Comparing Centralized vs. Distributed Models of Biologics Manufacturing and Supply for Global Health:

A Discussion of Challenges and Opportunities

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Abstract

In recent years, the price of lifesaving or life-extending biologic drugs as a barrier to access has been a contentious topic in the US and Europe. Questions of pricing and access are perhaps even more salient in a global health context, as the demand for biologic drugs grows in emerging and developing markets. Recognizing the rapidly changing global health landscape, this paper seeks to better understand competing factors, specifically within the current biomanufacturing and supply chain ecosystem, preventing the global supply of biologics to match projected demand. It unpacks the complex system of drivers and barriers surrounding the global supply of affordable, high-quality biotherapeutics, provides a qualitative analysis of the centralized-distributed spectrum of manufacturing and supply chain models, and provides both technology and policy recommendations towards increasing global supply. Finally, the paper identifies key questions that provide a basis for future research and dialogue amongst stakeholders interested in ensuring a sustainable global biologics supply to deliver quality care to all who need it in a timely, reliable, and affordable manner.

Preliminary Thesis

Historically, the biomanufacturing industry has concentrated manufacturing of biologic products to several geographic locations, largely in developed countries, to take advantage of economies of scale needed to make up for the large capital investment cost in stainless-steel plants. Manufacturers have also aimed to locate these in settings that provide tax break and subsidies, taking advantage of unique laws in certain jurisdictions. More recently, there has been increased interest in establishing manufacturing sites in multiple locations at a time to lower risk of interruptions in the supply chain, as well as in emerging markets. This is a driven host of factors, including economic incentives, increasing nationalization (manufacture in market to sell in market), and expand supply to new, emergent markets. While this has brought some products in closer proximity to markets that currently lack access, it has not led to the increase expected in resources-depleted regions. Given that the existing biomanufacturing process requires high costs of capital, highly-skilled labor (much more than small molecule drugs), and reliable infrastructure (e.g. clean water, energy, etc.), a more centralized approach that leverages economies of scale appears to still be more cost-effective. However, as manufacturing and supply chain technologies and policies evolve toward lower cost of capital, distributed models may become more financially attractive and a promising avenue for expanding global supply.

In this paper, we seek to better understand if such emerging manufacturing and supply chain systems can lead to expanded supply, as well whether the drivers of such change are different depending on the product, regional context, regulatory jurisdiction, geopolitical zone, and sociocultural differences. End-to-end solutions across health systems coordinated among all relevant stakeholder will be key to overcoming global biologic shortages and closing the widening gap between supply and demand. Such solutions are becoming increasingly urgent, especially if we are to achieve intergovernmentally, globally agreed targets on enhancing access to medicines, including biologics, to achieve universal health care, as outlined in Sustainable Development Goal 3.8 and 3.b of the 2030 Agenda for Sustainable Development.

Conclusions

In the current manufacturing and supply chain paradigm for biologics, a centralized model is more cost-effective for bulk supply, with potential areas of improvements. It is important to note variation in product requirements, with some better suited for decentralized manufacturing, such as stem cell therapies given their very short shelf life. A decentralized model has the potential to expand non-traditional markets as well as avoid single source supply dependence for a given country. In either case, technology and policy play a tantamount role in making different manufacturing and supply chain models more competitive in different contexts. Continued analysis of comparative costs and risk-benefit tradeoffs, as well as exploratory research informed by data on the current state of biologics supply, are key to inform decisions to meet future projected demand, especially in low-and-middle income countries (LMICs). Innovations in technology and policy could help narrow gaps between supply and demand of biologics. Moving forward, a multi-layered, dynamic understanding of the relationship between the building blocks leading to reliable service and delivery of biologics is key to making appropriate predictions and recommendations.

I. INTRODUCTION

Background

Global agreements have outlined measurable targets for medicines access in order to galvanize efforts and increase coordination amongst stakeholders. The WHO Global NCD Action Plan has outlined a global target of 80% availability of affordable basic technologies and essential medicines, including generics, required to treat major non-communicable diseases in both public and private facilities by 2020[1]. A 2009 paper by Cameron et. al found that the average availability of medicines across 36 countries was only 38% in the public-sector and 64% in the private sector, while patients purchasing from private-sector suppliers paid 9-25 times international reference prices[2].

Low- and middle-income countries (LMICs) across Africa, Asia, Europe and Latin America face a growing burden of chronic and other diseases that require biologic drugs, with close to 80% of NCD-associated deaths reported in those regions[3]. However, to date the biopharmaceutical market has been heavily concentrated in the US, Western Europe, and Japan. Identifying barriers and potential solutions to high-quality, affordable, and reliable biologic drug supply in LMICs is an important first step to ensure that the growing demand for lifesaving treatments is met.

[1] WHO Global NCD Action Plan 2013-2020, http://apps.who.int/iris/bitstream/10665/94384/1/9789241506236_eng.pdf?ua=1

[2] Cameron A, Ewen M, Ross-Degnan D, Ball D, Laing R. Medicine prices, availability, affordability in 36 developing and middle-income countries: secondary analysis. Lancet 17 Jan 2009; 373:240-249.

[3] Terzic, A. and Waldman, S. (2011), Chronic Diseases: The Emerging Pandemic. Clinical and Translational Science, 4: 225–226.

Barriers to sustainable supply exist throughout the entire value chain of biologics, as seen in **figure 1**. Beyond the high cost of research and development (R&D), these include complex biomanufacturing processes and regulatory requirements, challenges with last-mile delivery and stock outs due to poor forecasting. Additional barriers arise from the unique economic, regulatory, political, social, and cultural environment of individual local markets. The extent to which these factors influence supply vary greatly over context, geographies, and products. However, improvements and potential solutions can be identified at each step of the value-chain to close the gaps between the supply and demand of biologics. This paper focuses on the manufacturing and supply chain portion of the value-chain, analyzing the drivers and barriers influencing a provider to take on different manufacturing models across the spectrum of centralized-distributed supply and delivery.

