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BioManufacturing Resilience:

Secure Supply Chains for Biologics

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BIOMANUFACTURING RESILIENCE: SECURE SUPPLY CHAINS FOR BIOLOGICS

There is widespread agreement among the global health community that long-term investments in resilient biomanufacturing capacity and supply chains will be needed to ensure the reliable delivery of health technologies such as vaccines, even during crisis conditions.[1] This paper contributes to discussions about how best to achieve this outcome, drawing on the experience of Merck Life Science[2] during the global pandemic response and looking forward to how governments and the private sector can most effectively work together to deliver healthcare post-pandemic. The analysis focuses on biologics, that is, vaccines, monoclonal antibodies, certain therapeutics, and new modalities manufactured by biotechnology companies and institutes. It complements the 2021 Merck Life Science publication Making Biologics.[3]

During the COVID-19 pandemic, a sudden surge in demand for equipment and ingredients to make biologics, alongside counterproductive policies in some cases, overwhelmed biopharmaceutical supply chains. Once vaccines were developed and financing was available for their manufacture, companies found themselves in a tight spot, facing high demand yet unable to rapidly ramp up production for various reasons that included timelines to build additional manufacturing facilities, difficulty increasing staffing and training during a global crisis, and constraints on supplies of raw materials.

The lessons learned during the pandemic are now being applied by companies and other stakeholders to reinforce biopharmaceutical value chains, extend manufacturing capacity across regions, improve health regulatory systems, and create the right conditions for ongoing biopharmaceutical innovation and technology diffusion. These actions aim to create sustainable development and delivery of products like vaccines, therapeutics, and diagnostics even during crises, and their effectiveness depends on ongoing investments to provide universal access to healthcare in all countries.

The lessons learned during the pandemic are now being applied by companies and other stakeholders to reinforce biopharmaceutical value chains.

Pandemic preparedness is but one motivation for these efforts. Focusing on resilience is an imperative for global health community to successfully respond to the growing demand for and production of biologics over time, which increases demand all along the biopharmaceutical value chain. At the same time, we will need to address geopolitical developments, market volatility, uncertainty, and the evolution of manufacturing, all of which will likely place further pressure on supply chains in the coming years. The need for crisis preparedness and response adds further complexity to this landscape.

1 The importance of ensuring improved and continued availability of vaccines, therapeutics and diagnostics has been endorsed by the G20 leaders, who identified lessons to be learned from the pandemic, including making sure that there are resilient supply chains and robust manufacturing policies and capacities. (G20, 2021).

2 Merck Life Science is a biopharmaceutical manufacturing company providing state-of-the-art technology and services that support discovery of cutting-edge and life-saving products, process, and research. Merck Life Science, known as Millipore Sigma in the United States, also supports companies with contract development and manufacturing, in addition to delivering products and services for mRNA development, vaccine development and manufacturing, and CRISPR-based gene editing. (We Are Merck, 2022).

3 *Making Biologics: Strategies and Policies for Enhancing Capacity* (2022) provides an overview of the biologics sector and describes ways that countries in all regions have built biomanufacturing capacity.

Below, insights from Merck Life Science's experience with biomanufacturing are presented in the hopes they are useful for policymakers as they build systems for reliable access to quality, affordable biologics for patients everywhere. Promising strategies for companies and governments are presented at the end of the paper.

BIOLOGICS AND GLOBAL HEALTHCARE

Biologics are increasingly central to healthcare delivery, as incomes rise and populations age. They are also more likely to be prescribed as health systems improve and the diagnosis and incidences of noncommunicable diseases (NCDs) rise. The global human biopharmaceutical, or "biologics", market accounted for nearly USD 294 billion in 2021 with estimated 9.24 per cent growth between 2022-2027.[4] Biosimilars, which are near copies of biologics, are experiencing similarly explosive growth, particularly since they are relatively cheaper than originator products and thus may be more cost effective. The global market for biosimilars is expected to grow from USD 13 billion to USD 60.8 billion from 2021 to 2027,[5] with emerging countries, notably India and China, accounting for an increasing percentage of manufacturing.[6]

What are Biologics?

Biologics are large molecules produced in living organisms or extracted from biological materials; this category of products encompasses vaccines, gene therapies, monoclonal antibodies, and certain diagnostics. They differ from small molecules, which are chemically synthesized. They are particularly challenging to make since they derive from living organisms, and even minor changes to the manufacturing process can alter the final product. For this reason, some have observed that "the process is the product" in relation to these products.

Manufacturing biologics – whether originator products or biosimilars – requires a high level of expertise. These products are subject to the most stringent regulatory and quality standards, in part because they are typically administered by injection. The manufacture of biologics requires several steps, and many producers enter these global value chains by completing the final stages, such as packaging and distribution, or fill and finish, which is a highly technical endeavor. With the support of international technology transfer partners, many of these new entrants gain skills and expertise that enable them to move up the value chain to complete higher-value activities, in a process known as "backwards integration" (Figure 1). Working side-by-side, the partners exchange know-how and build capacity over time.

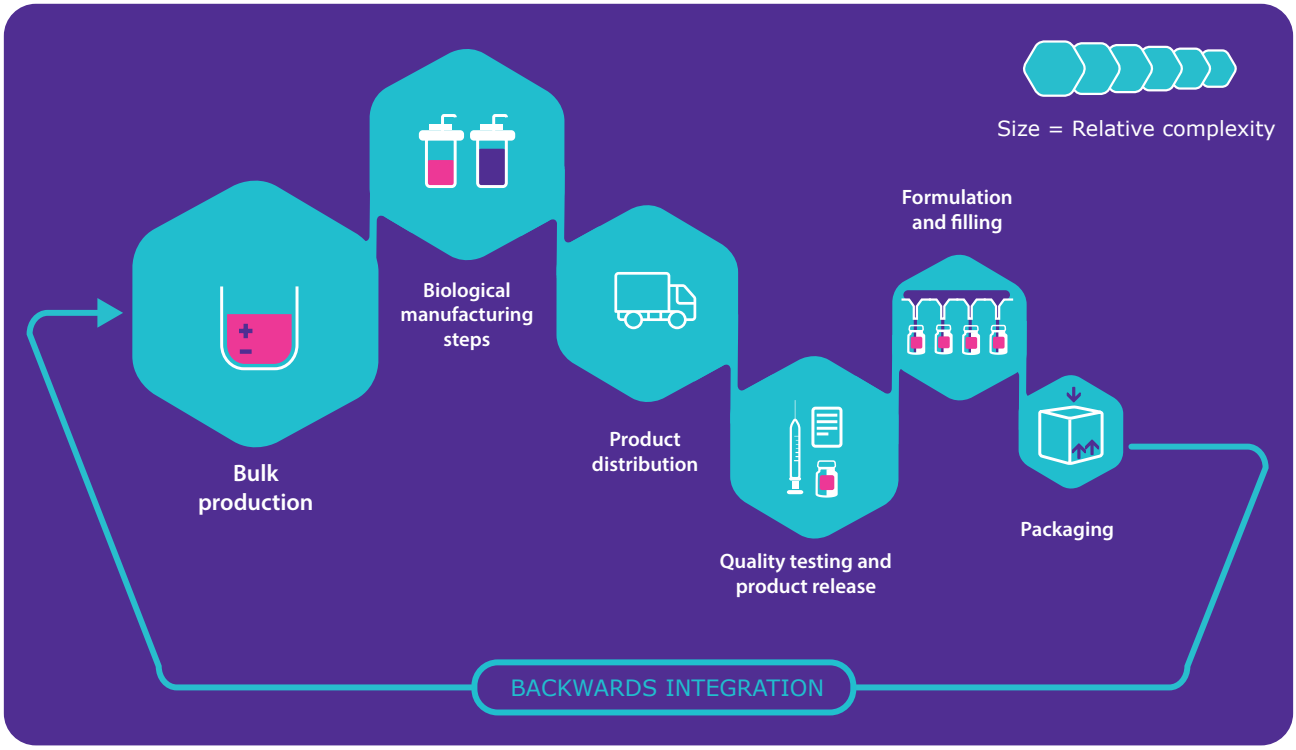
The experience of Biovac, a public-private vaccine developer and manufacturer that was founded in 2003 in South Africa, gives a sense of how organizations move along this pathway. In 2021, Pfizer announced that Biovac would become a partner for manufacturing the Pfizer-BioNTech mRNA vaccine for distribution within the African Union. Biovac had already worked with Pfizer and other international tech transfer partners, such as Sanofi Pasteur, for many years. This enabled the organization to improve its technical and scientific capacity. Biovac's various collaborations included producing innovative, complex vaccines such as Pfizer's polyvalent pneumococcal vaccine, Prevenar 13. Continuing its progression via backwards integration towards the

4 (Research and Markets, 2022b).

5 (Research and Markets, 2022a).

6 See *Making Biologics*, 2022.

Figure 1. Backwards Integration



highest value activities in manufacturing, Biovac recently announced a tech transfer and licensing deal with the non-profit International Vaccine Institute, headquartered in South Korea, to manufacture an oral cholera vaccine. This project will enable the Biovac Institute to gain capacity to manufacture drug substance, a step in the vaccine manufacturing value chain that does not yet exist in Africa.[7]

what is clear is that collaboration, which often involves knowledge and technology sharing, is necessary for developing health technologies, especially in an emergency.

LESSONS FROM THE COVID-19 PANDEMIC

A clear takeaway from the COVID-19 pandemic is that no single company, research institute, global health organization, or other actor can do everything on its own. The pandemic stimulated a rapid innovation response from the biopharmaceutical industry. Alongside efforts from the private sector, government support in all regions was instrumental in supporting R&D for novel technologies, clinical trials, assessment of manufacturing infrastructure, derisking investments to upgrade manufacturing capacity, and other activities that were needed for the pandemic response.

Facilitating Collaboration

What is clear is that collaboration, which often involves knowledge and technology sharing, is necessary for developing health technologies, especially in an emergency. By summer 2022, there were 381 recorded partnerships in the COVID-19 vaccine space, 88 per cent of which involved technology transfer.[8]

7 (BioVac, 2022) and (Biovac, 2012).

