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REVIEW

BIOTECHNOLOGY PROGRESS

The pandemic and resilience for the future: AccBio 2021

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Abstract

The year 2020 brought the onslaught of a global crisis in the form of the COVID-19 pandemic. While nearly every facet of everyday life and work was impacted by the pandemic, the biopharmaceutical industry found silver linings in innovation, partnership, and resiliency, all of which contributed to unprecedented speed in developing and delivering vaccines and therapies. The 7th International Conference on Accelerating Biopharmaceutical Development (AccBio 2021) brought together industry leaders to share experiences from the past year and discuss how lessons learned from the pandemic can be carried forward into the future of biopharmaceutical development. Presenters highlighted examples such as introducing biotherapeutics derived from non-clonal cell pools into the clinic, developing modular or platform technologies, and taking novel risks, among others. These strategies for enabling speed to clinic and launch, as well as for sustaining a robust supply chain, are likely to be integrated into future programs to ensure biomanufacturing resiliency and get medicines to patients faster than pre-pandemic times.

KEYWORDS
accelerating, biopharmaceutical development, biopharmaceutical industry, commercialization, COVID-19 pandemic, speed to clinic

1 | INTRODUCTION

The emergence of a novel coronavirus, designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2),[1] marks the third zoonotic human coronavirus to surface in the 21st century, following severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV).[2,3] The disease caused by SARS-CoV-2, known as coronavirus disease 2019 (COVID-19), has resulted in a global pandemic far surpassing its predecessors. Just over 1 year after the World Health Organization declared a pandemic,[4] COVID-19 has a rising death toll of greater than 4 million people globally.[5] Beyond health implications of the disease itself, the COVID-19 pandemic has led to drastic alterations to daily life and work, including but not limited to social isolation, remote working, business closures, supply chain blockages, and resource pivoting. The biopharmaceutical industry has faced its own crises amidst herculean efforts to develop, manufacture, and supply novel therapeutics and vaccines for COVID-19, while continuing to produce and deliver critical therapies for patients afflicted with other diseases.

Yet "crisis really is a crucible for creativity and change." These are the words of Julie Gerberding of Merck & Co., Inc., Kenilworth, NJ, (MSD) during her keynote speech at the 7th International Conference on Accelerating Biopharmaceutical Development (AccBio 2021). Throughout history, durable innovations have been born out of times of crisis. Referencing Larry Clark from Harvard Business School,[6] Gerberding pointed out that crisis drives alignment of priorities, facilitates an opportunity to identify strengths and weaknesses, and creates a bias for action—all of which encourage teams to focus and be willing to take risks.

This past year, biopharmaceutical companies succeeded in producing novel coronavirus treatments as well as non-COVID-19 therapeutics at remarkable speeds and despite unique challenges. AccBio 2021 brought together scientists and leaders from across the industry to share experiences of developing biotherapeutics during the pandemic and collectively learn from

