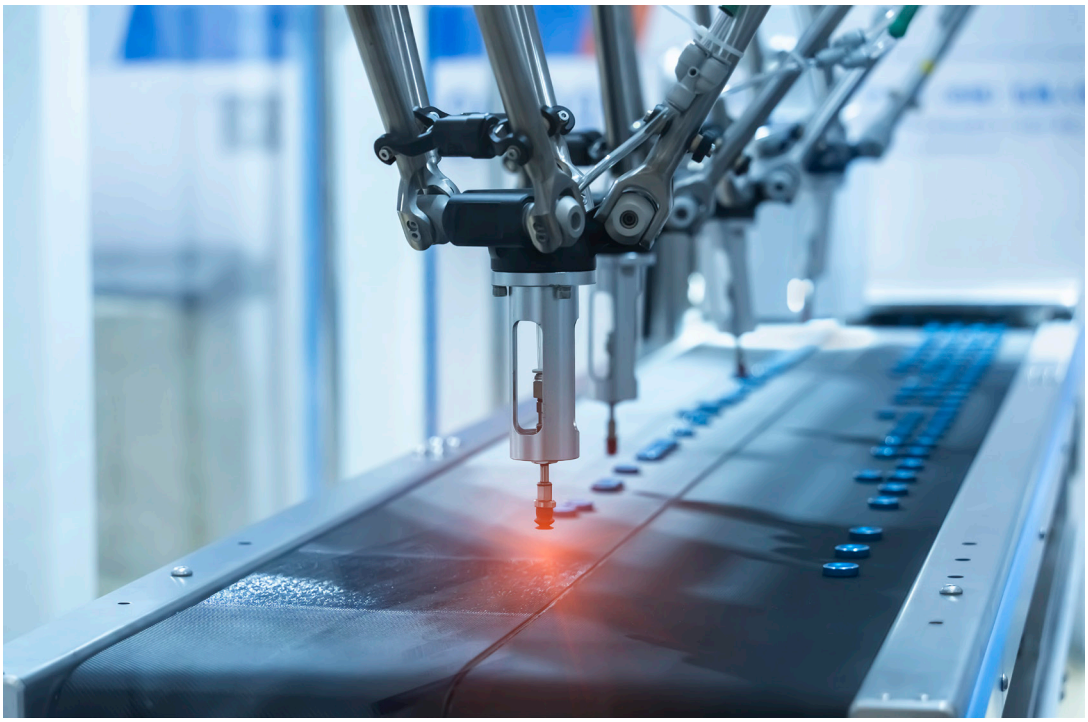
regulatory authorities are talking to each other about the same companies, the same products or sometimes very similar products with slightly different formulations in one country versus another. Much of this limits communication and weakens the understanding of problems and the opportunity to work together to solve them."

There is reason for optimism, though. Specifically, two significant global coalitions show a melding of the regulatory minds:

First, the **ICMRA** is helping to create a global architecture to increase collaboration, strengthen regulatory sciences and harmonise requirements across jurisdictions.[49]

"The ICMRA was very important during covid in terms of shared standards and approaches, both scientifically in terms of what studies should look like and what kinds of data was going to be important, as well as in streamlining administrative activities. Such discussions began even before the covid vaccine efforts were significantly under way," says Dr Hamburg.

Second is the **Access Consortium**, a coalition of regulatory authorities in the UK, Australia, Canada, Singapore and Switzerland that aims to promote greater regulatory collaboration and alignment of regulatory requirements.[50] "We're really pleased to join the Access Consortium because it speaks to an established work sharing principle," says Dame Raine. "Countries do different parts of an assessment and that has really begun to come into its own with new drugs. We see opportunities for biosimilars, generics etc... I think our future most definitely is through collaboration. And we've made a good start, but there's lots more to do."



[49] ICMRA, https://icmra.info/drupal/en

[50] Access Consortium, https://www.gov.uk/guidance/access-consortium

"People now realise that if you're not thinking about manufacturing, even as you design your product, and if you're not investing in getting the manufacturing capabilities up and going early, you can have literally years of delay."

Dr Peggy Hamburg, former commissioner of the FDA

Funding partnerships

The vast funding available for R&D during covid-19 will likely never be achieved for drugs that do not address such imminent public health needs. "The funding we saw during covid was a very appropriate response to the public health crisis, but that's not going to be for every product that comes along," says Mr Johnson.

Nevertheless, experts believe funding partnerships will still play a large role in future innovations. Investment in public-private or public-public partnerships for life sciences, such as the **Innovative Health Initiative**, an EU partnership for funding health research and innovation, will be important for providing diverse sources of funding for R&D.[51,52] Such partnerships could play a large role in speeding up the regulation process and enabling early uptake of innovative and effective drugs.

Advanced pharmaceutical manufacturing

A key learning is that developing a new medicine or vaccine and getting it approved is only half the battle—manufacturing is just as challenging.