The global health community, spearheaded by UN Agencies such as World Health Organization (WHO) and UNICEF, philanthropic organizations such as the Bill & Melinda Gates Foundation, and Non-Governmental Organizations such as PATH are intensifying efforts to comprehensively map barriers hindering and drivers enabling global access to medicines. However, much work remains to accelerate global supply and access to biologics. In particular, one potential lever that needs further exploration, with limited available public information, is the extent to which lower manufacturing and supply chain costs can increase global supply and drive down prices for enhanced patient access.

A growing trend among pharmaceutical companies is to establish production facilities in emerging markets, sometimes to supply regional or local markets. Some companies are also moving toward smaller, more flexible and scalable production technologies that could open the door toward localized "distributed" manufacturing, whereby production takes place close (or closer) to the end-patient.

Yet there is a gap in publically available research or data on the potential impact of distributing biologics manufacturing more globally. In an effort to close such a gap, this paper seeks to address the following key question: given the current state of the industry, could a distributed model reduce manufacturing and supply chain costs of biologics, with the ultimate goal of increasing access to biologic medicines? What are the risks, benefits, and tradeoffs of such an approach? The paper also explores how emerging technological and policy innovations have the potential for shifting cost-benefit analyses in decision-making.

The paper compares a traditional centralized manufacturing model with more "distributed" manufacturing models, discussing the extent to which these differences could impact production, supply and costs (e.g. regulation, operations, etc.). It also outlines the broader, non-cost benefits and risks of decentralized manufacturing models, as well as an analysis of factors that drive company decisions on which manufacturing and supply chain models to adopt. Recognizing the influence of local context in such analysis, accounting for differences between and within countries, as well as between and within companies and products will be a continued challenge.

The paper is structured as follows: a summary of our methodology; context on the growing demand for biologics in emerging markets; an overview of costs in the traditional centralized

manufacturing model; a discussion of financial and non-financial implications of a distributed model; policy and technology recommendations; and questions for further research.

Methods

To inform the findings of this paper, we interviewed 11 experts from the biopharmaceutical industry and global health field, including leaders from multinational companies, start-ups, regulatory agencies, academia and non-profit foundations. The interviews involved discussions on the major cost centers, as well as other competing risks and drivers, in choosing one model over another for manufacturing and supply of biologics. The information utilized in this report has been anonymized and de-linked from its source to ensure privacy of interviewees. Insights gained from the interviews were supplemented with secondary research of existing literature, public company documents, and reports prepared by consulting firms and other agencies.

The paper leverages the existing network of MIT's Center for Biomedical Innovation (CBI), which has extensive experience in biomanufacturing through its programs and pre-competitive consortia engaging a variety of stakeholders, including pharmaceutical companies, regulatory agencies, and academia.

Definitions

There exists a spectrum of geographic models for biomanufacturing. Defining the difference between centralized, de-centralized, and distributed models is subject to interpretation and depends on the metrics use for comparing them. This is an initial challenge in comparing models that have fluid boundaries between them, especially as they can be thought differently even within the biopharmaceutical industry when thinking about manufacturing plants (API), fill-finish-plants, and network of suppliers and distributors.

In the context of this paper, different models are compared from the perspective of where and how one specific product (e.g. insulin) is produced by a given manufacturer (e.g. Novo Nordisk). At one extreme, a company may have one or a few manufacturing facilities for a product in developed countries (typically near company headquarters) as is the case with Genentech, which has three sites in California[4]. At the other end of the spectrum, a company may have manufacturing facilities for the same drug in every region (or even country) where its products are sold. The most extreme case of distributed supply of biologics, currently under research, are portable, on-demand, personalized production systems that provide small volumes at the point-of-care[5]. In between these extremes are a diverse range of models that may distribute its manufacturing sites and supply chain across several countries. For example, Amgen does most of its clinical manufacturing in Rhode Island, bulk manufacturing in Puerto Rico, and fill-finish

[4] Genentech company website, accessed November 2016, https://www.gene.com/media/company-information/manufacturing

[5] Pardee, Keith et al. Portable, On-Demand Biomolecular Manufacturing. Cell, Volume 167, Issue 1, 248 – 259.

activities in its Netherlands site, while building a new production facility in Singapore[6]. This could be considered a centralized system spread over a few global centers, showing the complexity in characterizing such systems in practice. Similarly, the Indian company Cipla has manufacturing capacity in India and the US, while building a state-of-the-art plant in South Africa, increasingly expanding its reach to new markets[7]. In another case, some manufacturers supplying biologics to small markets, may only have production plants in that country (e.g. Julphar, insulin manufacturer in UAE).

Distributed manufacturing is generally defined as a system in which "raw materials and methods of fabrication are decentralized, and the final product is manufactured very close to the final customer," in or near the end-market of the product[8]. For example, Novo Nordisk set up local production capacity in China in order to better serve the Chinese diabetes market, as well as increase operation efficiency of insulin supply in China and better respond to shifts in market demand[9]. In contrast, many manufacturers have offshored manufacturing capacity, shifting the location of their global production centers without expanding through a decentralized model. Using the definition of distributed manufacturing as having a network of localized production sites to expand supply to local markets, distinct risks and benefits can be identified, especially when operating in LMICs.

In **figure 2**, panel A shows a centralized model where one primary manufacturer produces and supplies final products to intermediary providers. In the context of biomanufacturing, panel B shows a decentralized model in which a company has a main manufacturer that supplies to additional subsidiaries that either also produce final product or perform fill-finish of API to generate final product; final products are then further distributed from the subsidiary. Panel C shows a distributed manufacturing and supply chain network in which many producers are co-localized with markets in order to meet demand. For a given product, the colors demonstrate different manufacturers, some of which have multiple sites globally, while others only have one or few sites at regional or local levels, even up to small-scale production at the point of care.