8 (IFPMA, 2022b).

These collaborations were necessary to develop the vaccines and, especially, to establish geographically distributed manufacturing and distribution networks to connect biopharmaceutical value chains.

Through partnerships, essential equipment like filters and single-use systems reached vaccine developers and manufacturers. Also, manufacturing and distribution of vaccines was fast-tracked thanks to services like process optimization. To provide one example, Merck Life Science had been working since 2018 with the Jenner Institute at Oxford University to develop a robust, scalable manufacturing process for the adenovirus vaccine.[9] This work intensified when the pandemic started, and the years of partnership, trial and error, and practice resulted in rapid scale-up in response to the pandemic.[10]

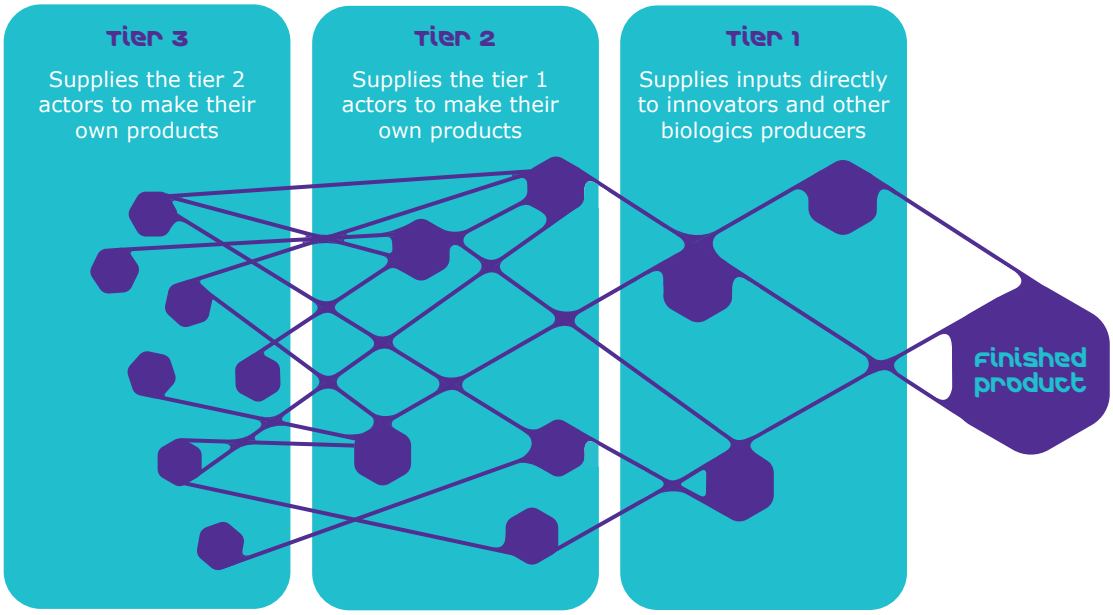
Other forms of collaboration also accelerated the pandemic response; for instance, innovators worked closely with regulatory agencies to expedite review without sacrificing patient safety or quality. Global health experts have pointed to an unprecedented level of cooperation between regulatory authorities, on the one hand, and clinical researchers, academics, large and small pharma companies, non-profit institutions, and other government agencies. They recall constant dialogue and expedited turnaround of clarification and data requests, on both sides.[11]

Looking to the future, engagement among government officials, industry, research institutes and universities, NGOs, and others will be needed to create resilient systems for developing and delivering biologics and other health technologies.

Considering the Full Value Chain

The importance of considering the entire value chain is another key lesson from the pandemic. Biopharmaceutical value chains today are globally distributed and can be viewed in tiers, with tier 1 supplying inputs directly to biopharmaceutical innovators and their partners making the finished products, tier 2 supplying the tier 1 actors to make their own products and equipment, and so on (Figure 2).

Figure 2. Tiers of Biopharmaceutical Value Chains



9 (Pharmaceutical Technology, 2018).

10 (Clinical BioManufacturing Facility, n.d.).

11 (Economist Impact, 2022).

Extending manufacturing capacity requires investments in and consideration of all parts of the value chain; this is because, even if end-product manufacturing capacity is available, insufficient availability of inputs may create bottlenecks.

During the pandemic, as biopharmaceutical innovators' research programs showed promise, they adopted new ways of approaching regulatory approval and manufacturing at scale, moving both efforts forward at the same time. They sought inputs and equipment – but, without additional financial support, and due to the time it takes to upgrade or establish facilities, upstream suppliers had limited ability to quickly expand production in response to the surge in demand.

The pandemic-induced spike in demand came against a backdrop of growing demand for biologics worldwide, which was already straining supply chains, and it raised important ethical questions as to whom should receive available supplies. An unsurprising reflex among many customers was to order more raw materials and equipment than they needed, creating further uncertainty and strain. Alternative suppliers were not readily available because they had not been identified and qualified before the pandemic. It became clear that maintaining sustainable availability of biologics will require resilience at all tiers of the biopharmaceutical value chain, and thus action beyond the end-product level.

Shifting Away from a National Outlook

During the pandemic, many governments took a "my nation first" approach, underlining how difficult a truly global response is to achieve in the real economy. International development organizations lamented that the value chain disruptions that emerged as a result of the pandemic were compounded by national trade restrictions implemented by over 80 countries.[12]

> **in the current global biotechnology innovation ecosystem, a successful strategy for resilience must include openness to the flow of goods, technology, and components across borders.**

Countries with a large role in the production of biologics, or of components vital to their value chain, restricted their exports, compounding an already disparate distribution of equipment, consumables, and raw materials.

Once one country institutes export restrictions, others may be tempted to act similarly to ensure needed products stay at home. This increases the risk of a policy arms race. The result is an impossible situation for companies focused on manufacturing products and getting them to where they are needed, since value chains are geographically distributed. For some, the answer is to onshore everything in a biologics value chain – but this is not possible given the geographic diversity of value chains and the continued evolution of technology. To illustrate the latter, no pandemic preparation program pre-COVID would have included mRNA technologies and the related inputs, such as nanolipids, which proved critical to the global COVID response.

A national approach to ensuring the availability of biologics will necessarily remain too limited. Particularly in the event of a global crisis we should recognize and expect the political reality that governments must and will look after the interests of their own citizens first. At the same time, such an

12 (Peters & Prabhakar, 2021).

approach does not necessarily preclude successful collaboration and cross-border supply chains. To the contrary, in the current global biotechnology innovation ecosystem, a successful pandemic preparedness strategy must include openness to the flow of goods, technology, and components across borders. Geographic diversity is a strategy that companies such as Merck are pursuing today, as a risk mitigation approach and as a way to respond more effectively to regional needs.

During the pandemic, government mandated orders requiring suppliers to prioritize domestic customers, under certain circumstances, affected suppliers across tiers of the value chain. This type of policy measure in one country can disrupt supply for everyone, even before other governments follow suit. Such policies reflect policymakers' instincts to take care of their own populations first. They may enable a country to speed up domestic vaccine, testing, and personal protective equipment production but, undeniably, they cause disruption to the global supply chain.

The reality is that, first, goods used in biopharmaceutical production, such as single-use assemblies, are often customized to a specific product or medicine, and, second, production in advanced manufacturing facilities is carefully planned to maximize output, especially during a crisis. When government mandated orders enter the picture, key components for healthcare delivery may remain unavailable when needed for medical care delivery elsewhere. These and other coercive measures are blunt tools that create chaos throughout supply chains, with inadvertent knock-on impacts for patients. They potentially disrupt the manufacture of life-saving therapeutics that are unrelated to the crisis response. Many industry experts cite these policies as having been highly disruptive to the global pandemic response.

In the future, regional approaches to managing value chains could replace national approaches. A hub model, with demand and manufacturing capacity lined up to serve the needs of a particular region, and operating within an ecosystem with the right incentives, enabling policies, and regulatory framework, seems promising. Regionalization can help to offset risks associated with national policy responses and bottlenecks arising in parts of the supply value chain, which may prevent manufacturers from reaching full capacity during times of exceptional need.[13] Regionalization also ensures that capabilities are better distributed should production be disrupted in one area due to a pandemic or geopolitical crises such as wars, natural disasters, or political instability.

Promoting Resilience in Value Chains

Resilience is top of mind for policymakers and business leaders alike, in part as a response to COVID-19 and its impact on biopharmaceutical value chains. For businesses, "resilience" refers to the ability to adapt, resist, and recover from disruptions and includes ensuring business continuity and supply chain management (Figure 3).

Manufacturers are developing plans for business continuity in all circumstances; business continuity provides the foundation for "robustness", that is, the ability to continue activities during a crisis, and "resilience", which is the ability to recover and restart activities once a crisis ends. There are many approaches to building more resilient value chains, including inventory management and

13 A number of global health organizations have endorsed enhancing regional manufacturing capacity, including CEPI (CEPI, 2022), the ACT-A Facilitation Council Vaccine Manufacturing Working Group, which was set up and politically mandated by the G20, (WHO, 2021), the Pan American Health Organization (PAHO, 2022), and the EU and WHO based on their "common ambition to boost local production capacity". (European Commission, 2022).

Figure 3. Ensuring Consistent Availablity of Biologics

stocking, effectively evaluating and managing risk, introducing redundant production and dual sourcing, applying digital tools, and regionalizing value chain operations.

Finally, it's crucial to recognize the costs associated with maintaining surge capacity, and the impracticality of this approach. It costs substantial resources to build and maintain manufacturing facilities; if the facility sits idle, there is no business case for investing in a facility. Also, machinery, processes, and people must remain current in order to assure the production of quality, safe biologics. A biomanufacturing site cannot be simply turned on or off. It requires numerous inputs including trained staff, clear procedures and processes, quality control labs and testing facilities, logistics links, supplies of raw materials, and up-to-date regulatory approvals, licenses, and audits. The cost of manufacturing extends well beyond building the facility, and typically the building itself will represent a fraction of the total cost of operations.[14] (Figure 4) Because of this reality, there is not generally idle capacity available, nor would creating and maintaining such capacity be sustainable or logical.