No longer an afterthought

The pandemic exposed several cracks, foremost among these is supply-chain vulnerabilities, both in terms of raw materials and manufacturing materials. And when a vaccine seemed increasingly likely, a multitude of manufacturing facilities with the expertise and scale around the globe were not waiting to switch on.[53]

Costly adjustments had to be made and other products put on hold. Furthermore, it takes years to build manufacturing centres, and experts shared that there are limits to the number of professionals trained for the necessary roles.[54]

"Most manufacturing operation managers run to five-year plans, and they probably have two years' worth of production already in their schedules. So when a crisis comes along, we have to really look at the risk of taking that manufacturing slot out and giving it to something new. What happens to that product? Are we going to stock out? You've got to make some really big decisions," says Mr Hoare.

Regulators are also aware of the risks around manufacturing. "People now realise that if you're not thinking about manufacturing, even as you design your product, and if you're not investing in getting the manufacturing capabilities up and going early, you can have literally years of delay. So the regulator needs to be working closely throughout that process with the company," says Dr Hamburg. "Covid has obviously shown a very bright spotlight on why manufacturing is so important."

[51] Innovative Health Initiative, https://www.ihi.europa.eu/

[52] European Commission, "Affordable, accessible and safe medicines for all: the Commission presents a Pharmaceutical Strategy for Europe", November 25th 2020, https://ec.europa.eu/commission/presscorner/detail/en/ip_20_2173

[53] Chemistry World, "Why manufacturing Covid vaccines at scale is hard", March 23rd 2021, https://www.chemistryworld.com/news/why-manufacturing-covid-vaccines-at-scale-is-hard/4013429.article

[54] Design World, "How to quickly build a pharmaceutical facility", June 10th 2014, https://www.designworldonline.com/quickly-build-pharmaceutical-facility/

Continuous manufacturing

Dr Marianthi Ierapetritou is the Bob and Jane Gore centennial chair of chemical and biomolecular engineering at the University of Delaware. She says that even if the rest of the industry and regulation were to speed up drug development and approvals, the bottleneck in manufacturing would slow time to market.

There is, however, a solution that the market is working towards, one that many of our experts believe will come to dominate in time: continuous manufacturing.

While most drugs today are manufactured in batches, a lengthy, multi-step process, the continuous approach—which combines the full manufacturing process into a single, integrated flow—is gaining traction. There are two core reasons for this.

First, continuous manufacturing provides increasingly important cost and flexibility benefits. It offers the ability to quickly accelerate and scale up production, the ability to make post-approval changes and the ability to process the drug in a single facility (rather than intermittent steps across locations). All of these create efficiencies, helping companies rapidly respond to market opportunities.[55, 56]

Second, continuous manufacturing is more appropriate for many of the biological products that are being produced now, in greater numbers, as Dr Ierapetritou explains. "There is a trend of moving away from the small molecules to much more complex biological drugs. Most of the things that we can do with small molecules we

[55] USP, "Pharmaceutical continuous manufacturing: What drug makers need to know", June 9th 2022, https://qualitymatters.usp.org/pharmaceutical-continuous-manufacturing-what-drug-makers-need-know

[56] FDA, "Advanced Manufacturing", https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/advanced-manufacturing

"We learned that flexible approaches should be developed to allow fast and continuous supply from multiple manufacturing sites based on product sameness and appropriate inspections."

Nathalie Moll, director-general, European Federation of Pharmaceutical Industries and Association (EFPIA), EU

have done already, and there's a lot of promise to address the complicated diseases in alternatives, in biologicals, monoclonal antibodies, vaccines and gene therapies.... This balance is moving swiftly."

As far as time saving, a recent FDA self-audit found shorter times to approval for manufacturers that submitted continuous manufacturing applications than traditional batch manufacturing processes. They found no regulatory barriers relative to batch process application, or changes to pre-approval inspections. The assessment concluded that this translates to an estimated US$171m – US$537m in early revenue benefit.[57]

Nevertheless, uptake of new manufacturing processes is slow.[58]

"From my perspective, the reluctance to upgrade and modify [manufacturing processes] was, in part, one of uncertainty about the regulatory environment," says Dr Hamburg. Nevertheless, the FDA is certainly eager to facilitate the drug industry's adoption of advanced manufacturing.

Regulatory flexibility for manufacturing

During the pandemic, manufacturing needs for the covid-19 vaccine were considered in parallel with development rather than sequentially. "The issue was you couldn't wait for the trials to be finished before you were already putting into place the manufacturing capabilities," explains Professor Lim. It was a deeply collaborative approach between regulators and stakeholders that led to profound time savings in time to market.

How can we exploit these efficiencies going forward? The key, experts say, is regulatory flexibility.

In the EU, Ms Moll says the pandemic showed that flexibility in regulatory requirements for manufacturing is a more significant tool than reserving manufacturing capacity. "We learned that flexible approaches should be developed to allow fast and continuous supply from multiple manufacturing sites based on product sameness and appropriate inspections," she says. "We could have done better with a modern framework, and this has to be a key learning for next time and in view of the review of the EU pharmaceutical legislation that is currently ongoing."