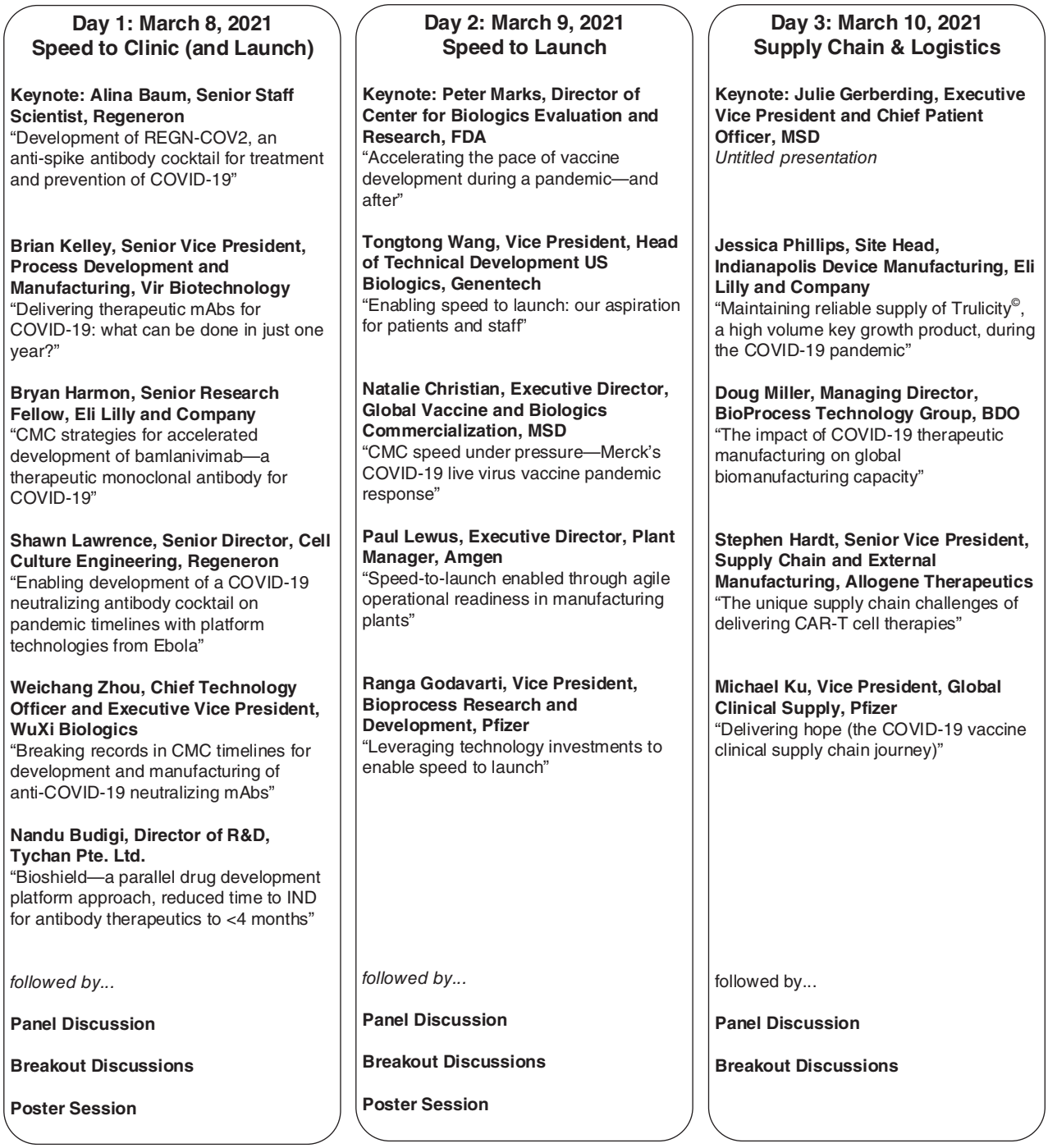

FIGURE 1 Overview of AccBio 2021 schedule and speakers

innovations and failures alike. The virtual conference centered around the themes of Speed to Clinic and Launch, and Supply Chain and Logistics (Figure 1). While many of the examples presented at the conference focused on monoclonal antibodies (mAbs) for treatment of COVID-19, the takeaways are applicable to other therapeutic targets and modalities. There is opportunity to embrace an innovative mindset to carry the momentum of the past year into the future, examining every step from molecule selection all the way to the patient to ensure the industry continues to move forward.

2 | SPEED

The biopharmaceutical industry has long been in a race against itself to achieve faster timelines in drug development. Over the past 5 years, companies had already drastically shortened the timelines for mAb candidate discovery to investigational new drug (IND) application from up to 24 months to approximately 10 to 12 months.[7] Time to initial marketing application (IMA) could take a decade. Vaccines often took much longer, given the start-stop nature of a highly de-risked development process.

During the COVID-19 pandemic, companies were able to shorten timelines even further to unprecedented speeds. In the race to develop its COVID-19 antibody cocktail (casirivimab and imdevimab), Regeneron shrunk its lead identification timeline to 70 days, with top candidate mAbs derived from human plasma identified in 33 days, followed by isolation of the candidates from immunized mice. The selected molecules were introduced into the clinic only 56 days after lead selection. Similarly, Eli Lilly cut down its traditional 17 month timeline for transfection to first-in-human (FIH) to less than 2 months for its COVID-19 antibody, bamlanivimab. This led to an Emergency Use Authorization (EUA) filing just 6.5 months after discovery, and approval within 8 months total. For the Pfizer-BioNTech COVID-19 vaccine, Michael Ku of Pfizer said it was just 266 days from the declaration of a pandemic to EUA.