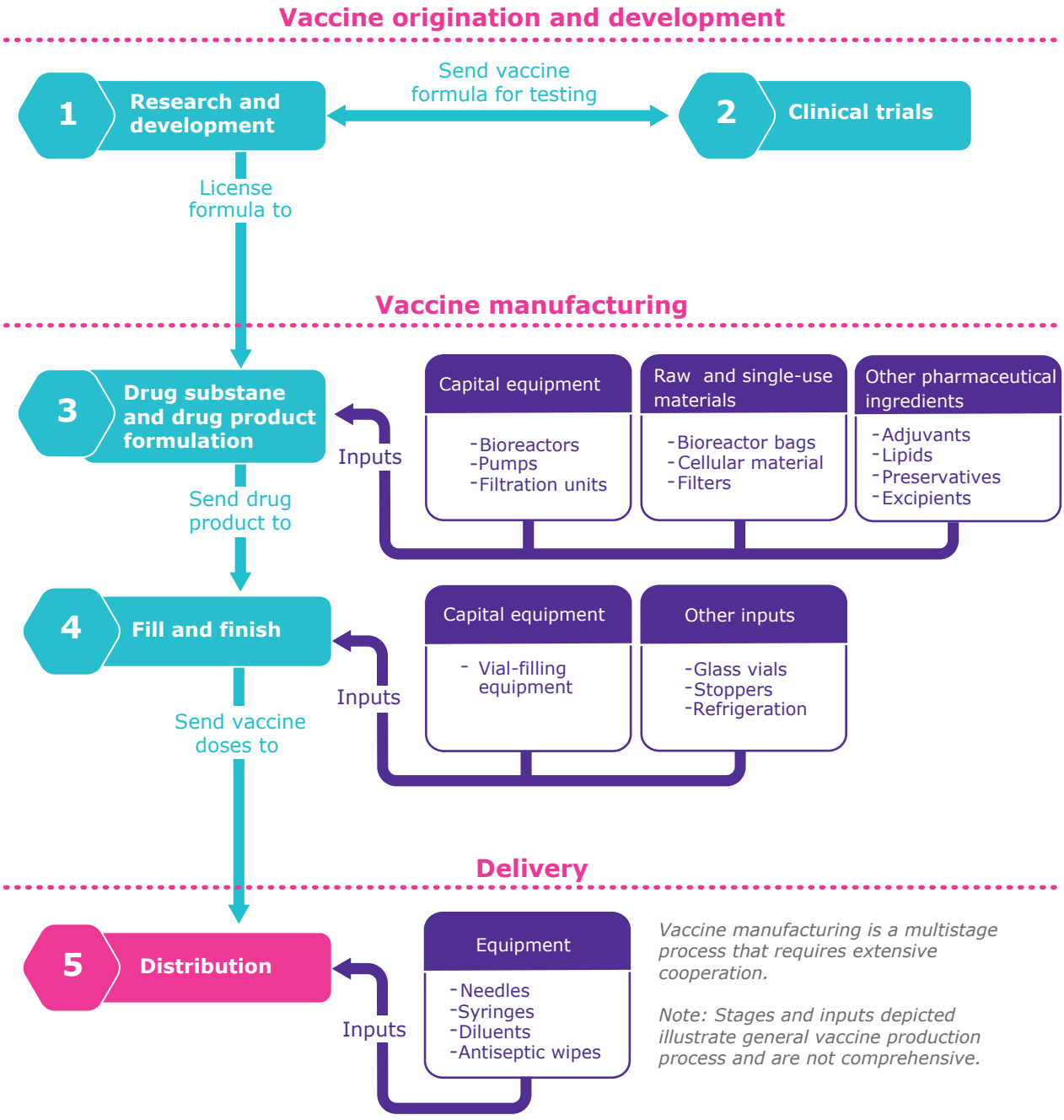
Companies redirected resources slated for product launches to address the increased capacity needed during the pandemic. Delaying launches that would normally have required manufacturing capacity, whether in-house or via partners, freed up a certain degree of capacity for producing the goods needed during the crisis. Flexibility and the ability to ramp up rapidly proved the most important factors. The global push for COVID vaccines resulted in 11 billion doses produced in 2021, a remarkable achievement – but one achieved at significant cost.

This extra capacity became available primarily at the customer-facing level of the value chain, that is, tier 1. It was rapidly integrated into the newly established global manufacturing networks for COVID-19 vaccines. However, it was impossible to quickly liberate additional capacity at the upstream tiers, 2, 3, and so on, leading to bottlenecks compounded by the scarcity of crucial supplies, surging demand, national policies, and the regulatory environment.

Industry experts and government officials will need to discuss what is and is not possible for manufacturers and their

14 (Snyder et al., 2020).

Figure 4. Stages of Biologics Manufacturing: Vaccines



Source: Based on Bown and Bollyky (2021).

partners at different levels of the value chain, with and without government financial support. Developing vibrant regional biomanufacturing ecosystems, with government incentives for additional capacity potential that can be rapidly activated and support for upstream manufacturers of key materials and components, offers the most feasible route to greater resilience.

RESILIENCE: BUSINESS INSIGHTS

New directions are taking shape across the biopharma industry, as companies take action to reinforce and reorganize value chains to improve resilience and robustness.[15] This section provides insights into some of the approaches being adopted – and their implications for policymakers. It's important to underline that certain approaches can improve resilience but are not cost effective. In such cases, there may be no business case for taking action, and government support and incentives may be needed to shift the calculus.

Developing vibrant regional biomanufacturing ecosystems, with government incentives for additional capacity potential that can be rapidly activated and support for upstream manufacturers of key materials and components, offers the most feasible route to greater resilience.

Flexibility and Innovation

Product and process innovation are central to ensuring the availability of biologics. Modular facilities that can switch between product lines in response to changes in the marketplace mark an important, cost-saving departure from the expensive brick-and-mortar facilities of the past. Turnkey facilities are designed in advance to make certain products, or modalities, and can be set up and operational in as little as one year. Another advantage is these facilities can be moved relatively easily to where production is needed. The technologies making it less costly and faster to set up facilities, which are themselves more nimble, has contributed to democratizing biomanufacturing. That is, today biologics manufacturing can take place in virtually any location provided there is basic infrastructure.

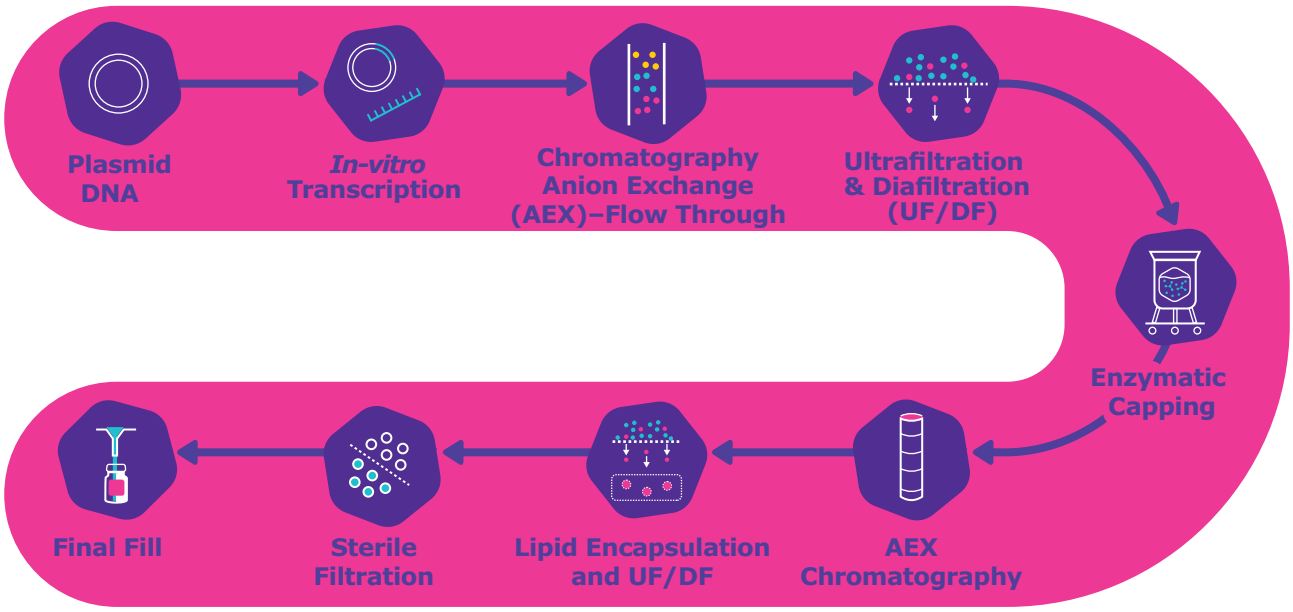
The application of new technologies and approaches – developed by companies such as Merck Life Science – continues to drive major improvements in biomanufacturing around the world. Bio-processing 4.0, which is the combination of continuous processing solutions and software, automation, and analytics, operates on the cutting edge of biomanufacturing. Innovations like single-use bioreactors also enhance efficiency, along with compliance with Good Manufacturing Practices. Novel testing solutions are being applied to confirm safety and quality at all stages of manufacturing, and to accelerate the delivery of new treatments to patients. And new offerings resulting from research programs that were advanced during the pandemic, such as lipid nanoparticles, have been crucial to the commercialization of promising platforms, such as the mRNA platform used for COVID vaccines (Figure 5).

Services and Training

Services supporting product and process innovation are a vital part of securing the availability of biologics. Services are critical for the design, building, maintenance, and operation of manufacturing facilities and equipment.