In the US, Mr Stewart says "there isn't the kind of regulatory guidance or requirements that facilitate an equal expedited way for manufacturing as it is for clinical [research] under Breakthrough Therapy Designation, for example. Fortunately, under PDUFA VII [Prescription Drug User Fee Amendments for FYs 2023-2027], there is a commitment to have a manufacturing readiness for expedited programmes. But these are global programmes. So if the other agencies don't have harmonisation, then Pfizer conducting a global programme can only go so fast. This is an area that urgently needs harmonisation."

[57] Adam C. Fisher et al, "An audit of pharmaceutical continuous manufacturing regulatory submissions and outcomes in the US", *International Journal of Pharmaceutics*, Volume 622, 2022, 121778, https://doi.org/10.1016/j.ijpharm.2022.121778

[58] Pharmaceutical Technology, "Continuous manufacturing builds on hype but adoption remains gradual", May 20th 2022, https://www.pharmaceutical-technology.com/analysis/continuous-manufacturing-builds-on-hype-but-adoption-remains-gradual/

"I don't think there is a limit to rolling reviews. I think the message about our approach is to think about the right design of studies and the right data sources. Clearly there are certain types of data that we would always wish to have, and some may be more decision relevant than others."

Dame June Raine, chief executive, Medicines and Healthcare Products Regulatory Agency (MHRA), UK

Rolling reviews start to trickle down

As the name implies, EUAs are unlikely to be seen trickling down to non-emergency use. But there's a rising expectation that we may, in due time, see rolling reviews used for less crisis-level biopharmaceuticals.

Consultancies such as McKinsey, for example, see a potential expansion of rolling review in coming years, especially in cases of rare diseases and pathogens with antimicrobial resistance.[59]

Regulators agree that there will be times when rolling reviews should be applied, particularly in urgent situations such as rare diseases or when there is a very small patient population and clinical trials cannot be run on a large scale.

Ms Moll is unsure what would be the acceptable circumstances and timeframe in which rolling reviews are ready to become "the norm". In the EU, where the first vaccine received conditional marketing authorisation 76 days after the start of the rolling review, Ms Moll says "the amount of resources that it took to give those expedited pathways and the rolling reviews was enormous on both industry and [the] regulators' side... It's a big ask in the short term but definitely something we should strive for in the future."

In the UK, there are already hints at making rolling reviews more permanent. "I don't think there is a limit to rolling reviews," says Dame Raine. "I think the message about our approach is to think about the right design of studies and the right data sources. Clearly there are certain types of data that we would always wish to have, and some may be more decision relevant than others.

"There are different models for doing studies. It may well be that the rolling review is re-thought depending on the individual product."

To that end, she says the MHRA's Target Development Profile for drug developers following the Innovative Licensing and Access Pathway seeks to do exactly that.[60] "It's a bespoke development package." It includes several tools such as rolling reviews and continuous benefit risk assessments that integrate RWE.[61]

Rolling review: reimagined and dynamic

Still, members of industry are pushing to lower the bar for rolling reviews and see it applied outside of health emergencies. According to a January 2022 study by experts from Sanofi, "the health care system has demonstrated how fast it can respond to an unmedical need. Should this not become a benchmark beyond the covid-19 pandemic?"[62] They suggest the process continue to be optimised to become less resource intensive and more manageable under normal conditions.

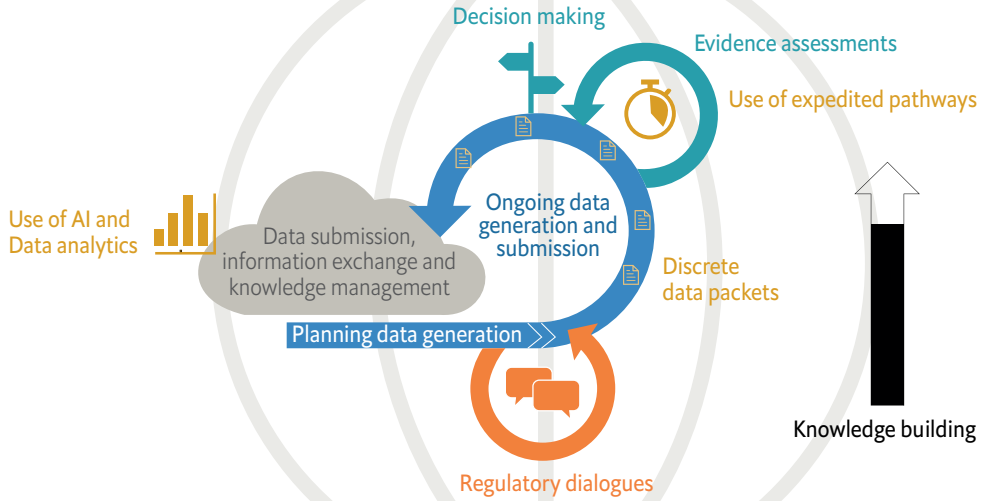
[59] McKinsey & Company, "Fast-forward: Will the speed of COVID-19 vaccine development reset industry norms?", May 13th 2021, https://www.mckinsey.com/industries/life-sciences/our-insights/fast-forward-will-the-speed-of-covid-19-vaccine-development-reset-industry-norms