II. BIOLOGIC ACCESS IN EMERGING MARKETS

Rapidly changing global health landscape

Studies have shown that LMICs are disproportionately impacted by ***both*** infectious and chronic non-communicable diseases (NCDs), partly due to disparities in access to diagnosis, prevention, and care[10]. The burden of chronic diseases is not just disproportionately higher in LMICs, but

[6] Amgen company 2015 annual report, 2016, http://investors.amgen.com/phoenix.zhtml?c=61656&p=irol-reportsannual

[7] Cipla company 2015-2016 annual report, 2016, http://www.cipla.com/uploads/investor/1472556329_Annual%20Report_2015-16%201.pdf

[8] World Economic Forum, Emerging Tech 2015: Distributed manufacturing, https://www.weforum.org/agenda/2015/03/emerging-tech-2015-distributed-manufacturing/

[9] Novo Nordisk, "The Blueprint for Change Programme: Changing diabetes in China," February 2011 https://www.novonordisk.com/content/dam/Denmark/HQ/Sustainability/documents/blueprint-changing-diabetes-in-china.pdf

[10] Council on Foreign Relations, Global Health Taskforce - The Emerging Global Health Crisis: Noncommunicable Diseases in Low- and Middle-Income Countries, 2014

onset of NCDs are also observed at an earlier age (ibid). While infectious diseases continue to be a concern for health systems across LMICs, they are now faced with the added burden of chronic diseases despite limited capacity and resources. These already overstretched and fledgling health systems are expected to be further strained by the growing double burden of disease and inadequate shifts in health response. Uncertainty surrounding the needs for adequate local response also contribute to the growing gap between demand and supply of affordable, quality, and consistent health services – including diagnostics and medicines.

The global health landscape is experiencing rapid shifts in the prevalence of different diseases, especially with the increased morbidity and mortality of NCDs. NCDs account for approximately 70% of deaths worldwide, 75% of which occur in LMICs[11]. Of these, 40% are considered to be "premature", preventable deaths that occur before the age of 70, happening most often in LMICs. The shift to NCDs has led to major social and economic loss, cumulatively more than $7 trillion in LMICs alone between 2011-2015. It has also increased pressure on health systems dealing with the double burden of NCDs and infectious diseases (ibid).

These projections are expected to worsen in coming years due to multiple interconnected factors, including demographic transitions such as increasing life expectancy, economic growth, urbanization, and other social and environmental factors such as tobacco use and air pollution, respectively[12]. Changes in lifestyle, such as shifts to processed food and reduced exercise, further exacerbate the exposure to risk factors and earlier onset of diseases. **Figure 3** outlines some of the driving factors in the shift from infectious to chronic diseases and the public health impact. Figure 3 also highlights the necessary attributes of a responsive health system, which is highly dependent upon the reliable supply and access to high quality, safe, efficacious and affordable medicines as noted by the WHO Building Blocks of health systems[13]. Access to medicines is intrinsically dependent on the other building blocks such as good governance and financing in order to ensure quality health service delivery.

Growing demand for biologics in emerging markets

In order to empirically assess disease burdens and the projected increase in demand for biologics in LMICs, we analyzed WHO data[14] providing global and regional projections of mortality by cause for years 2015 and 2030. Data is provided for the mortality by disease type and further disaggregated by gender, region, and income groups. For the purposes of our analysis, we only included diseases from the top 20 causes of death for which medicines, small molecule drugs or biologics, are potential preventative or curative therapies.

Comparing the projected change in disease burden between 2015 and 2030 provides insights on epidemiological transitions expected over time, as well as raises questions on whether current health system capacities will be able to meet future projected health care demand in terms of

[11] Global status report on noncommunicable diseases 2014 http://apps.who.int/iris/bitstream/10665/148114/1/9789241564854_eng.pdf?ua=1

[12] Bloom, D.E et. al (2011). The Global Economic Burden of Noncommunicable Diseases. Geneva: World Economic Forum

[13] WHO's Framework for Action, Everybody's business: strengthening health systems to improve outcomes, http://www.who.int/healthsystems/strategy/everybodys_business.pdf

[14] WHO Projections of mortality and causes of death, 2015 and 2030

quantity, quality, and affordability. As seen in **figure 4**, the projected increase in disease mortality during the 15-year interval is largest for diabetes mellitus (58%), trachea/bronchus/lung cancer (47%), liver cancer (43%), stomach cancer (43%), breast cancer (43%), colon and rectum cancer (42%), COPD (42%), and Alzheimer's disease (40%). The disease burden is expected to decrease for diarrheal disease (12%) and tuberculosis (33%). Further analysis, shows that the diseases with the highest positive projected change in burden are ***all*** NCDs, while those with the smallest positive projected change or decreasing burden are infectious diseases.

The change in disease burden between 2015 and 2030 was compared across income groups in order to assess relative impact of different diseases. As shown in **figure 5**, the total change in disease burden was disaggregated into four income groups (low, low-middle, upper-middle and high) for each disease type. As expected, the increase in disease burden for many chronic diseases is concentrated in low-and-middle income regions. While that is where a bulk of the population lies, it is also where health systems are least equipped to deal with the shift to NCDs and increase in demand for care. Additionally, some cancers and Alzheimer's disease are expected to have greater burden in upper-middle and high income regions, while the decrease in infectious diseases is expected to be highest for low-income regions.