15 Resilience is the "company's capacity to absorb stress, recover critical functionality, and thrive in altered circumstances". (Reeves & Whitaker, 2020). Business continuity helps to "minimize the impact on your business regardless of the incident and helps you return to normal operations as soon as possible". (Yale University, 2022). Robustness is "the ability of an organization to adapt, develop, and evolve to navigate uncertainty while preserving its functioning, competitive stance, and long-term growth". (Roland Berger, 2022). Redundancy is when an organization "buffers systems against unexpected shocks…by duplicating elements (such as by having multiple factories that produce the same product) or by having different elements that achieve the same end (functional redundancy)". (Reeves & Whitaker, 2020).

Figure 5. Making mRNA Based Vaccines Using Single-use Technology



Source: Based on MilliporeSigma Solutions Vaccine Platforms Handbook 2022

Knowledge and technology from multinational tech transfer partners, shared while working side-by-side over many years, is integral to improving local capacities.[16] These partnerships require support from companies that deliver complementary services to get production up and running, while ensuring the right quality and timelines. These actors address the need for optimizing manufacturing processes for partners new to novel biologics, and develop programs needed to train personnel.

M-Lab™ Collaboration Centers

Improving biomanufacturing and R&D capacity requires investments in human capital. Multinational partners are stepping in to provide training and other services that build scientific expertise so local companies can provide biologics to more patients, more efficiently and with more confidence. For instance, Merck Life Science maintains a global network of 8 non-GMP facilities that are equipped with innovative technologies and staffed by scientific experts, to empower drug developers and manufacturers of all sizes to achieve manufacturing excellence and innovation. Through hands-on learning and virtual experiences, they can explore novel modalities or test drive advanced techniques across the entire biomanufacturing process, from upstream to downstream and through final fill, without disrupting their own operations. These M-LabTM Collaboration Centers are recognized as having made a substantial contribution to the development of scientific and technical talent in multiple countries, such as Singapore.

16 See *Making Biologics* for detailed process and case studies.

Evolving Supply Chain Management Approaches

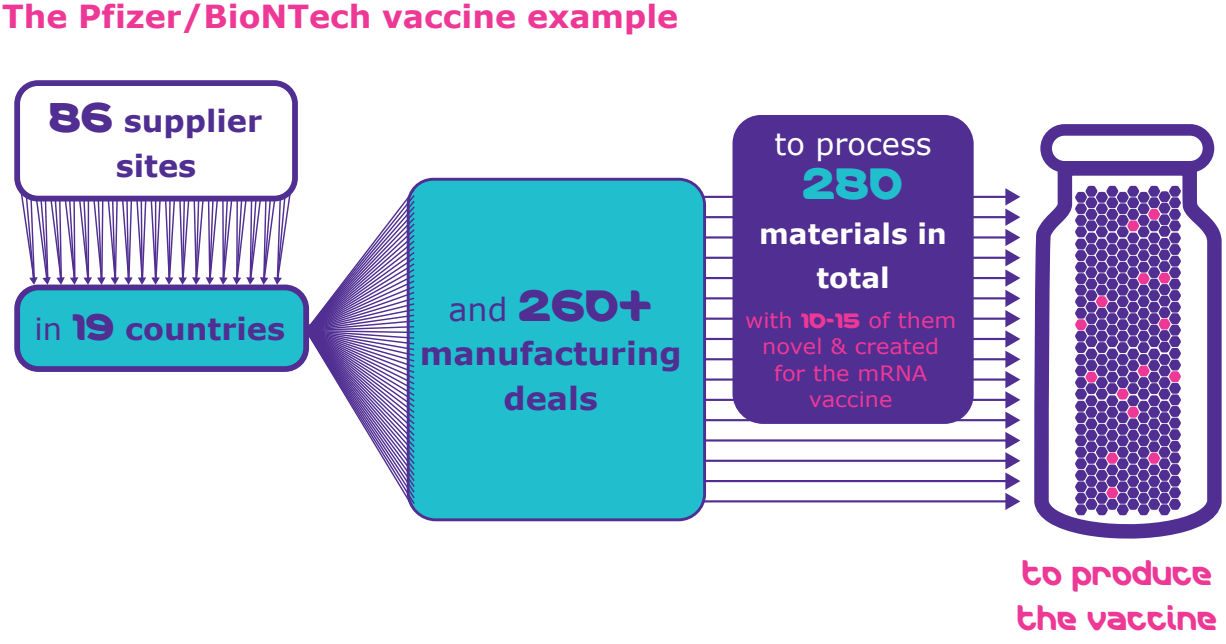
Companies in the life sciences sector rely on a mix of in-house and contracted capacity to make their products. Those that manufacture via Contract Manufacturing Organizations (CMOs) typically contract their services with months or more of lead time, so they can set up their own value chains, upgrade facilities, train people, purchase equipment, and participate in the technology transfer that will enable them to successfully make the relevant product. It is likely that companies will continue to rely on global networks of manufacturing partners for production.

During normal times, the question of manufacturing outsourcing – make versus buy – is top of mind for biopharmaceutical companies, and it becomes particularly relevant during a crisis. During the COVID-19 pandemic, innovators had to rely on global networks of CMOs. Without this added capacity, it would have been impossible for them to produce the volume of vaccines required (Figure 6).

A regional approach can give rise to new opportunities for countries to take part in global biopharmaceutical manufacturing.

CMOs have an inherently agile set-up, thanks to evolving manufacturing technology solutions and services. Networks for contract development and manufacturing, as well as testing, can be established more rapidly and at a lower cost than previously possible. This is due to advances in technology combined with new offerings from experienced service providers, who help companies to optimize, scale, and validate manufacturing processes for intermediate and finished biological products. Some service providers offer assistance spanning the entire value chain, helping customers move products from pre-clinical through commercial stages, and they can even set up entire manufacturing facilities for the customer.

Figure 6. Global Networks for Vaccine Manufacturing



Source: Authors with data from Brant and Schultz (2021).

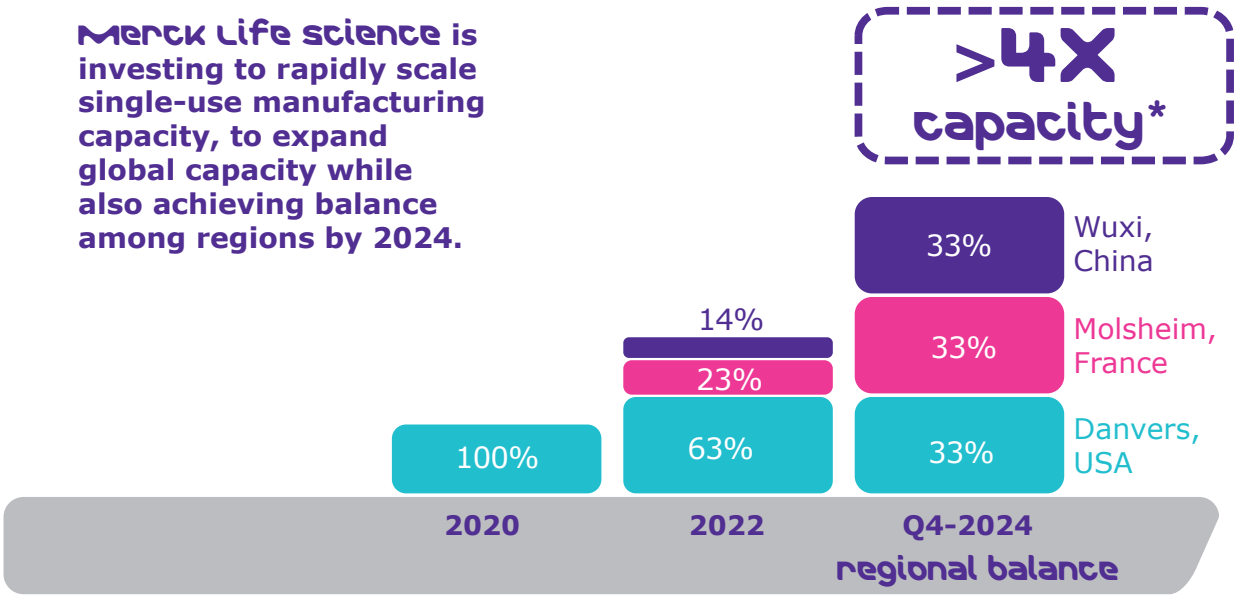
Companies are adopting new approaches to managing value chains, including reorganization to reflect more of a regional focus, which can help to hedge against risks such as localized crises or counterproductive policy actions by one government. This approach can help to manage risk in the event of a crisis, by offsetting the shortcomings associated with national or global responses (cited above). On the flip side, today, value chains are global so it will necessarily take time and effort to shift value chains to be more regionally focused (Figure 7).

A regional approach can give rise to new opportunities for countries to take part in global biopharmaceutical manufacturing. All regions have entities – whether research institutions, universities, or private companies – with knowledge and experience that, when combined with support from an international technology transfer partner, make it possible for them to participate in global biologics value chains. Focusing on matching regional supply and demand can enhance the industrial base and pool of skilled labor in emerging regions. It can create a basis for regional actors to respond to regional outbreaks and diseases that may not rise to the attention of global innovators. Over time, such actors can develop the capacity to conduct their own R&D to develop novel treatments, processes, and other tools to target regional health challenges. They can also gain valuable business, engineering, scientific, and manufacturing expertise.

Imposing restrictions on investments, talent, and other inputs shared across borders would be counterproductive. An appropriate enabling policy environment is crucial for success.

Regional collaborations remain at risk, however, due to spillover effects from escalating technology competition between countries in other industrial fields. Biomanufacturing is exclusively focused on the production of needed

Figure 7. Evolution of Manufacturing Capacity: Spotlight on Regionalization



*By 2025 when compared to 2020 Global Capacity

Source: Authors based on Merck's Mobius® Single-use Capacity Expansion Plans presentation

medicines and diagnostics, and so should be consciously shielded from measures designed to restrict cooperation. Government officials in many countries correctly view biotechnology as an important growth engine for their economies. Imposing restrictions on investments, talent, and other inputs shared across borders would have harmful effects, fragmenting a global biology innovation environment that proved critical to the pandemic response and global health. An appropriate enabling policy environment is crucial for success.