[60] Gov.uk, "The Target Development Profile Toolkit", https://www.gov.uk/guidance/the-target-development-profile-toolkit

[61] *Ibid*

[62] Marinus, R., Mofid, S., Mpandzou, M., & Kühler, T. C, "Rolling Reviews During COVID-19: The European Union Experience in a Global Context", 2022, *Clinical Therapeutics*, 44(3), 352-363 DOI:https://doi.org/10.1016/j.clinthera.2022.01.001 https://www.clinicaltherapeutics.com/article/S0149-2918(22)00005-4/fulltext#%20

Figure 2: The Dynamic Regulatory Assessment (DRA) Concept: an iterative and flexible drug assessment mechanism



Source: https://www.sciencedirect.com/science/article/pii/S0149291821004562

But how can regulators more efficiently conduct rolling reviews? That question has long been under review.

In light of covid-19, in November 2021 the pharmaceutical industry body EFPIA reiterated the need to reimagine the regulatory review process across a product life cycle.[63] It coined the phrase: "Dynamic regulatory assessment", or DRA. (See Figure 2 for how the industry wants the regulatory system to evolve).

DRA envisions a common (cloud-based) platform where data for regulatory decision-making would be uploaded on a continuous basis (as they become available) instead of submitting it as a complete and validated dossier.

EFPIA's assessment process is also believed to help support collaborations across multiple regulatory jurisdictions globally in a simplistic manner. It concludes that the rolling review process can be beneficial not only to the pharma sector, but also to the patients when improved through digitalisation, operational excellence and innovation.

Clinical trials will never be the same

There is near universal agreement that clinical trials will not revert to pre-pandemic norms but instead increasingly digitalised and decentralised. "More and more we will see companies utilise these decentralised clinical trials to conduct new studies on their products," says Professor Kaitin. Already, with the pandemic largely behind us, there is evidence that conducting clinical trials in this way is trickling down to other therapeutic products.

"From a regulatory perspective, they are more than happy with remote trials as long as the data

[63] Herrero-Martinez, E., Hussain, N., Le Roux, N., MacDonald, J., Mayer, M., Palacios, R., & Kühler, T. C, "Dynamic Regulatory Assessment: evolving the European Regulatory Framework for the Benefit of Patients and Public Health—an EFPIA View", 2022, Clinical therapeutics, 44(1), 132-138. https://www.sciencedirect.com/science/article/pii/S0149291821004562

"With remote trials, patients are more enthusiastic, less likely to drop out and more willing to participate in some of these clinical trials."

Professor Kenneth Kaitin, senior fellow, Tufts University School of Medicine, Tufts Center for the Study of Drug Development, Tufts, US

quality is high," says Professor Kaitin. "And so far, we are seeing very high-quality clinical studies being done with a good collection of data."

Professor Kaitin says that studies, including from his Tufts group, show that patients prefer the remote setup, as it removes the need for travel.[64] Researchers, he adds, prefer them for largely the same reason: without patients on site, processing their digitally submitted data is more time and cost effective.[65]

Another advantage is cracking the longstanding issue of diversity in the clinical trial population. Diverse communities, the poor and rural populations are often underrepresented because they struggle more with the time, costs and distance of travel to clinical sites. (Consider a finding by PwC's Health Research Institute that found that consumers—Black, White and Latinx—were far more likely to participate in a clinical trial for a covid-19 treatment if they could do so from home or in their local area.[66]) Now, subjects can be enrolled from almost anywhere.

"With remote trials, patients are more enthusiastic, less likely to drop out and more willing to participate in some of these clinical trials," says Professor Kaitin. "I think for the most part that's something that regulators are aware of and are favourably inclined toward."

Experts agree that despite all the efficiencies currently on offer, there is still room for improvement to the digital infrastructure that supports remote, decentralised trials. Particularly regarding integration with RWE (more on this later).

"What is most important going forward is the focus in building, and maintaining, quality clinical trial infrastructures," says Dr Hamburg. "I think it's a critical time to invest. It costs a lot to build them, staff them and keep them going, and that's not so much a regulatory role but the regulator has a place in the conversation."