Biologic drugs are often used as primary therapeutics for management or treatment of NCDs, either as the only or most effective options for extending and improving quality of life. Table 1 highlights indications for which biologics in many cases offer an effective therapy, while small-molecule drugs are not as common or appropriate for long-term management of disease. With the significant growth in case of NCDs, the effective treatment of these diseases will require that patients have access to high-quality, affordable biotherapeutics either as a primary or as a follow-on to small molecule, drug. Therefore, adequate global supply of cost-effective biologics to meet demand is necessary to make access possible. This is especially true in LMICs and emerging markets, where socioeconomic growth together with the projected increase in disease burden will drive an increased demand for affordable and comprehensive care.

The above data and analysis points to an increase in the projected demand for biotherapeutics. This will likely be accompanied by increased pressures to make biologics more accessible globally through improved manufacturing systems and more reliable supply chains, especially in emerging markets and low-income regions that have larger global health gaps to fill. Further, our analysis may in fact *underestimate* the actual burden of disease in 2030, and thus the expected demand for biologics, due to several reasons:

- Predictive models often involve many assumptions that attempt to capture real-world trends of disease burden, employing deterministic relationships for complex, non-deterministic variables such as sensitivity risk factors or predispositions to diseases.

- Using mortality as a metric for burden instead of prevalence may not reflect the real-time demand for biologics, as more people have a disease (or multiple ones simultaneously) than those who die from that disease as reported in health records.

- The difficulty to diagnosis chronic diseases in LMICs means that many more people may need biologics than those who seek treatment. According to the Rule of Halves,

approximately half of most common chronic disorders are undetected, half of those detected are not treated, and that half of those treated are not effectively controlled[15]. To address this gap, the Department of Essential Medicines and Health Products at the WHO put out a proposal for a WHO Model List of Essential In Vitro Diagnostics[16].

In order to provide high-quality and effective treatments to those who need it, drastic shifts in the technology, business, and innovation space will need to take place in order to adequately supply biologics in response to growing demand.

Initiatives to meet growing demand

The last two decades have seen a proliferation of initiatives to expand supply and access to biologic products, especially for patients in LMICs. The majority of efforts to date have focused on infectious diseases and small-molecule drugs, but increasingly encompass biologics.

Ensuring affordability of biologics presents a unique set of challenges, given the complex manufacturing process and supply chain requirements needed to delivery biologics, as well as unique political contexts within different regulatory jurisdictions. Several trends have emerged:

- **Pricing:** Some countries, especially in Europe, have mandated price caps on biologics, while some states in the US have placed caps on out-of-pocket payments by patients in private health insurance plans[17]. Other countries utilize external reference pricing, also known as international price benchmarking, to calibrate prices across markets[18]. Some, such Sweden, have employed value-based or therapeutic reference pricing to derive prices based on perceived health outcomes and efficacy of treatments. Companies have also adopted tiered or differential pricing when the same product is sold to different customers at different prices, based on their purchasing power[19]. For example, the Roche Patient Access Programme has tripled access to Herceptin by providing qualified patients in the Philippines with discounted rates[20]. Other health systems have developed tiered formularies, in which providers place a drug at a preferred formulary position, thus larger

[15] Hart J, Rule of halves: Implications of increasing diagnosis and reducing dropout for future workload and prescribing costs in primary care. British Journal of General Practice 42(356):116-9 · April 1992

[16] Department of Essential Medicines and Health Products, World Health Organization, Proposal for a WHO Model List of Essential In Vitro Diagnostics (or the EDL), January 2017.

[17] States Limiting Patient Costs for High-Priced Drugs, 2015, http://www.pewtrusts.org/en/research-and-analysis/blogs/stateline/2015/07/02/states-limiting-patient-costs-for-high-priced-drugs

[18] European Drug Prices: New Commission Report on What Policies Work and What Could Work http://raps.org/Regulatory-Focus/News/2016/02/25/24409/European-Drug-Prices-New-Commission-Report-on-What-Policies-Work-and-What-Could-Work/#sthash.TWeY9Jxx.dpuf

[19] Affordability and Accessibility to Medicines in EMs: Differential pricing is the solution, 2016 http://isbinsight.isb.edu/affordability-and-accessibility-to-medicines-in-ems-differential-pricing-is-the-solution/

[20] Improving access: overcoming barriers: Roche's commitment to sustainable healthcare http://www.roche.com/dam/jcr:a9c0006a-fed9-4864-a8c9-d8ffec6ca508/en/access_to_healthcare.pdf

market share, if they are more favorably priced[21]. An report from the Organization for Economic Co-operation and Development (OECD) on pharmaceutical pricing in global markets highlights additional variants to pricing such as price-volume and risk-sharing agreements, confidentiality agreements, and various reimbursement mechanism that all point to the lack of any consistency or harmonization in pricing policies, thus differentially influencing the equitable supply of and access to biologics in different markets[22].

- **Bundling:** Companies are experimenting with bundling several drugs as a single product at a lower package price than the sum of the price of each individual drug. For example, through the Novartis Access Program, LMIC governments can purchase a bundle of 15 on-and-off-patent medicines to address NCDs at a price of USD 1 per treatment per month[23].

- **Negotiations** over prices are employed by companies to gain access to new markets or expand market share, or by buyers to drive down prices through competitive bargaining. For example, Brazil negotiated a 40% price decrease for the HIV/AIDS drug Viracept manufactured by Roche after the health ministry threatened to break the patent on the drug to locally produce it[24].

- **Biosimilars:** The entrance of biosimilar drugs is expected to increase competition and drive down price, especially as major innovator biologics go off-patent and lose market exclusivity. The first approved biosimilar in the US, Sandoz's Zarxio (Filgrastim), was marketed beginning in March 2015 at a launch price 15% below the reference biologic Neupogen. While the full impact of biologics on prices remains to be seen, it is unlikely to reach the ~80% reduction seen with generics for small-molecule drugs[25]. This may be due to the complicated biomanufacturing process and quality control systems unique to biologics. While extensive regulatory barriers to entry promulgating the rise of large monopoly-like markets through exclusivity, many of the highest grossing biologics are expected to go off-patent in the coming years, which has incentivized rapid growth of biosimilars and can possibly lead to price reduction through increased competition[26].