As Nandu Budigi of Tychan Pte. Ltd. said in his presentation, "It took a pandemic for us to collectively realize that reduction of drug development timelines is not just a nice to have, but indeed an imperative." Yet such drastic timeline cuts require both process and mindset alterations, including a different approach to risk tolerance and mitigation. While the pandemic environment provided unique advantages for speed (e.g., relatively unlimited budgets, clear alignment of priorities across companies and regulatory agencies), other key enablers were already in place prior to COVID-19.

2.1 | Innovations

When faced with pandemic pressure to deliver drugs as fast as possible, biopharmaceutical companies had to think creatively and make decisions quickly to realize impressive timelines. The presenters at AccBio 2021 offered numerous examples of how their respective companies implemented novel solutions to speed up their processes.

Non-clonal pools: Several speakers highlighted the use of non-clonal cell pools for manufacturing protein therapeutics for FIH. Since the late 1990s, a health authority expectation has been that protein therapeutics are generated from monoclonal cell lines to ensure high quality and reproducibility.[8] However, with improved cell-line-development technologies (e.g., targeted integration), the use of pools of individual clones has become increasingly popular for early stages of development. In the past several years, companies have begun leveraging pooled clones for IND-enabling toxicology studies to save time, since developing a clonal cell line adds more than 3 months to the timeline.[9] With the recent urgency of the pandemic, companies like Vir Biotechnology, Tychan Pte. Ltd., and Eli Lilly further pushed that boundary by not only using stable bulk cultures (i.e., pools that are not clonally derived), but also using them all the way into the clinic. As Bryan Harmon discussed during his presentation, Eli Lilly used the non-clonal pools through phase II to keep pace with the accelerated clinical development timeline.

Use of nonclonal pools required partnership with the health authorities and innovative mitigations to address potential concerns. Harmon explained that close communication with the FDA on the strategy and use of nonclonal pools during product development provided confidence to both parties. One of the main concerns with non-clonal pools was the risk of product variability and population drift, which was resolved by implementing solutions such as: using frozen cell pools to ensure consistent cell age; establishing stringent in-process controls (e.g., to limit population doublings); and employing extra characterization testing to ensure consistency of product quality and process performance. Comparability risks were addressed by using product quality as the basis for criteria to select the final clone. For example, Weichang Zhou described how WuXi Biologics employed a battery of analytics (e.g., peptide map, glycan profiling, higher-order-structure analysis, virus neutralization assays, Fc functional and binding assays) to verify comparability between pools and clones, in parallel with next-generation sequencing to prevent selecting clones carrying sequence variants. Zhou showed data from a panel of ~12 molecules that demonstrated that non-clonal pools generated similar product quality to the final selected clones all the way up to the 2000 L production scale.[10]

While the presenters noted that using non-clonal pools for FIH was not yet routine for non-pandemic applications, discussions during the panel portion of the conference emphasized that COVID-19 had led to bold strategies like this one that may have relevance for future adaptations. It was noted that both the FDA and EMA accepted the use of these pools for FIH during the pandemic, and future collaboration between biopharmaceutical companies and health authorities may expand upon such examples of flexible and innovative thinking to bring new medicines beyond COVID-19 therapies to patients more quickly.

Modular approaches: Other presenters highlighted significant speed attained by downstream innovations, such as modular approaches to facility design or unit operations. Ranga Godavarti of Pfizer reported on the company's integrated, flexible, fully automated, and disposable modular drug substance (DS) manufacturing system. Paul Lewus of Amgen described employing standard equipment designs that enabled rapid assessment of facility fit. Such approaches provide flexibility to increase DS production capacity (by "scaling out" rather than the traditional "scaling up" approach), expedite equipment purchases, and enable transfer to new facilities without having to perform full validation on new equipment. The trend toward rigorous modularity will likely become the norm, and future technology designs would benefit from demonstrating utility across molecules, modalities, and facilities.

Modularity can also be useful in drug product (DP) operations. While aseptic robotic filling systems are becoming more available, Eli Lilly identified a unique alternative: bringing a mobile DP suite to the DS manufacturing site. A sterile mobile unit, qualified per USP<797>,[11] was used to compound sterile preparations for FIH (phase I) dosing. This mobile unit enabled on-demand small-batch manufacturing (capacity of 100 vials per batch) with thaw, filtration, filling, packaging, and labeling occurring on the same day. Since extemporaneous preparation in the mobile unit allowed for bypassing adventitious-agent and sterility testing, the DP could be released for dosing within 3 days as compared to 6 weeks.