According to one study by PwC, many biopharmaceutical organisations have already made significant investments in the technology infrastructure to build and manage decentralised trials.[67] Some governments are helping, for example, a UK-wide plan published June 2022 announced £175m for improving the national clinical research system.[68]

Updating guidance for clinical trials

It took a pandemic for the widespread adoption of decentralised, virtual clinical trials, largely because stakeholders were concerned by how diversions from the norm would be perceived by regulators. It should not take another public health emergency for pharma companies and

[64] Florence, "What do patients think about decentralized clinical trials?", https://florencehc.com/learn/blog-posts/what-do-patients-think-about-decentralized-clinical-trials

[65] Van Norman, Gail A, "Decentralized Clinical Trials: The Future of Medical Product Development?*", *JACC, Basic to translational science* vol. 6,4 384-387, April 27th 2021, doi:10.1016/j.jacbts.2021.01.011

[66] PwC, "Consumer health behavior and the COVID-19 pandemic: What have we learned?", https://www.pwc.com/us/en/industries/health-industries/library/hri-insight-consumer-health-behavior-and-covid-19-pandemic.html

[67] PwC, "How retailers are disrupting the clinical trial delivery model", https://www.pwc.com/us/en/industries/health-industries/library/retailer-disruption-decentralized-clinical-trials.html

[68] News Medical Life Sciences, "Patients to benefit from a super-charged clinical research system", June 30th 2022, https://www.news-medical.net/news/20220630/Patients-to-benefit-from-a-super-charged-clinical-research-system.aspx

regulators to explore changes that could add further efficiencies without compromising safety.

Regulators appear open to change. The FDA, the MHRA and the EMA all issued guidance in support of virtual trials during covid-19.[69, 70, 71] But it's uncertain how adaptive they will be in the years ahead.

Mr Hurts hopes the new approaches to clinical trials could be a catalyst to simplify what he believes are onerous requirements in the EU: "If you look at the number of European patients involved in covid-19 clinical trials, it was less than 10%. I really believe in the system but what we always do is add new rules, new procedures and new requirements and we never remove one. It has grown very complex. We should consider simplifying to keep being a competitive part of the world and keep attracting clinical trials to Europe."

"At the moment," he adds, "there are debates going on in Europe; should we also make the system more risk-based to make it easier for relatively simpler products and keep watching all the details for the complex ones?"

Following Brexit, the UK's MHRA became independent of the EMA, allowing it to innovate free of EU constraints. When Dame Raine was asked what the MHRA may do differently, she acknowledged Mr Hurts' concern. "We've begun to look at greater opportunities to improve the efficiency and the inclusiveness of clinical trials... Ideally, we'll be able to see trials monitored

[69] FDA, "Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency: Guidance for Industry, Investigators, and Institutional Review Boards", August 2020, https://www.fda.gov/media/136238/download

[70] Gov.uk, "Managing clinical trials during Coronavirus (COVID-19)", https://www.gov.uk/guidance/managing-clinical-trials-during-coronavirus-covid-19

[71] EMA, "Guidance on the management of clinical trials during the COVID-19 (Coronavirus) pandemic", 2022, https://ec.europa.eu/health/system/files/2022-02/guidanceclinicaltrials_covid19_en_1.pdf

in a really efficient way and achieve results in the shortest possible time." She adds that the MHRA understands the challenges for industry of maintaining compatibility with other major jurisdictions, and changes are being designed on the back of the UK's membership of The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use,[72] as well as membership in the Access Consortium.

In Japan, however, researchers we spoke with are sceptical of future changes to PMDA's clinical trial mandates, which require trials conducted on Japanese patients for approval. Dr Akihiko Ozaki, surgical oncologist at the MGRI, said it's a shame, because from the perspective of pharmaceutical companies, the expense and bother to conduct these trials, coupled with Japan's inconsistent and often low drug pricing, makes the Japanese market a low priority.[73]

Nor do they think remote clinical trials are on the near horizon. "The current technology is not yet accurate enough compared to conducting in-person trials for patients," says Mr Murayama. "And we have not seen any initiatives to change this [in Japan]."

A data-driven future of health

Increasing application of RWE

Across the globe, RWE is becoming more commonplace in regulatory processes, as well as in the design of clinical trials.[74, 75]

Real world data (RWD) relates to patients' health and is collected from a variety of sources. RWE, meanwhile, refers to the evidence for a medical product's potential benefits or risk derived from RWD.[76, 77]

During the pandemic, RWE was used alongside classical randomised controlled trials to provide speedy and impactful evidence on vaccine safety and effectiveness.[78, 79]

The use of RWE to support regulatory decision-making is not new. The EMA and FDA have been granting regulatory approval for pharmaceuticals based on RWE before. For example, one study found 40% of marketing authorisation applications submitted to the EMA in 2018-19 used RWE.[80]

However, RWE has been primarily used for pharmacovigilance—post-approval—but applications of RWE are expanding for pre-marketing authorisation and the future of clinical trials: "Investigational medicine will always start with clinical trials, it's then a question of once a

[72] ICH, https://www.ich.org/

[73] Fierce Pharma, "Japan sees 'drug lag' as foreign pharmas pass up the market amid pricing pressure, industry group warns", https://www.fiercepharma.com/pharma-asia/japan-sees-drug-lag-as-foreign-pharmas-skip-market-amid-pricing-pressure-industry-group