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[21] Patricia M. Danzon (2014), Pricing and Reimbursement of Biopharmaceuticals and Medical Devices in the USA, In: Anthony J. Culyer (ed.), Encyclopedia of Health Economics, Vol 3. San Diego: Elsevier; 2014. pp. 127-135.

[22] OECD Health Policy Studies: Pharmaceutical Pricing Policies in a Global Market, http://apps.who.int/medicinedocs/documents/s19834en/s19834en.pdf

[23] Novartis Access Program: https://www.novartis.com/about-us/corporate-responsibility/expanding-access-healthcare/novartis-access

[24] Kaiser Health News Brazil Intends to Break Patent on Roche's Nelfinavir to Produce Drug Locally, 2001
http://khn.org/morning-breakout/dr00006553/

[25] Deloitte - Winning with biosimilars: Opportunities in global markets
https://www2.deloitte.com/content/dam/Deloitte/us/Documents/life-sciences-health-care/us-lshc-biosimilars-whitepaper-final.pdf

[26] Fraser Institute, The Biologics Revolution in the Production of Drugs, 2016
https://www.fraserinstitute.org/sites/default/files/biologics-revolution-in-the-production-of-drugs.pdf

- **Philanthropy and partnerships:** A range of non-governmental stakeholders are moving the needle on global drug access, particularly in low-resource, humanitarian, and emergency settings. For example, the public-private partnership Gavi accelerates global vaccine access by pooling demand from the world's poorest countries, securing long-term funding and shaping vaccine markets. In 2009, the pharmaceutical industry spent more than $3 billion in corporate social responsibility projects in developing countries, including many drug donation programs.

- Relaxation of trade-related intellectual property (TRIPS) policies provide sovereign rights to governments to enter **compulsory licensing** and violate patents in order to enhance supply in times of national emergency by producing locally and made available at a lower price[27]. For example, CIPLA has requested the South African Department of Trade and Industry to issue compulsory licenses to patents on a range of HIV drugs to begin local production in order to close gaps between supply and demand[28].

- **Nationalization/Localization**: Some countries and companies (e.g., Cipla in India) are looking to establish local manufacturing and supply chains as a means to decrease costs, promote local economic growth, and facilitate technology transfer. Localization policies put forward by governments require manufacturers to conduct at least part of the production within the country in order to enter the market, not necessarily to reduce costs. For example, Indonesia's Decree 1010 requires foreign companies to manufacture locally or entrust manufacturing to a local company in order to receive marketing authorization, with some exceptions.

- **Technology and Innovation**: Ongoing process and technological improvements in biologics manufacturing have the potential to reduce costs and time to market[29,30]. For example, biologics production traditionally requires expensive stainless steel systems. In recent years, the emergence of disposable single-use technologies has driven down capital costs of production facilities and increased resource efficiency[31,32]. Other examples of technology and innovation that may improve global access include flexible modular systems, alternate host organisms, and automation[33]. The extent to which these technologies impact supply depends on their applicability, ability to perform effective

[27] TRIPS, Pharmaceutical Patents and Access to Essential Medicines: Seattle, Doha and Beyond, 2003 http://www.who.int/intellectualproperty/topics/ip/tHoen.pdf
[28] KEI: Recent examples of compulsory licensing of patents, 2007 http://www.keionline.org/content/view/41/1
[29] Enabling global access to high-quality biopharmaceuticals, Current Opinion in Chemical Engineering 2013, 2:383–390, 2013
[30] McKinsey Global Institute- Manufacturing the Future: The Next Era of Global Growth & Innovation, 2012
[31] Deloitte - Advanced Biopharmaceutical Manufacturing: An Evolution Underway https://www2.deloitte.com/content/dam/Deloitte/us/Documents/life-sciences-health-care/us-lshc-advanced-biopharmaceutical-manufacturing-white-paper-051515.pdf
[32] Bioprocess International - Global Evolution of Biomanufacturing, 2013 http://www.bioprocessintl.com/manufacturing/monoclonal-antibodies/global-evolution-of-biomanufacturing-340616/
[33] BioPharm International - Modular Manufacturing Platforms for Biologics http://www.biopharminternational.com/modular-manufacturing-platforms-biologics

technology foresight and impact assessment, and promote conducive innovation ecosystems.

While scaling global supply requires a multi-pronged approach, the focus of the paper will be on both a financial and non-financial analysis of tradeoffs within the manufacturing and supply chain of biologics, exploring both policy and technology dimensions to map risks and benefits across different models.

III. OVERVIEW OF CENTRALIZED MODEL

In order to assess whether a distributed manufacturing and supply chain model could be an effective approach to decreasing costs and expanding access to biologics, we first provide a discussion of costs observed in the current traditional, centralized model.

Manufacturing of biologics are generally more complex, costly, and time-intensive than for small-molecule drugs. Biologics are heterogeneous in nature due to complex biosynthetic processes including varied post-translational modifications that leads to biosimilar but non identical products. Therefore, extensive purification steps and rigorous quality control and assurance measures, as well as bioequivalent studies, are needed to ensure that efficacious and safe drugs are supplied to patients.

Assessing relative weight of cost centers

In our analysis, we focus on costs, risks, and benefits associated with the manufacturing and supply chain components of the biologics value-chain. We do not account for R&D or reimbursements from sales. While R&D costs are significant - for each successfully approved biologic product, the average cost and time from initial research to marketplace is $2.6 Billion and 10 years, respectively[34] - the manufacturing and supply chain models can be adapted drug approval. Whereas average R&D costs are likely to hold true across the industry, the cost of manufacturing and supply along the lifetime of a biologic can be influenced by many factors.