Built-in flexibility: The flexibility made possible by the various innovations noted by the presenters was necessary given the number of unknowns derived from the pandemic; companies had to make

decisions quickly but without the typical level of information needed to do so. Building this flexibility into the manufacturing process up front became another innovation in and of itself. For example, MSD accommodated multiple different scenarios at every stage of vaccine development, since they started building their manufacturing facility before they had even solidified their candidate selection. Natalie Christian spoke of MSD's investment in freezers that could accommodate temperature ranges from −20 to −80°C because a final storage temperature had not yet been determined. Christian also noted that MSD developed the DS formulation to be "as vanilla as possible" so that the DP formulation could be finalized later. Analytical validation was performed on worst-case formulations across a broad range of concentrations.

Such flexibility admittedly increased costs and required trained resources available for redeployment, which were luxuries afforded to biopharmaceutical companies during the COVID-19 pandemic. While such luxuries may not always be as readily available in the future, the mindset of thinking further down the line of development and proactively building in flexibility where appropriate can serve as an enabler for speed into the future.

Considerations for site transfers: Some of the innovations raised at AccBio 2021 were not invented during the past year, but rather are applications of established practices that additionally contributed to saving time and resources during the pandemic. In his talk, Paul Lewus of Amgen discussed the concept of utilizing a clinical site for process performance qualification (PPQ) and commercial launch of a product, which postpones the time required for a technology transfer to the commercial site until after launch. Similarly, Lewus posed that performing a commercial site transfer back to a clinical site that has already been used for a specific product could save qualification time (depending on the past experience and inspection history of the site) and provide flexibility to constrained commercial sites. While both scenarios have limitations, such as the smaller capacity of most clinical sites or the time required later in the product lifecycle due to the deferral of qualification activities, making decisions like these illuminates a company's possibilities for maximizing use of a manufacturing network. Lewus pointed out the potential for future dialogues with health authorities to determine if transfers to in-network sites or scaling out (i.e., in like-for-like equipment, rather than scaling up) could reduce the regulatory requirements for activities such as PPQ.

2.2 | Leveraging platform knowledge

Applying platform technologies and processes that already existed significantly sped up the development and rollout of therapeutics during the time of COVID-19. Shawn Lawrence of Regeneron emphasized that launching from a process that had already been used for dozens of molecules provided regulators with more confidence in the company's novel COVID-19 antibody cocktail. Lawrence explained that Regeneron was able to leverage 30 years of investments in platform development to inform decisions from candidate selection to process development. Their proprietary mouse technology allowed for rapid generation of high-affinity, fully human antibody candidates, while a separate platform enabled accelerated screening, isolation, and production of the candidates. Prior knowledge also allowed Regeneron to move directly to a subcutaneous-administration-enabling concentration, rather than having to gradually transition from low to high concentration during development. In addition, platform experience for viral retentive filtration saved time and resources as the company performed a retrospective review of previous processes combined with a prospective assessment of acceptable conditions prior to ever performing product-specific experiments.

Similarly, AstraZeneca was able to build on existing work to deliver a therapeutic antibody combination with just 3.5 months from gene to FIH. In his poster titled "'The need for speed'—The rapid development of antibody therapeutics for COVID-19," Albert Schmelzer of AstraZeneca described the company's use of a well-established platform process, which included choosing typical "off the shelf" raw materials, leveraging cross-molecular knowledge to identify common risk factors, and operating predefined upstream and downstream processes. AstraZeneca's long history and experience with the platform process reassured the health authorities and afforded confidence in the novel COVID-19 therapeutic. The MHRA granted a 1 year shelf life for the DP without any representative stability data, based on AstraZeneca's prior knowledge of other molecules.

Standardization efforts across platforms can significantly improve efficiency within company networks and allow for future use of standard processes and technology. Furthermore, standardization of data storage allows a company ready access to current and prior knowledge. Panelists speculated that availability of platform information and historical data might allow in silico approaches to reduce product-specific studies in the future.