[74] Clinical Trials Arena, "Rise in real-world evidence trials for 2021", https://www.clinicaltrialsarena.com/comment/real-world-evidence-trials/

[75] Li M, et al., "Integrating Real-World Evidence in the Regulatory Decision-Making Process: A Systematic Analysis of Experiences in the US, EU, and China Using a Logic Model", *Frontiers in Medicine*. May 31 2021. https://www.frontiersin.org/articles/10.3389/fmed.2021.669509/full

[76] EMA, "Advancing international collaboration on COVID-19 real-world evidence and observational studies", June 2021, https://www.ema.europa.eu/en/news/advancing-international-collaboration-covid-19-real-world-evidence-observational-studies

[77] FDA, "Real Word Evidence", https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence

[78] Fierce Pharma, "Industry Voices—COVID-19 vaccine rollout shows real-world evidence was ready for the spotlight", October 5th 2021, https://www.fiercehealthcare.com/tech/industry-voices-covid-19-vaccine-rollout-shows-real-world-evidence-was-ready-for-spotlight

[79] IQVIA, "Real World Evidence is Key to Better Understanding COVID-19 Vaccines: Lessons learned and how to anticipate evidence generation needs", https://www.iqvia.com/-/media/iqvia/pdfs/library/white-papers/real-world-evidence-is-key-to-better-understanding-covid-19-vaccines.pdf?_=1652866344265

[80] Arlett, P., Kjær, J., Broich, K., & Cooke, E., "Real-World Evidence in EU Medicines Regulation: Enabling Use and Establishing Value. Clinical Pharmacology & Therapeutics", 2022, 111(1), 21-23, doi:10.1002/cpt.2479

"One of the problems is that the data isn't collected with the purpose of R&D and licensing in mind, you then need to do a lot of work to make it usable. So, if early dialogue can be had with data custodians, you can begin to ensure that the data is actually collected in the way that's most usable."

Dr Jennifer Harris, director of research policy, The ABPI, UK

therapy is available for a small population, what can we do? Can we incrementally expand that using RWD?" says Mr Lipset.

"If regulators can keep pace with the learnings, we might event start to reduce or even eliminate control arms in our trials through the thoughtful and curated use of RWD," he muses.

Dr Hamburg is somewhat wary about RWE's pre-approval potential for new drugs. Her concern is that giving people medicine and waiting for them to report back is unreliable and potentially dangerous. Getting the answers of what works and for whom can be done just as quickly, and perhaps more accurately, in well-designed clinical studies. "We need to be more innovative and flexible in how we design and execute clinical trials, however."

She adds that for RWE to take off in other ways, it must be collected in a more structured, standardised way and with appropriate analysis—"truth doesn't just fall out because you have lots of data and AI [artificial intelligence]," she says.

Updated, global guidance for data and RWE

There is no doubt in the mind of stakeholders that digital tools, RWE and generally lots of data are on the rise as an important tool for regulation and speed to market.

Yet Dr Hamburg hit on an important point about RWE when she implied it can be challenging to get the data element right.[81] While individual companies may maintain good data practices for a given project, the healthcare industry does not have a fantastic record of sharing and consolidating data with others. The most prominent issue is that the data vary in quality and may not be from a trustworthy source, as well as timely access to the data.[82]

Health registries, for example, consistently struggle to standardise data and report inconsistencies among contributing bodies.[83] RWE is often partially generated from international databases, which means that it is likely difficult to translate or interpret in other contexts and populations.[84] When scaling up to international collaborations and databases, serious issues surface.

Globally aligned guidance and regulation around data standards and quality are desperately needed. National guidelines for RWE, for example, are only helpful to a point: "We increasingly have global clinical trials and global R&D programmes," explains Mr Hurts. "This

[81] ICMRA, "ICMRA statement on international collaboration to enable real-world evidence (RWE) for regulatory decision-making", https://icmra.info/drupal/sites/default/files/2022-07/icmra_statement_on_rwe.pdf

[82] ICMRA, "ICMRA meeting: COVID-19 Real-World Evidence and Observational Studies", May 2021, https://www.icmra.info/drupal/en/covid-19/10may2021

[83] Lazem, Mina, and Abbas Sheikhtaheri, "Barriers and facilitators for disease registry systems: a mixed-method study", *BMC medical informatics and decision making*, vol. 22,1 97. 11 Apr. 2022, doi:10.1186/s12911-022-01840-7

[84] ICMRA, "ICMRA meeting: COVID-19 Real-World Evidence and Observational Studies", May 2021, https://www.icmra.info/drupal/en/covid-19/10may2021

means that we need to see roughly the same bits of guidance, or at least some sense of how all of the regulators are going to agree on the types of evidence generation we need and the definition of quality data."