Digital Solutions

Because digital and forecasting tools will be critical to effective supply chain management in the future, companies are investing heavily in their development. Digital forecasting systems signal shifts in demand, with real-time systems being the most valuable.[17] They can enable companies to rationalize supply, especially during a crisis when customers may have the instinct to order more than they need, and suppliers may struggle to efficiently prioritize orders based on need, stock, and other criteria. These systems may include alerts about relevant world events and early warning systems so that risk management actions can be taken, for instance re-routing supplies from warehouses outside of the affected region.

Digital and forecasting tools require information sharing and transparency along the value chain, to the extent possible, taking into account business confidential information and the reality that a company may be a supplier of one product but a competitor or customer in relation to another product. Although information and data exchange is one important component of supporting demand management during normal times and crises, in practice, transparency along value chains is difficult to achieve.

New cloud-based systems for collecting, analyzing, and sharing data can significantly reduce product development time within companies and consortia. Giving companies secure, performant systems for sharing data across locations and functions can enhance R&D efficiency, as can the development of networks that enable multiple actors to exchange information in the context of a specific product, project, or health challenge. During the COVID pandemic, innovators relied on virtual platforms to share information, including trade secrets, as part of technology transfers with CMOs and other partners. The creation and management of data lakes offers substantial potential for accelerating product development and commercialization, particularly as the number of participants grows. Application of these tools holds promise for supply chain management as well.

Different Strategies for Resilience

Redundancy can contribute to business continuity by providing more than one supplier for each key component (dual sourcing), or more than one facility for making the same product. Introducing redundancy into value chains can be challenging, given there is generally no business case for having multiple facilities to produce, or maintain suppliers of, the same product. In cases where producers are satisfied with their mix of suppliers and other partners, they have little incentive to introduce duplication, as this is not cost-efficient.

17 Digital Supply Chain Management Systems are platforms that apply digital technologies throughout the entire supply chain, creating better feedback loops and end-to-end visibility. To provide an example of how these technologies improve efficiency in biopharma value chains, they can be used to monitor the temperature of vaccines, assess any disruptions to the supply chain and assess how long it may take to resolve them, and provide extra security. Use of these technology solutions can provide real-time data to help companies know exactly how many vaccines are needed, in addition to creating a single platform for government procurement, thus helping to streamline that process.

Stocking inventory is another way to build redundancy into value chains. Companies can stock finished products, and they can establish stocking agreements with suppliers, to ensure they have an adequate volume of inputs required even during a crisis. They can also be contracted by governments to operate public stocks.

There are limits to stockpiling. This is particularly true in relation to finished products, given that it's often impossible to know in advance what health technology will be successfully developed and commercialized. Product expiry must be managed, through rotation of products to ensure the entire stock remains ready for use. Depending on the product in question, this may also be true for stocking inputs. A notable exception is diagnostics, for which select inputs are usually required regardless of the pathogen; in this case, stocking can be strategic. At the same time, depending on the circumstances, stocking may be inefficient and government support may be required to make such action feasible.

Supplier risk mitigation, that is, qualifying multiple suppliers and facilities, requires time and resources. This is even more the case where regulatory approval must also be secured for the product or facility (in addition to the internal vetting and qualification process). When companies are satisfied with their existing mix of products, suppliers, and sites, they may see no rationale for investing to diversify. At the same time, in the event of a crisis, having alternative suppliers can support business continuity.

Government incentives, including financing and making regulatory approval for additional suppliers or facilities quicker or less expensive, can foster diversification.

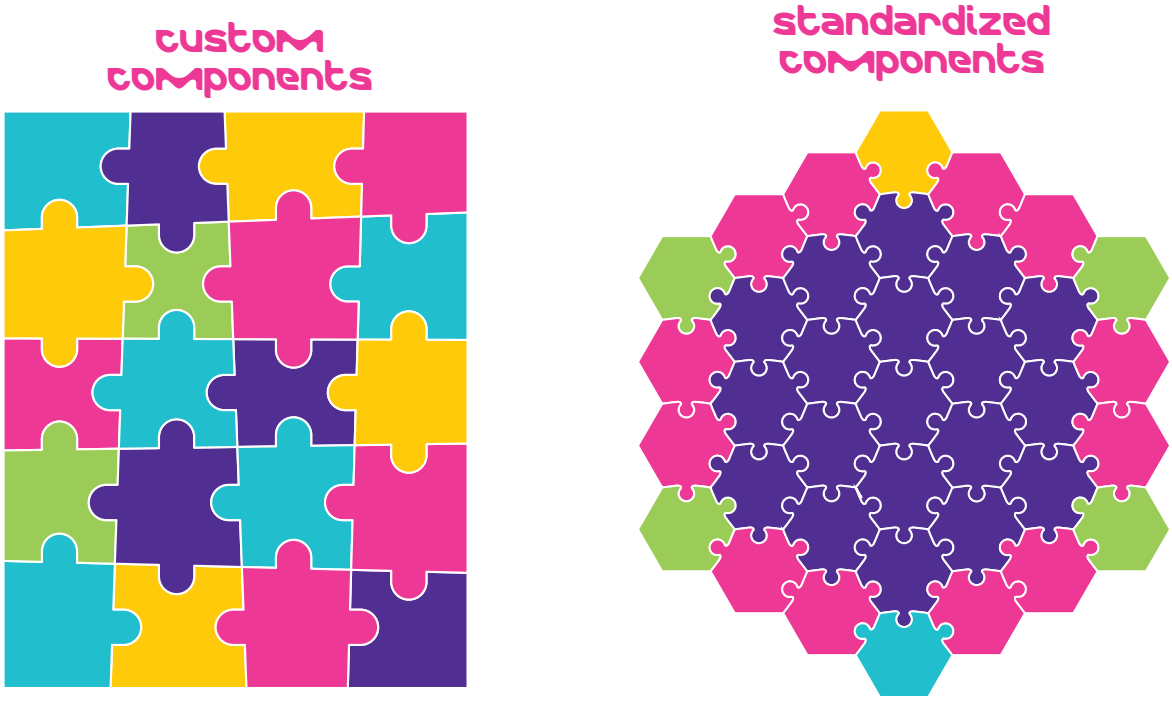
Increasing resilience in supply chains is not limited to redundancy. Companies can also more thoroughly assess risk

standardization is an innovative supply chain management strategy that can improve resilience. It is easier to stock standardized parts, simplifying the value chain.

across tiers of suppliers. The first step is supply chain assessment. Ideally the entire value chain should be mapped to identify risks, looking at the full range of products, processes, and services, including factors like transport. This requires collaboration along the value chain, which in turn depends on trust along with robust systems for the appropriate management of business confidential information. Companies can also develop scorecards for individual partners and suppliers, a process that helps to identify in advance their strengths and weaknesses. With this information in hand, companies can more readily plan for business continuity. Suppliers may be asked to develop risk mitigation plans.

Standardization is an innovative supply chain management strategy that can improve resilience (Figure 8). A single-use biomanufacturing system is made up of thousands of different components, many of which are custom designed for customers. Alongside customized parts, suppliers can provide standardized components for these systems. It is easier to stock standardized parts, simplifying the value chain. By way of example, to create its "Mobius® select" offering, Merck Life Science identified the 300 most frequently ordered components of the Mobius® single-use manufacturing system, offering these in a standardized format and stocking them to reduce lead time. Software tools were developed for the optimal management of stocks of the standardized components. Customers can still order custom parts, with longer lead time.

Figure 8. Standardization and Resilience



Maintaining the necessary manufacturing capacity is coming up frequently in policy discussions, with some officials and international organizations endorsing the maintenance of "idle" manufacturing capacity. In an ideal world, idle manufacturing capacity could be brought quickly online in the event of a health crisis.[18] In reality, as noted earlier in this paper, machinery, personnel, and processes must remain in use to ensure efficiency, quality, and safety. It's generally not possible to flip a switch and turn it on.

In some instances, businesses may decide to maintain some degree of extra capacity – for instance, for certain high-margin products – to hedge against risk. Factors such as margin and lead time for such products contribute to such decision making. Generally, however, maintaining idle capacity is not feasible for businesses. Governments can incentivize investments to maintain some surge capacity, for instance at existing facilities. It's crucial to remember that for surge capacity to exist in one part of the supply chain, it must also exist at the upstream tiers. For this reason, Merck Life Science works with companies to provide unified support along their entire value chains and drug development life cycle, from the laboratory through pre-clinical, testing, and regulatory approval across markets.

Since there is no rationale for locating biomanufacturing infrastructure in every country, a regional approach to extending capacity will likely be the preferred approach, both from a business and public policy perspective. Additional capacity can be developed at

18 So that extra manufacturing capacity doesn't sit idle between emergencies, some are proposing that such facilities be dedicated to manufacturing vaccines for routine vaccination programs or other biologics. This makes sense, and the business case for these proposals should be explored. The G7, as part of the Pandemic Preparedness Partnership, have suggested that manufacturing facilities be "kept warm" by producing for global vaccination programs, so that they are available to use in the case of another pandemic. (Cabinet Office et al., 2021).

Applying Lessons from the Pandemic: Extending Manufacturing Capacity

At the start of the COVID-19 pandemic, Merck Life Science already had a plan in place to expand its global manufacturing capacity to improve regional proximity to customers – however, it became clear that pre-pandemic estimations would not adequately meet the increased demand for products. The company acted quickly to expand capacity.

Existing capacity: The company managed surge demand by finding ways to optimize capacity. It invested in creating a "supply chain control tower" and a data insights platform to provide an in-depth view of supply plans, raw materials, and delivery dates. This helped to enhance the predictability and transparency of unforecasted demand. Merck Life Science reviewed processes and operations at its major manufacturing sites identifying opportunities to unlock additional output and adjust systems for efficiency gains. They then invested in new machinery to support production and optimization of all technology and processes and streamlined testing and production requirements.

New capacity: Merck Life Science refocused its investment program goals, developing a roadmap that applied lessons learned from the pandemic toward long term supply goals. They accelerated the completion of ongoing expansion projects bringing forward timelines and increasing the scope of planned new investments. The company also quickly brought new capacity expansion projects online in Europe (Ireland and France). These actions strengthened the redundancy and supply security.