2.3 | Parallel activities and operating at risk

To collapse timelines to accommodate pandemic speed, companies performed multiple activities in parallel and at risk. For example, Eli Lilly performed concurrent technology transfers to multiple drug substance and drug product sites. Regeneron proceeded using a new upstream platform process while comparison of the new and old platforms was still being performed. To accelerate their vaccine to market, Pfizer started building distribution and administration infrastructure in parallel with process development and human safety and efficacy studies. Pfizer also scaled up to commercial development at risk, matching the chemistry, manufacturing, and controls (CMC) activities to the clinical speed achieved by their combined phase I/II/III clinical trial.

Such timeline agility required an equally agile strategy for risk analysis and mitigation planning, since performing normally sequential activities in parallel increases the number of unknowns at each phase of the process, in addition to potentially increasing the cost. In a pandemic setting, companies and health authorities had to rapidly identify where benefit outweighed potential risks. As Weichang Zhou of WuXi Biologics noted, while companies were willing to accept business risks (e.g., parallel investment), they focused on implementing measures to

mitigate potential risks to product quality and patient safety. Similar to the comparability strategy for non-clonal cell pools, assessing product quality attributes across stages of development allowed companies to perform multiple steps in parallel and still maintain confidence in product comparability and overall quality. Often this included performing additional analytical assessments compared to traditional comparability; Regeneron, for instance, performed 12 different mass spectrometry exercises to establish comparability for its antibody cocktail.

2.4 | Partnerships

To paraphrase Julie Gerberding of MSD, companies "can't do it alone." Strong and strategic partnerships with both health authorities and external suppliers enabled success from development to supply and all the way to the patients.

Pursuing novel solutions to speed up the manufacturing process required regular and transparent communications with health authorities, guaranteeing that the innovations would be acceptable at time of market application (or EUA). In his presentation, Peter Marks of the FDA highlighted how partnerships between health authorities and drug manufacturers proceeded in two directions: the FDA welcomed ongoing conversations with pharmaceutical companies for COVID-19-related therapeutics/vaccines, and also issued guidance to help companies navigate the unconventional landscape of the pandemic. Marks discussed the 2020 guidance documents "Development and Licensure of Vaccines to Prevent COVID-19"[12] and "Emergency Use Authorization for Vaccines to Prevent COVID-19",[13] which are just two of the FDA documents released in 2020 to provide clear guidance on the health authority's expectations for COVID-19 products. Receiving clarifying instruction and advice from the health authority supports the race for development speed since the biopharmaceutical companies can act in a targeted and assured manner. Meanwhile, the feedback loop that arises with regular back-and-forth conversation benefits both the companies and the regulatory agency, promoting a mindset of speed, flexibility, and continuous improvement, as well as bringing to the surface new areas of thought and topics relevant to each party.

Many health authority conversations focused on the unique set of challenges surrounding raw-material supply during the pandemic. With COVID-19 affecting businesses and, therefore, exchange of goods worldwide, many supply chains suffered crushing delays. For instance, Natalie Christian of MSD talked about how her team realized early on from conversations with their vendors that materials such as vials and stoppers were going to be in short supply. MSD quickly engaged in conversations with the health authorities to discuss options around alternate suppliers so that the company could maintain their accelerated timeline. From his side, Peter Marks emphasized that the FDA is open to such conversations and is trying to be flexible in terms of raw material sourcing and qualification allowances, while staying within the bounds of the regulatory restrictions that are in place to protect the quality of the product for the patient. Panel discussions proposed that future conversations between biopharmaceutical companies and health authorities will likely center around the possibility of making certain raw materials (e.g., affinity resins, virus filters, depth filters) more interchangeable to avoid having to perform requalification each time a raw material or raw-material vendor is substituted.

Beyond discussing imminent supply fluctuations with the regulatory agencies, companies relied heavily on transparent communication with their suppliers to grasp the materials landscape and adjust strategies as needed. The proactive investment in partnerships with critical suppliers became the key for success during supply-chain panic. In explaining her experience securing supply for the existing non-COVID-19 therapeutic, Trulicity©, Jessica Phillips of Eli Lilly emphasized how important it was that her team already had strong relationships with suppliers in place prior to the pandemic. These secure partnerships, combined with robust supply-chain strategies and ready access to accurate supply-chain data, enabled sure supply of Trulicity© despite pandemic obstacles. Similarly, Stephen Hardt of Allogene highlighted in his talk how quickly the company acted to engage with existing partners, pivoting to alternative suppliers as needed to ensure uninterrupted supply.