Mr Hurts adds that regulators, globally, should also be more prescriptive about what data are most useful. "The endpoints and how you design the trial is becoming increasingly important because the more data you have, the more you're looking at and the more you're assessing, which means that pharma companies say, 'well, what do the regulators want us to look at?' And 'how do they want us to use this data in our dossiers, or in our clinical trial approvals or for licensing, even HTAs?'."

Dr Harris adds that regulators, industry bodies and data custodians need to work together more closely to support the use of RWD in clinical studies and regulatory decision-making. "One of the problems is that the data isn't collected with the purpose of R&D and licensing in mind, you then need to do a lot of work to make it usable. So, if early dialogue can be had with data custodians, you can begin to ensure that the data is actually collected in the way that's most usable. This needs to be accompanied with clear guidance from regulators, building on existing guidance from MHRA and FDA."

It's a challenge. But the regulators and companies are already working together on guidance to help work through the core issues. The ICMRA is helping to lead efforts in this area: in a July 2022 press release, the EMA, endorsed a joint statement following an ICMRA workshop co-organised by EMA, the FDA and Health Canada, calling for international collaboration to address these common challenges around data harmonisation to further enable the integration of RWE into regulatory decision-making.[85, 86]

However, it may be some time before actionable agreements are made. "We all want good data standards, and we want it now. But it is going to be difficult to get there," says Mr Hurts. "We need some patience. It is always a difficult issue when you badly need improvements, but there's a technical side to it. The data protection issue alone is very complicated if you look at the European regulation. So this is real hard work."

Digital platforms for faster regulatory decision making

Industry is also making noise on how data can be better shared with regulators. Pfizer's Mr Stewart was quick to point out that many regulators accepted electronic filing during the pandemic, rather than paper, and that regulators had digital platforms into which Pfizer could submit that documentation. This created huge time and resource savings.

However, PDFs were too prevalent for Mr Stewart's liking, and he hopes the next evolution of submission will accept digital data. "Imagine how much easier it would have been for a regulator or industry body to pull data [from the cloud] that could be evaluated and tested on the fly."

He is adamant that one thing this experience made clear is that a cloud-based platform is a missing tool. "As we look ahead to developing therapies to address the next medical emergency and other serious, life-threatening diseases, I hope we will be able to use tools that enable stakeholders to collaborate in real-time."

Fortunately, such a cloud-based platform

[85] EMA, "Global regulators call for international collaboration to integrate real-world evidence into regulatory decision-making", July 22nd 2022, https://www.ema.europa.eu/en/news/global-regulators-call-international-collaboration-integrate-real-world-evidence-regulatory-decision

[86] ICMRA, "ICMRA statement on international collaboration to enable real-world evidence (RWE) for regulatory decision-making", https://icmra.info/drupal/sites/default/files/2022-07/icmra_statement_on_rwe.pdf

Regulatory science is entering a new phase, one that will be far more collaborative and innovative, spurred by all the learnings of the pandemic.

is actively being developed by Accumulus Synergy, a non-profit company sponsored by ten biopharma companies, including Pfizer, with active participation by regulators. One of the goals is to have a parallel review platform so that industry would upload data, which regulators could view simultaneously, conduct their reviews, then share their assessments within the cloud-based platform.

Such a platform, he believes, would remove a majority of submission activity and be of particular use in promoting reliance, which helps smaller, less resourced regulatory agencies rely on a review done by larger ones, such as the FDA, the EMA or the MHRA. Reliance also enables countries with less developed regulatory agencies to move forward with confidence. The WHO, in a recent publication of its new guidance on good reliance practices, says reliance has been key in facilitating emergency authorisation for covid-19 health tools.

"The platform would also add transparency," Mr Stewart adds. "This is needed to build that reliance because one of the elements where a regulator may be reluctant to rely on, for example, an FDA approval, is the trust and understanding about any unshared discussions that may have been relevant to the review. Now they could be invited to this cloud-based platform and see first-hand what the FDA is looking at."

AI is (finally) taking off

Covid-19 also catalysed AI's adoption. Its uses are numerous: screening molecules and compound libraries for potentially active substances, using machine learning (ML) to conduct decentralised trials, employing natural language processing to allow for the effective utilisation of unstructured data, and much more. Its use in the interpretation of unstructured data, for example RWE and electronic health records, is also helping to scale their application.

But Professor Kaitin says we are only still scratching the surface of how we can use that across the spectrum of research, clinical trial, manufacturing, pharmacovigilance and regulation. The more data that are produced in these processes, the more opportunity there is to feed data into ML models and evolve them.

"I think that's something that we're well on the way to and we're going to see even more of it," adds Professor Kaitin. "AI is going to benefit the health of nations, and a company that doesn't yet use it is already at a competitive disadvantage."

"Hopefully, AI will be used a bit more," says Ms Moll. "Of course, AI feels a little bit experimental, but there are some elements that are already used and useful, and I really think that there are ways to lean on what's already been developed."

Advancing regulatory science

Regulatory science is entering a new phase, one that will be far more collaborative and innovative, spurred by all the learnings of the pandemic.