In biomanufacturing, small fluctuations in upstream processes can have amplified downstream effects on the efficacy, safety, and quality of end-products. Historically, biologics have been manufactured through centralized models that supply products to every market where the drug is sold. While such costs are spread over the manufacturing and supply chain of the product, estimating the scale and relative contribution of each cost center is challenging due to the lack of publicly available data.

For biologics production, fixed costs typically exceed variable costs. Some of the largest contributors are the cost of capital, cost of operations/goods, and regulatory costs. In a centralized model, investments in the form of land, buildings, equipment (typically large stainless steel reactors) and infrastructure are the biggest driver of fixed costs. Several years of construction, site validation, and regulatory inspection are usually required before initiating the

[34] Biopharmaceutical Research & Development: The Process Behind New Medicines http://www.phrma.org/sites/default/files/pdf/rd_brochure_022307.pdf

manufacturing process, which itself will delay introduction of finished products into the market. High-volume plants are thus preferred in a centralized model in order to amortize initial capital investment and production costs over more units (e.g. number of batches).

Although the cost of operations/goods can vary across companies, it accounts for another large cost contributor, including expenses associated with the upkeep of processes, skilled labor, regulatory compliance, oversight, and facility utilities (e.g., processed water and energy)[35]. Efficient utilization of manufacturing capacity is crucial, as low-utilization is a more expensive alternative, with economies of scale highest with large production volumes. Once demand is met, excessive production or shifting to another production process, is less costly than stoppages in operation activity.

Other factors influencing costs of operation/goods are the number of batches produced, size of reactors, turnover time between batches or products, yield, and success rate. There exists a tradeoff between bioreactor size and productivity. While productivity decreases with bioreactor size, larger reactors may be favorable if the number of batches required to meet demand is reduced, resulting in lower labor, QA/QC, and material costs.

Cost of operations/goods also includes raw materials, accounting for about 5-10% of the total manufacturing cost. Cost of goods (COGs) can be further disaggregated into the COGs of API (e.g., insulin) and COGs of the formulated and finished product (e.g., syringe/vial). The choice of finished product form, for example multi-dose vial or single-dose syringe, can impact costs for global supply, not just the COGs of the finished product. If a diabetic patient comes to a clinic with only multi-dose vials of insulin, but no other patients present, delivery will likely be denied to avoid wasting product in favor of waiting for more patients to reap maximum utility from this one vial.

More downstream costs arise in the packaging, shipping, and storage of finished products, as well as marketing in local markets. Marketing costs can be high when introducing a new biologic with existing competitors or into a new market that has not yet developed trust for the company or product. These costs are likely to be less sensitive when comparing between a centralized and distributed systems, though enhancing global supply may lead to costs scaling proportional to volume. Local and last mile delivery continue to pose both a significant financial and technological challenge for global supply. Contributing factors include temperature and motion sensitive formulations, inaccessible ground routes, unreliable energy sources for refrigeration, non-ideal storage conditions, unexpected delays, and mishandling[36].

IV. DISTRIBUTED MODEL COMPARISON

[35] The Biomanufacturing of Biotechnology Products, Biotechnology Entrepreneurship, Chapter 26. http://dx.doi.org/10.1016/B978-0-12-404730-3.00026-9

[36] Value of the Cold Chain: Relevance of Cold Chain in Site Selection for the Life Sciences Industry, Deloitte. http://lifesciences.georgia.org/master/files/tmp/GA%20Cold%20Chain%20Logistics.pdf

The following section outlines how the cost centers identified above would be impacted under a more distributed model.

Cost implications of a distributed biomanufacturing model

Figure 6 outlines how the shift to a distributed model would impact the cost centers identified in the centralized reference model. In this scenario, a centralized model with one high-volume production plant is compared to six smaller production plants, one per region, needed to satisfy the same production output. Therefore, this is analysis assumes a 1:1 total production volume comparison. The different cost centers in the simulated distribution model, as well as related risks and benefits, were qualitatively ranked as being better (strength/green), approximately the same (similar/yellow), or worse (weakness/red) than the comparative centralized model. These estimates are based on discussions with experts and literature research under the current state of biomanufacturing and supply of biologics.

The following trends emerged as the most relevant cost considerations of a distributed model:

- **Cost of Capital & COGs:** While the capital cost of single plant within a distributed model is likely lower than that of large-scale centralized facility, the sum across the network of all distributed plants will be higher. Since economies of scale occur over large volumes, a distributed model that spreads out production over multiple sites is typically inefficient and leads to loss. Depending on the location of the distributed facilities, capital costs may be higher or lower depending on the subsidies offered. Initial research indicates tax incentives as being the primary cost-related drivers to open plants abroad. However, with taxes varying between 0-40%, due to regional or bilateral trade agreements and other political incentives, its effects are difficult to forecast[37]. For example, the biotech market has rapidly expanded in Singapore with industry-specific tax incentives that drive economic competitiveness and enables cost-saving such as access to reliable utilities and a skilled, English-speaking labor force[38].

- **Labor:** Wages are often lower abroad, particularly in emerging markets, which can reduce the cost of operations for a distributed manufacturer. However, biomanufacturing has remains skill-intensive, making it costlier to find, train, monitor, and retain the right labor. Some regions may lack local talent, therefore potentially increasing upfront costs if implementing the appropriate training. As one example, Singapore offers both lower wages and a highly-educated workforce, attracting large biotechnology growth over the past few years. Other companies working in other emerging markets invested significantly in training programs to build local workforce capacity and incentive low attrition on the job. Further, if a company is manufacturing the same product across several production sites, it may require a higher aggregate volume of labor than in a centralized model because certain functions (e.g. technicians, management, etc.) will

[37] Industry Issue Report: Taxation in the Pharmaceutical Industry, 2011
https://kelley.iu.edu/CBLS/files/Courses/Hall-Kitto%20Pharma%20Tax%20Issues.pdf
[38] Industry Specific Tax Incentives in Singapore
https://www.guidemesingapore.com/taxation/corporate-tax/industry-specific-tax-incentives

need to be duplicated at each site.