3 | SUSTAINING IMPROVEMENTS FOR THE FUTURE

As Tongtong Wang of Genentech said during her presentation, "The learning from COVID [from] last year and this year will continue to enhance the agility and speed of biologics for the future." Outside of a pandemic setting, the risk–benefit calculation of speed-enabling decisions will be weighed differently; yet there are numerous innovations and advancements that were born out of extraordinary circumstances that the biopharmaceutical industry will strive to apply as the new normal.

One of the biggest questions is whether the sheer speed of drug development achieved during the pandemic can realistically be sustained. Panel discussions among presenters seemed to reach a consensus that no, the speed could not be maintained since the heroic efforts, arduous hours, unlimited budgets, and governmental support necessitated by a pandemic are not realistic during normal times. However, the industry cannot and will not settle for pre-pandemic timelines. As Brian Kelley of Vir Biotechnology put it, "I am a little bit addicted to the speed." While this desire for speed is shared among industry members, the panelists agreed that a balance between pandemic heroics and realistic expectations is necessary. Not only must companies consider the amount of work they can ask of their employees within a certain amount of time, but also they must decide what risks (e.g., product-quality risks) are worth the faster timeline. A post-conference survey from AccBio indicated that most attendees believed CMC timelines of 10 to 12 months from sequence to IND are realistic for a mAb, and 2 to 4 years from FIH to CMC launch readiness (with slightly longer predictions for non-mAb therapeutics).

Any opportunities for speed require the infrastructure and mindset to support them. The high cost of many of the efforts companies employed during the pandemic would likely be difficult to maintain across a portfolio, especially in the absence of clearly aligned internal and external priorities. Yet many presenters emphasized the importance of other speed enablers (e.g., partnerships, platform

processes, standardization) that were in place before the pandemic struck. A proactive investment in people, practices, and partnerships creates the stable foundation that allows companies to be prepared to address unknown circumstances that may arise in the future. More than just money and time, mindset and culture are critical pieces of this investment. Several speakers at AccBio delved beyond examples of monetary investments in technology or resources to touch on their companies' efforts to change the way employees think about their processes and make decisions. For instance, Jessica Phillips highlighted Eli Lilly's mindset to build simplification into the process from the beginning, noting that her team scrutinized elements like single-sourced raw materials to determine whether they could be substituted with more flexible options or eliminated completely. Tongtong Wang of Genentech described how the company underwent an organizational change to bring decision making closer to the teams. Empowering teams to make decisions, while making leadership available at every stage to help inform those decisions, can enable the experts to pursue innovations and develop timelines to follow the speed the science allows. Such shifts in a company's culture can also encourage employees to examine their current processes for improvement opportunities and question whether the right risks are being taken in the right places.

4 | CONCLUSION

Bringing together leaders from across the biopharmaceutical industry provided a forum to learn from each other and share best practices and ideas for the future. The pandemic achievements and knowledge shared at AccBio 2021 can be used as stimuli for companies to examine past or current processes to determine areas for improvement. Therein lies an opportunity for companies to proactively identify potential enablers for speed and develop the infrastructure to facilitate the kind of progress inspired by the COVID-19 pandemic.

The endeavor for speed in drug development will continue into the future and companies will continuously seek to improve how to achieve it. The camaraderie and competition among biopharmaceutical companies, fortified during cross-industry meetings like AccBio, propel the science forward. As Michael Ku of Pfizer concluded in his talk, "We need to have the courage to advance not only best practices but to co-create the next practices for our industry and deliver hope to patients and their families with velocity." It is not just a matter of improving and quickening the process from molecule discovery to launch, but ensuring supply resilience and maintenance of quality end to end to ensure life-saving medicines are made available to everyone who needs them.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

Aine McGovern: Conceptualization (lead); writing – original draft (lead); writing – review and editing (equal). **Cleo Salisbury:** Conceptualization (supporting); writing – review and editing (equal). **Gregg Nyberg:** Conceptualization (supporting); writing – review and editing (equal).

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