Source: (MilliporeSigma, 2022)

an appropriate pace and scale across regions, bringing production closer to customers and patients. Capacity expansion must be rooted in a clear business case along with, ideally, government support and incentives. Based on experience, this process takes several years, substantial investments, and partnerships to succeed.

Forced localization policies are unlikely to accelerate this process or to deliver the intended results, that is, a stronger industrial base and more competitive position for local companies. Compulsory technology transfer approaches make it risky for innovators to share openly with local partners, which is the foundation for their successful integration into global value chains. Faced with government efforts to force investment and technology transfer, innovators are likely to avoid sharing their highest value technology and know-how, or to invest elsewhere. They may move existing operations to another location, which is possible to do today with modular facilities. When a government does not ensure intellectual property protection, particularly for trade secrets, this likewise makes it less attractive to invest and partner in that country.

Despite the trend of regionalizing value chains, some activities may nonetheless be carried out with a global focus. One example is global quality systems. Quality management systems and operational procedures can be standardized across locations to ensure consistent product performance regardless of where products are manufactured. To this end, along with Good Manufacturing Practices (GMP) compliance for facilities, companies may rely on global standards such as ISO certifications.

Despite the trend of regionalizing value chains, activities like quality management may be carried out with a global focus.

Korea's Journey to Become a Global Biomanufacturing Hub

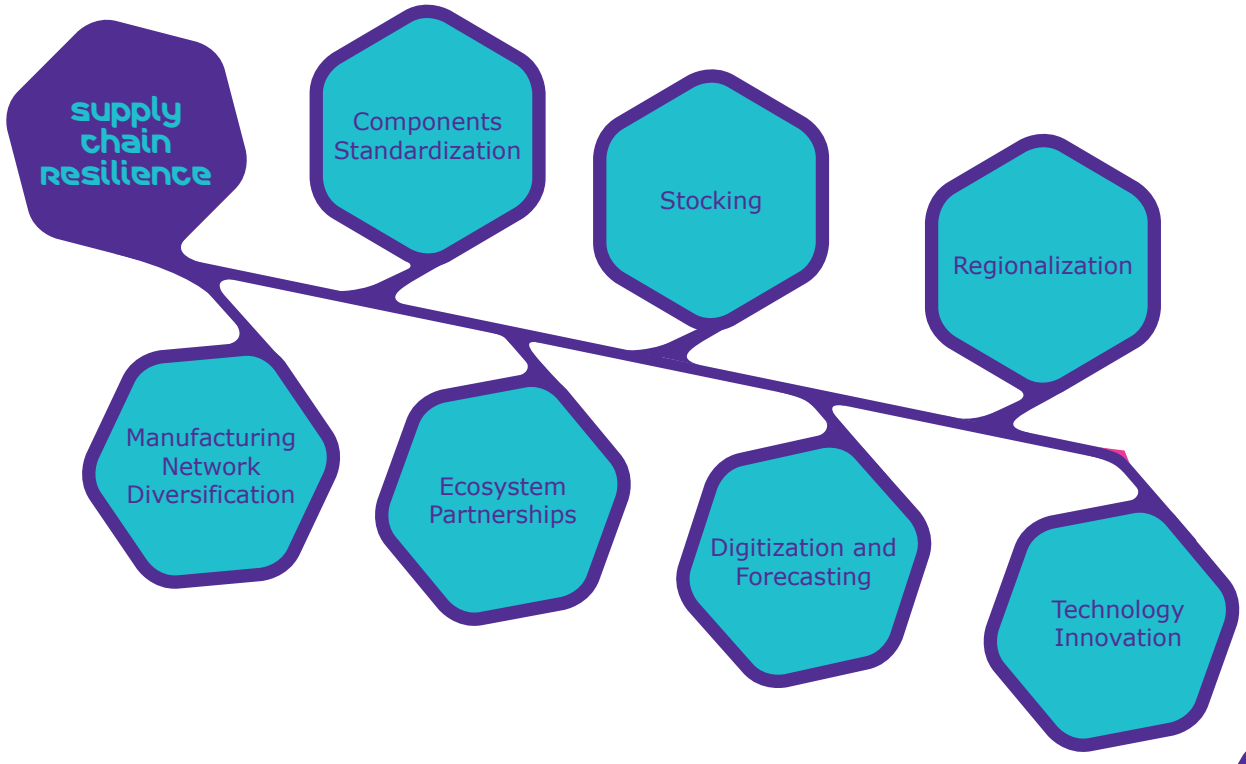
The Republic of Korea is a prominent success story for developing a robust biomanufacturing industry and regional hub. The government began focusing on the industry in the 1990s, building an important foundation for success through actions such as increased R&D funding and the development of university programs to nurture life sciences talent. By the 2010s, these strategies, combined with the country's openness to trade, its strong intellectual property rights protection, and the global network of relationships developed by leading Korean multinationals, provided the right elements for Korea to seize the opportunity to become a biomanufacturing center. Led by Samsung Biologics, the country established itself as a major player, as other companies such as Celltrion followed suit. Today, the country boasts the largest bioreactor capacity in the world.

Korean companies continue to target opportunities in the booming global CDMO market, estimated at 177 billion USD in 2020. And they are actively pursuing the rapidly expanding biosimilars market, which is expected to reach 143 billion USD by 2031. Alongside the domestic Korean pharmaceutical market, with a value of about 18.6 billion USD, Korean companies are targeting a much larger global market and, most importantly, have developed competitive strengths to succeed in this endeavor.

As other competitors, especially in China and India, target the same opportunities, Korean industry leaders are aware of the need to continuously invest and innovate. The government is adopting policies such as the Global Vaccine Hub strategy to help transition Korea from a biomanufacturing hub to an innovation hub for new therapies. Ongoing collaboration between global technology partners and domestic players, and support from global health organizations such as the World Health Organization and the Coalition for Epidemic Preparedness Initiative, has reinforced Korea's leadership in biomanufacturing.

Sources: (Expert Market Research, 2022) (Prathmesh & Onkar, 2022) (Statista Research Department, 2022)

Figure 9. Business Strategies for Resilience



GOVERNMENT LEADERSHIP FOR RESILIENCE

Companies can contribute to building resilient health systems through innovation, the delivery of valuable products and services, technology transfer, and capacity building. Ultimately, though, they are limited in what they can do. For instance, one company does not have a holistic view of the biomanufacturing ecosystem. That company may not even know precisely what percentage of capacity its activities represent for a particular nation or product, which is vital information when planning for or reacting to a crisis. And certainly, the private sector cannot shoulder responsibility for challenges like vaccine nationalism. Thus, governments must provide leadership and coordination, including engagement at the global level to build appropriate architecture to ensure Pandemic Preparedness and Response (PPR) and to secure other health priorities. They should consult with and be supported in such endeavors by industry players.

Leadership and Coordination

In light of the above, government policies are essential in providing leadership and coordination, for instance to evaluate existing capacity and identify gaps. To this end, they are principal conveners, bringing together companies and their innovation partners to contribute to the development of crisis and other plans.

Companies simply cannot direct this type of planning. They may be familiar with their own role in the value chain, and potentially that of their immediate suppliers and customers, but they don't have access to further information. Governments are thus needed to convene the private sector and other actors to map the sustainable delivery of health technologies in different scenarios, including crises. They can discuss questions with industry experts, such as:

- How can manufacturing capacity be brought online quickly when required and what resources are needed to accomplish goals?
- Does the government have the ability to support producers to stock inputs or finished products?
- What financing would be required and available for the ramp-up?
- What national needs can companies reasonably commit to delivering?
- How will IP rights be treated in this context?

When appropriate channels for communication exist between governments and the private sector, governments can share information and objectives with companies, so they can provide their views, self-assess, and come forward to offer support for the innovation and manufacturing needed, in line with their capacities and expertise.

> **Governments and international organizations can help bridge the gap between the potential future need and the lack of business case for investing in surge capacity.**