- **Cost of Regulation:** Each facility and manufacturing process must be qualified and validated, so costs would scale with the number of facilities. Further, because laws and regulations vary by jurisdiction, companies that manufacture in several countries may have higher costs of regulatory compliance costs, as well as experiencing delays implementing process changes. This may also increase the risk of non-compliance, which can be very costly for manufacturers. Determining the change in costs may not be easy to conclude, as there are also regulatory costs associated with selling in different markets, even without having manufacturing capacities within them. If distributed systems enhance subsidizes or other financial incentives, especially if benefitting local economy and labor, it may be more complex.

- **Shipping and storage:** Costs of shipping and storage, particularly for products requiring cold chain, would likely decrease compared to the centralized model. However, companies may incur new raw materials shipping and storage costs so the net effect is not clear. Shipping and storage costs currently tend to be a relatively negligible piece of the total cost, given that we rely on capital-intensive systems and that the majority of the market is currently clustered in the US and Western Europe. As manufacturing technology evolves and emerging and developing markets take on a greater share of the market, this may change. Some analysts have argued that gains from temperature stabilizing technologies will be most effective if employed across the entire supply chain, not just at last mile delivery. Distributed systems likely reduce total shipping, as products are prepared closer to markets. Estimating changes in storage costs is more difficult since it depends on the amount of time a drug spends in storage, as well as volume of storage, which differs across sites. Time and volume may decrease in the distributed system, but since there are more sites, the costs many only marginally change.

Contextual considerations for distributed models

Beyond costs, other factors in the form of tradeoffs between risk and benefits unique to different contexts can have substantial influence on decisions to move across the centralized-distributed spectrum of biomanufacturing and supply chain delivery:

- **Politics:** There can be both political advantages and disadvantages to manufacturing outside established markets (US, Europe, Japan) under a distributed model. Beyond the immediate tax incentives or subsidies discussed above, governments may provide more indirect incentives, such as preferred access or higher prices for a company's products. Alternatively, countries like China and Brazil *require* that a product be (at least partially) produced in-country in order to be licensed for sale in that market. In such cases, a company may opt to manufacture in the country, even if the costs are *higher*, if projected profits from entering this new market will exceed the initial investment. In such scenarios, being first-to-market may be crucial for market capture and building trust with local suppliers and health providers. These politically-motivated decisions carry their risks, however, as a government may change the regulations and leave manufacturers saddled with a huge capital investment that no longer makes economic sense. For

example, Puerto Rico's tax incentives that led to a booming pharmaceutical industry were overturned when the US passed a bill that phased out subsidies in 2005[39].

- **Infrastructure:** Biomanufacturing processes require highly consistent and reliable infrastructure, such as a supply of clean water and utilities. The availability and cost of such infrastructure is an important consideration when thinking about distributing manufacturing across multiple sites. Transitioning from a centralized to a more distributed model may be difficult if the company is bound to physical sites as a result of previous investments in large, steel-based plants.

- **Knowledge / Tech transfer**: Companies may face challenges related to knowledge transfer in a distributed model, especially in politically volatile contexts. Co-locating manufacturing processes with R&D can facilitate transfer and cost-savings in a way that a distributed model cannot. Also, because biologic products are often tightly linked to their processes, the manufacturing method must be well validated and verified. Companies may also be wary of transferring technologies into new markets because it may involve sharing proprietary technology (such as host cell lines), company secrets, or other knowledge to expand market access.

- **Risk diversification:** A motivation for companies to set up decentralized production is to diversify risks. If one plant breaks down, another plant would be able to fill the gap, assuming that second plant is able to meet the demand and that it has been approved to do so from a regulatory standpoint. However, in a truly distributed model - where each site can only supply its local market - having multiple plants does not necessarily mitigate this risk, as the other plants may not have the capacity to supply beyond their designated regional coverage.

- **Local economy:** Likely not of primary concern to a manufacturer, establishing manufacturing capacity can have significant positive externalities on a local economy. It creates jobs, offers training opportunities, and facilitates the transfer of knowledge and technology for local capacity building of the biopharmaceutical industry, as well as providing patients with closer access to potentially life-saving therapeutics. From the perspectives of the country, governments are increasingly passing policies that mandate in-country production for in-country marketing in order to promote local economic growth, or providing subsidies to incentivize company's to operate plants within their borders.

- **Other local risks**: Manufacturing in non-traditional regions can come with a wide range of risks to the manufacturer, including intellectual property or equipment theft, corruption, political volatility and violence, cultural or ethical differences, natural disasters, and disruptions of supply chains.

[39] Puerto Rico Tax Credits Phasing Out
http://www.thepharmaletter.com/article/puerto-rico-tax-credits-phasing-out

V. TECHNOLOGY & POLICY FORESIGHT

Analysis of shifts in cost centers for the manufacturing and supply of biologics when switching from a centralized to distributed manufacturing model provides insights into the considerations taken for decision making. A centralized system is more cost-effective under the current state of the industry. Given that pharmaceutical business models are driven primarily by volume, gains from economies of scale are most evident in the centralized model. The following discussion highlights incentives unique to certain local contexts that may make distributed models more appealing, especially when both subsidies and expanded market access are provided. To better predict future levers that may influence global biologics supply, there is value in also reviewing the dynamic innovation space and rapidly changing policy landscape for biologics.

With increased demand and pharmaceutical competition, there is accelerated investment in innovations across the manufacturing process in order to improve efficiency, enable increased flexibility in production systems, and lower costs while still maintaining quality[40]. Increasing scale and supply to more markets will also require improved coordination and capacity between manufacturing plants, CMOs, suppliers, and distributors in order to meet demand and maintain high customer approval.