Janet Woodcock, former acting commissioner at the FDA has said that only a small percentage of the clinical studies in the US on covid-19 therapeutics provided actionable data.[87]

[87] AMA, "FDA experts discuss COVID-19 therapeutic clinical trials", March 17th 2021, https://www.ama-assn.org/delivering-care/public-health/fda-experts-discuss-covid-19-therapeutic-clinical-trials

Dr Hamburg believes that if there was a better understanding about the regulatory science among the academic research scientists and institutions, those figures—for covid-19 and other clinical trials—would be much better.

"Unfortunately, many studies were done without an understanding of the critical questions to ask and answer from a regulatory perspective. They weren't adequately designed. They weren't adequately structured. They weren't adequately powered."

"It's not for nothing that so much attention has gone to regulatory science over the last few years," adds Dr Hamburg. Regulators understand that some innovations under development will need to be evaluated in untraditional ways. New data types and product developments will also challenge traditional methods.

"The regulatory system itself, and the rules that we apply in evaluating all these products need to be under constant reconstruction," she adds.

However, regulatory authorities are very willing to learn. Regulatory science networks are already helping regulators to enter unknown territory by setting joint priorities with industry and academia and prompting open dialogues about what adaptions are needed in the future.

Ready for next time: a new mindset

The pandemic has revealed what can be possible for future health emergencies, which might be even more severe than covid-19. The speed of product approval was down to several factors but mostly driven by the collaborative effort of key stakeholders, including researchers, drug regulators and pharmaceutical companies.

In the future, faster development and availability of vaccines and biotherapeutics could be hoped for as the science progresses and the experience of the last three years is embedded and not forgotten. Already, various initiatives are building on this experience such as the work of the ICMRA, the Access Consortium and cloud-based platforms to support regulatory science and the evolving pharmaceutical ecosystem.

One of the greatest achievements has been a new mindset that adds hope for better dialogue around the development of new biotherapeutics.

"The covid-19 crisis has shown the value of several innovative solutions but has also highlighted the need for further improvements, which will also be relevant for future vaccines and therapeutics," says Ms Moll. "We have a golden opportunity in Europe to review pharmaceutical legislation to the adjustments we need to be even more high performing in the future."

Through our research and discussions with experts, here are the key takeaways that can help build regulatory and industry efficiencies in bringing biotherapeutics to market, and embed readiness into the system for future health emergencies:

- **Regulatory science is evolving: don't fear experimentation and speed.** Covid-19 vaccines were successfully brought out at speed without compromising safety due to collaboration and bringing underutilised regulatory tools (rolling reviews, EUA) into action for the first time at scale. For regulators, there is a lesson here to simplify and evolve existing procedures and experiment with new regulatory tools that could make a difference. Openness and dialogue were at the fore, and this approach should be taken forward in the interest of research that benefits people.
- **Manufacturing must not be seen as a postscript.** The pharmaceutical sector needs to reappraise current approaches in manufacturing and build a manufacturing ecosystem that matches other industries. It could embrace continuous manufacturing (versus batch manufacturing) to better adapt to market needs in a cost effective and more timely manner. Regulators need to help create

a supportive environment as companies may be wary of making the leap.

- **Continue to emphasise harmonised data standards.** Experts have spoken at length about the importance of harmonising the health data space for improvements in pharmaceutical R&D. Efforts are under way, and although it was accelerated by the pandemic, there is still a long way to go. Momentum cannot be lost, and targets should be moved up so that many efficiencies pending this harmonisation can take off. Concepts such as cloud-based platforms need to be fully explored for benefit and risk. The role of RWE in pre-marketing assessments of drugs is starting to be used, but further study is needed on its value and data standard gaps fully addressed.
- **Address global regulatory variability.** Drug development programmes are often run at a global scale, so regulators need to continue to address global variability, and wherever possible, use the same tools and approaches for studies—otherwise, they end up conforming to the lowest common denominator, and in some cases that could lead to lower quality outcomes and delays. However, some initiatives in this area look promising and show regulators are taking action.
- **Clinical research is going remote.** The pandemic showed that decentralised and remote clinical trial research can be done effectively. Regulators and industry need to continue to be progressive in communicating what they're thinking about for these new approaches to ultimately benefit research and patients. Clinical trial infrastructure also needs continuous investment and innovation to build out the potential efficiencies.
- **Don't be afraid to try for other serious disease areas.** Experts have been wary that the collective effort applied to covid-19 therapeutics could be applied to other disease areas unless it is of high benefit. But some, such as Professor Kaitin and Mr Stewart, have suggested that it could be a wise use of resources to reapply all the resources that were at play during the pandemic for a different disease area, like Alzheimer's or heart disease. "We won't know until we try," says Mr Stewart. This collaborative effort could not only result in innovative treatments that benefit global populations, but the exercise would help reaffirm what works and prioritise the remaining challenges.

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