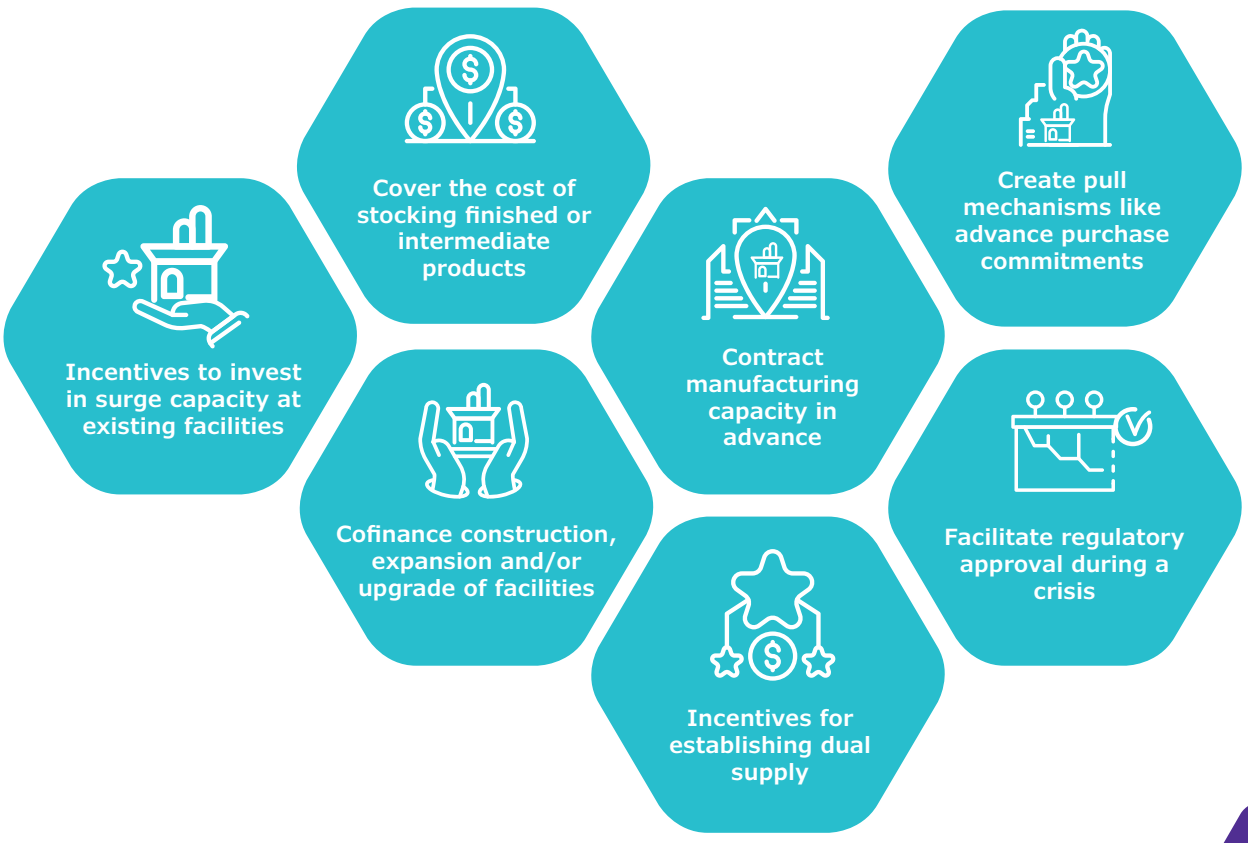
Derisking Investments for Resilience

Additionally, a key role for governments, especially but not only during crises, is to derisk investments required where there is no business case for private actors to step forward. In this sense, rapid, large-scale clinical trials for a pandemic vaccine or building extra manufacturing capacity can benefit from some government support. Examples of these types of government interventions during the COVID-19 pandemic include cofinancing projects to assess existing manufacturing capacity, to rapidly

conduct clinical trials, or to improve manufacturing capacity. Governments continue to pursue such actions, which advanced the pandemic response. By way of example, in late 2021, investments to create lateral flow membrane production capacity in Wisconsin, United States, received USD136.7 million in government investment. The production of this facility, expected to take three years, will give the United States domestic manufacturing capacity for this critical input for diagnostics.

As noted above, maintenance of extra manufacturing capacity for biologics falls into the category of investments that generally require government intervention. Proposals that such "idle" capacity be created and maintained, ready to be brought online immediately in the event of a crisis, do not reflect the reality of biomanufacturing. This is due not only to cost but also to practical and safety concerns like the need to keep machinery, personnel, and processes up-to-date in order to perform to current regulatory and quality guidelines. At the same time, the global health community does need to plan for a future event when manufacturing a substantial volume of therapies, vaccines, and diagnostics may suddenly become necessary. Governments and international organizations can help bridge the gap between the potential future need and the lack of business case for investing in surge capacity today. Various actions can help, including: offer incentives to invest in surge capacity at existing facilities; cover the cost of stocking of finished or intermediate products; and cofinance the construction of new facilities or the expansion or upgrading of existing ones. Governments can also contract manufacturing capacity in advance, for use in the event of a crisis. They can also create pull mechanisms like advance purchase commitments, one incentive that was successfully deployed for COVID-19 vaccines and therapeutics (Figure 10).

Figure 10. Governments Can Help to Bridge Gaps in Surge Capacity



If building redundancy into supply chains is to be counted on as one strategy for improving resilience, it will undoubtedly require government support to succeed. On their own, companies may choose to maintain some surge capacity for strategic business reasons, but this will be far from adequate to address a major crisis. Governments can complement existing private sector efforts by financing the establishment of redundant facilities, for instance factories for producing certain inputs or equipment that they want made domestically for strategic reasons.[19]

Action by Regulators

Engagement between government and industry is particularly important in the area of regulation, and during COVID such engagement was a critical tool for bringing vaccines to market so quickly.

Redundancy is one area for engagement to improve supply chain resilience. A strategy that can be used by companies to enhance resilience is dual sourcing for critical products and equipment. At the same time, this is expensive – especially in relation to situations where a product, process, or facility requires regulatory approval before integration into the value chain. An experiment to validate a new partner or technology, to ensure that it performs as needed, can be carried out relatively quickly by a company. The challenge, however, comes when regulatory approval is also needed, given that this process, in addition to being costly, is time-consuming, with procedures taking, on average, 6-12 months to complete.

To qualify, and then seek regulatory approval for multiple suppliers is beneficial from a resilience perspective, but it's not cost-efficient. When faced with significant time and cost hurdles in bringing products to market, companies may hesitate to undertake the process of qualifying extra suppliers or inputs if they are likely to be used only during a brief period, for instance during a health crisis.

Important areas for future collaboration include the growing digitization among regulators as well as acceptance by regulatory authorities of digital processes for activities like clinical trials management at a distance.

Governments can help to address such challenges by taking the following types of actions:

- Streamline regulatory approval processes
- Reduce the timetable for completing the regulatory process
- Reduce the cost of securing approval for alternative suppliers or products
- Rationalize the criteria for approving novel products
- Review recommendations for required endpoints and safety testing
- Consider ways to further expedite approvals during a crisis
- Consider mutual recognition with other regulatory authorities during a crisis
- Develop crisis plans together with other stakeholders then publish widely

Faster regulatory approval, along with measures to reduce cost, can help with diversification and, especially, crisis response. During the pandemic, regulators provided emergency use authorization (EUA), regularly evaluating this status as new information became available about performance in real time

19 (U.S. Department of Defense, 2021).

(a process called rolling review). They expedited regulatory approval processes where possible, given the urgency of the situation, working closely with innovators to get the data and other information they needed on an accelerated timeline. Measures such as EUAs are effective during a crisis, and certain efficiencies, for instance those related to engagement with industry, may be maintained post-pandemic.

Engagement with industry can help regulators to secure the right information and analysis about novel products, facilities, ingredients, and processes. Regulation tends to lag behind science, so industry experts can provide insights into cutting-edge solutions. Considering current efforts to enhance resilience in biopharmaceutical value chains and expedite the delivery of new solutions to market, while preparing for future health crises, such engagement becomes even more important.[20] Important areas for future collaboration include the growing digitization among regulators, for filings and data exchange, as well as acceptance by regulatory authorities of digital processes for activities like clinical trials management at a distance.

Similar to the need for government incentives for cofinancing and other support across the full value chain, regulators should consider the entire value chain, including raw materials, when undertaking the above efforts. Lipid nanoparticles, for example, are a vital component of mRNA vaccines; these and other raw materials must have regulatory approval before they can be integrated into finished products. And facilities, like raw materials and finished products, require approval, to confirm they comply with strict health and safety requirements.

Governments should also work towards the creation of globalized regulatory standards, to enhance efficiencies and enable patients to access new treatments as quickly as possible.

Coordination among regulatory authorities can expedite the process of getting new treatments to patients. This is especially important during a crisis, when it may be appropriate to go so far as to institute mutual recognition due to the urgent need to get vaccines and other health technologies to patients as quickly as possible.

Outside of crises, convergence among regulators as to endpoints, the types of testing necessary for regulatory approval, and how to classify different types of treatments can help to make new biologics available to patients more seamlessly. Governments should also work towards the creation of globalized regulatory standards, to enhance efficiencies and enable patients to access new treatments as quickly as possible. Promising initiatives in this regard include the Access Consortium, a coalition of regulatory authorities in the UK, Australia, Canada, Singapore, and Switzerland that aims to promote greater alignment of regulatory requirements, and the ICMRA, which works to build global architecture to increase collaboration among agencies and harmonize regulatory requirements across countries.[21]

A biopharmaceutical industry group recently pointed out that, today, "we have high heterogeneity in terms of dossier reviews, approval processes and timelines, with each country having specific data requirements and processes

20 (Pandemic Preparedness Partnership, 2021).

21 (Medicines and Healthcare Products Regulatory Agency, 2022) (ICMRA, 2022).

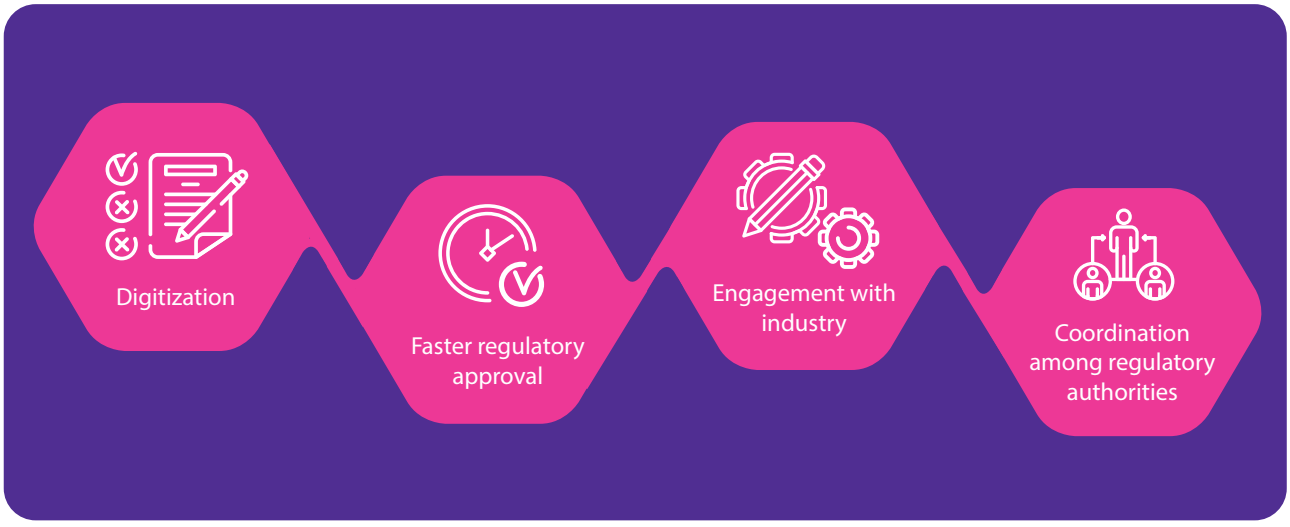
which often differ between countries.[22] As such, it is virtually impossible for every country in the world to have access to medicines and vaccines at the same time".[23] Indeed, coordination among regulatory authorities, for instance in terms of the evidence they request, could enable applicants to enter the market more quickly without sacrificing quality and patient safety. If the same data was assessed by all regulators, comparisons could be easier, thus bringing further robustness to regulatory findings and decisions, while increasing public confidence.[24] The Coalition for Epidemic Preparedness Initiative (CEPI) was already studying the case for greater regulatory coordination before the pandemic.[25] More recently, the organization convened a group of experts to consider how global regulatory requirements could be aligned in the event that a new infectious disease breaks out.[26]

Enabling Policies for Biomanufacturing

Private companies and their innovation partners do not bring new biologics or other health technologies to society in a void. Their activities are necessarily influenced and shaped by the policy environments in which they conduct

governments are crucial partners for innovators, investing in education, instituting enabling policies for innovation and growth – such as IP and trade policies – and pursuing a vision and strategy for universal healthcare delivery.

Figure 11. Features of Regulation for Resilience



22 (Barbosa, 2021).

23 Researchers have found "at least 51 pathways to various types of accelerated vaccine approval in a group of 24 countries". (Nature, 2020).

24 While many regulatory authorities ask for similar data, there are differences. According to one author: "The FDA requires drug companies to submit all the raw data from laboratory, animal, and human trials so that it can do its own statistical analysis. In contrast, the EMA relies more on drug companies' own analyses". (Nature, 2020).

25 (Nature, 2020).

26 CEPI hosts the International Coalition of Medicines Regulatory Authorities (ICMRA) which "allow[s] regulators to share information and agree on approaches. The ICMRA has 29 members, including regulators from China, Europe and the United States. Through it, members have been able to reach a consensus on the best animal models for testing COVID-19 vaccines, the ideal clinical-trial endpoints and the complicated issue of continuing placebo-controlled trials after vaccine roll out begins. The coalition's COVID-19 working group is now trying to harmonize the monitoring of vaccines once they have been deployed, because faint signals of adverse effects might be too weak to spot in any one country". (Nature, 2020).

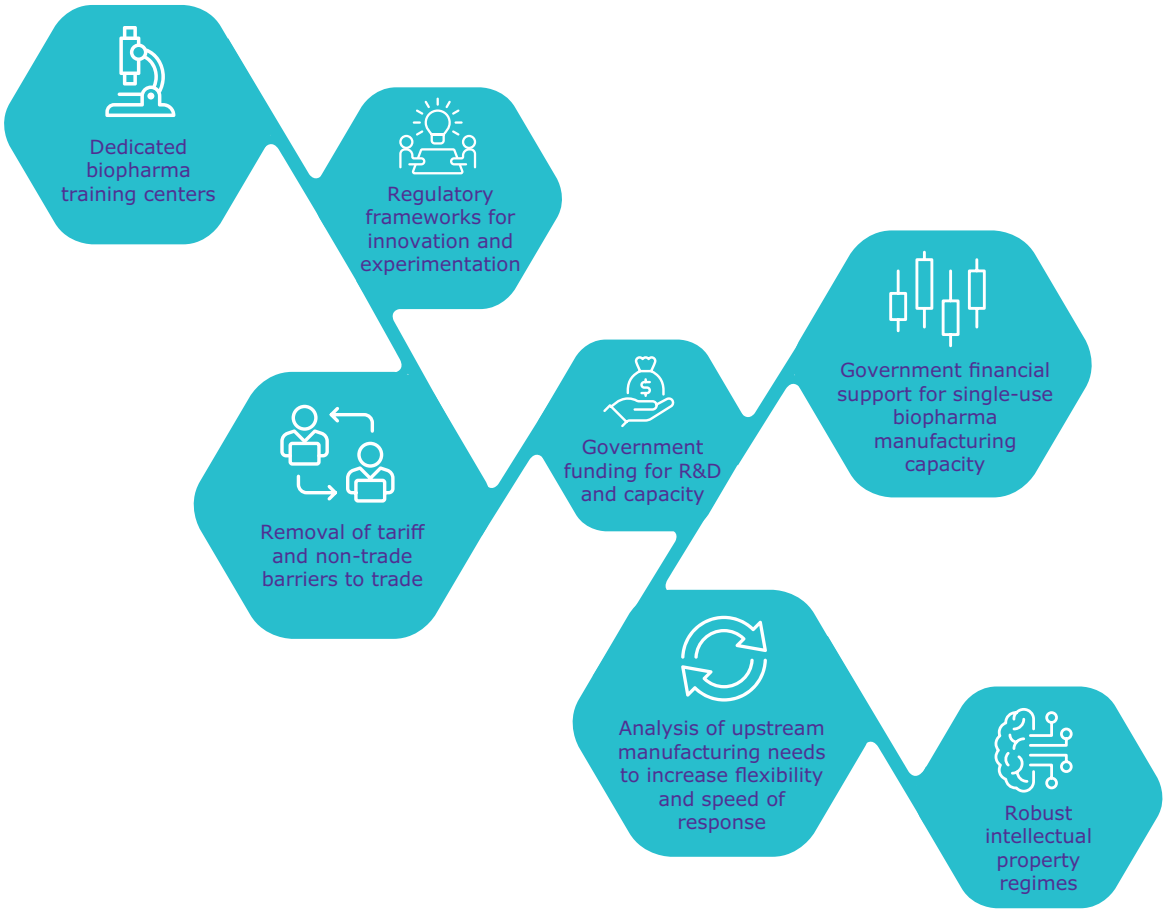
R&D, manufacturing, and other activities. Governments are crucial partners for innovators, investing in education, instituting enabling policies for innovation and growth – such as IP and trade policies – and pursuing a vision and strategy for universal healthcare delivery (Figure 12).

The pandemic experience led governments to enact a number of promising practices. Close coordination between innovators and regulators helped to accelerate the commercialization of novel health solutions like COVID-19 vaccines without sacrificing quality and safety. Governments helped to cofinance investments in clinical trials and to upgrade manufacturing infrastructure. They offered advance market commitments, which enabled innovators to start manufacturing and stocking vaccines even before regulatory approval had been secured. At the same time, however, in some instances governments reacted to COVID-19 with counterproductive policies like export restraints and intellectual property weakening.

governments cannot assure access to biologics – particularly during health crises – without working with other stakeholders, and in partnership with international health organizations, to set up effective global PPR and health architecture including financing mechanisms.

Vaccine nationalism complicates the response to health crises. The pandemic

Figure 12. Optimal Policies for Biomanufacturing



showed, unfortunately, that countries that take a place in line to receive health technologies under international mechanisms are often the last to be served – if they are served at all. This creates an incentive to, in effect, jump the line and adopt a "my nation first" attitude. Ideally, new global architecture for PPR – with appropriate rules, better preparation, and adequate funding – can help with this. Governments must work together, and with other stakeholders, to find solutions in this regard, given the ethical and human welfare considerations at stake.

LOOKING AHEAD

This paper presents different approaches for improving the availability of biologics such as vaccines and monoclonal antibodies. It focuses on ways to build resilience in these global value chains, to improve healthcare delivery during normal times as well as PPR. It presents actions that companies are taking in view of these goals, applying lessons learned during the COVID-19 pandemic, together with government strategies to accelerate and expand the availability of safe, quality biologics.

Underlying the entire analysis is the expectation that investments to improve healthcare systems in every part of the world will be prioritized, as sound health systems provide the necessary foundation for the sustained availability of biologics, including in relation to PPR.

Policies and actions to improve biologics equity are necessarily part of the equation, to correct the disparities that arose during the pandemic. Companies, governments, and global health organizations are taking important steps to increase the chances of vaccines, therapeutics, and diagnostics reaching all patients during a future health crisis. To this end, biopharmaceutical innovators recently endorsed the IFPMA "Berlin Declaration", committing to reserve a portion of real-time production for priority populations in lower income countries during a future pandemic.[27] The reality is that industry will not be able to translate this commitment into improved health outcomes without engagement with and support from governments.

collaboration will be critical to the full range of activities needed to assure widespread access to vaccines and other biologics in the future.

Likewise, governments cannot assure access to biologics – particularly during health crises – without working with other stakeholders, in partnership with international health organizations, to set up effective global PPR and health architecture including financing mechanisms. The way that global health organizations and others manage procurement will certainly affect the medium- to long-term sustainability of geographically distributed biologics manufacturing, and the future of new producers in places like Africa.

The value of collaboration was highlighted during the COVID-19 pandemic, as it became clear that no single actor could develop and deliver solutions to fight the pandemic on its own. This lesson is more relevant than ever in the wake of the pandemic. Collaboration will be critical to the full range of activities needed to ensure widespread access to vaccines and other biologics in the future, including financing, R&D, hand-off between researchers and private companies and among companies, creation of global PPR architecture, manufacturing capacity, more efficient

27 (IFPMA, 2022a).

regulatory systems, performant distribution networks down to the last mile – and policymaking.

The pandemic also underlined the critical role of enabling policies, such as appropriate IP protection, in supporting collaboration for innovation and manufacturing. Patents and trade secrets enabled innovators to rapidly share technology and know-how with partners without losing their competitive edge. This is supported by decades of experience, which show that legally certain, predictable environments for doing business provide a foundation for local companies to enter and move up biologics value chains, with support from tech transfer partners.

MilliporeSigma is at the heart of the ecosystem described in this paper, supplying equipment and other products, along with services, to biopharmaceutical innovators in all regions for R&D, regulatory approval, and manufacturing activities. During the pandemic, our company played a role in the value chain for every major COVID vaccine. We are committed to applying lessons learned from COVID-19 to build resilient systems that deliver biologics to patients who need them, under all circumstances, working with governments and other stakeholders.

To this end, we stand ready to share further insights and to start a conversation about resilience with governments, together with our customers and partners in the biopharmaceutical industry.

Figure 13. Biomanufacturing Ecosystem: Strategies for Resilience

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