Below is a list of opportunities in technology and policy that have the potential to shift levers influencing tradeoffs between centralized and distributed models:

- Increasing efficiency across manufacturing - lower resource use, less energy/waste, maximize capacity utilization
- Improved production processes - alternate host organisms, reducing purification steps
- Innovative manufacturing systems - single use technology, continuous manufacturing, modular designs, automation/digitization
- Improved product – temperature stability, improved shelf-life, increased potency
- Regulation - harmonizing regulatory standards across jurisdictions and facilitating process changes over multiple sites, ensuring quality
- Technology transfer - nationalization (in-country, for country), risks, IP rights

Furthermore, we present in this paper a preliminary, qualitative model assessing manufacturing capacity required to meet total product demand in order to determine which manufacturing and supply chain designs would lead to shared value for both patients and producers.

Future of distributed models

Most of the discussion above is in the context of current approaches to biomanufacturing – capital-and labor-intensive and depending on economies of scale to make profitable returns on investment. However, emerging technologies may disrupt this paradigm entirely and change the economics of distributed models. It is important to note, however, that many of the innovations

[40] Advanced Biopharmaceutical Manufacturing: An Evolution Underway, Deloitte. https://www2.deloitte.com/content/dam/Deloitte/us/Documents/life-sciences-health-care/us-lshc-advanced-biopharmaceutical-manufacturing-white-paper-051515.pdf

discussed may benefit both centralized and distributed manufacturing approaches, thus requiring further analysis as to whether they actually shift the balance away from the current system. A few examples, as illustrated above, have the potential to act as key drivers to overcome barriers to distributed manufacturing models:

- **Disposable, single-use systems**: Single-use systems have become especially popular for multi-product facilities, as it reduces the time lag between batches and between products, while also reducing consumption of utilities (e.g. water, energy)[41,42]. In these systems, time is saved by skipping cleaning and quality validation steps before initiating the next biomanufacturing campaign, thus also reducing risk of contamination. An analytical study done by BPTC for a typical facility show a 25% lower capital expense for single-use facilities compared to stainless-steel, as well a 23% decrease in the cost per gram of mAb manufactured[43].

- **Small-scale, closed systems**: Companies like Just Therapeutics are innovating biomanufacturing "pods" that could efficiently produce low volumes of product in a closed system. These types of pods could potentially be highly-automated with low-labor requirements – they would be built in the US and then deployed around the world, where they would require almost nothing but water and electricity. Such a model turns the existing capital-intensive model on its head.

- **Standardized modular facilities**: Flexible, modular facilities increase flexibility within biomanufacturing plants by allowing for rapid configuration of facilities in order to more adequately respond to changes in market demand[44]. It allows for optimal capacity utilization by building in options for scaling-out and allowing for parallel processes to take place. For prefabricated modular plants, construction is outsourced to trusted contractors, such as GE's Kubio, for quality assurance and standardization, while assembly take places at the final site. These have shown to reduce the time from plant design to production to about 18 months, compared to approximately 3 years for a traditional plan[45]. On average, energy costs decrease by 15%, waste and environmental footprint is reduced, and capital investment decreases by 25%. As countries in emerging markets increasingly adopt "in-country, for-country" policies, lower-risk flexible modular facilities can incentivize production through distributed models to meet local demand. For biologics with lower-volume demands, modular flexible facilities appear to be more

[41] Single-Use Systems: Enabling the Future of Biologics Manufacturing, Pharmtech, 2014 http://www.pharmtech.com/single-use-systems-enabling-future-biologics-manufacturing

[42] Efficient, Flexible Facilities for the 21st Century, BioProcess International, 2012. http://www.bioprocessintl.com/manufacturing/facility-design-engineering/efficient-flexible-facilities-for-the-21st-century-337813/

[43] Economics of Modular Facility Design and Construction, BioProcess Technology Consultants, 2014 http://www.bptc.com/sites/default/files/presentations/levine_hl-economics_of_modular_facility_design_and_construction-rprint_0.pdf

[44] New Directions in Modular Manufacturing, Pharmtech, 2016 http://www.pharmtech.com/new-directions-modular-manufacturing

[45] KUBio Manufacturing Facility http://bioprocess.gelifesciences.com/enterprise-solutions/kubio-biomanufacturing-facility/

cost-effective, while the economies of scale of centralized facilities are likely to dominate in the case of high-volume products.

- **Targeted therapies:** The incentives and risks associated with the distributed model may be influenced by the type of product. Some therapies, such as gene therapy and CAR-T cell therapies, have hours-long shelf-life that requires close proximity to patients, making distributed models the only option in the current state of industry to reasonably make such therapies accessible. While a distributed model may be the only viable option, global supply may not be the foremost priority as they are still very resource-intensive, expensive, and address needs of a small proportion of patients.

- **Regulatory Harmonization**: Efforts to streamline regulatory requirements and standards across different contexts, such as ICH Q12[46] and the WHO Prequalification Program[47], can reduce costs and time for ensuring compliance, as well as ease supply to new markets. This may also speed up approval of process changes in manufacturing, which can currently take several years, when seeking to integrate improvements that will lead to increased productivity.

VI. CONCLUSION

The shift in disease burden from infectious to chronic diseases, with disproportionate impact on LMICs, puts pressures on the need for adaptation within the biopharmaceutical industry to better supply biologics to patients who need them. Furthermore, highly priced biologics have been a major source impeding many people, including within the US and EU, from accessing life-saving-or-extending therapies. In order to address the rising demand for biologics, as well as competitively position biopharmaceutical companies in emerging markets, the current practice will have to change in some fundamental ways.

In this paper, we focus on the biomanufacturing and supply chain components of the biologics value-chain, as one area where disruptive changes have the potential to lower costs in efforts to increase global supply of biologics. Outlining the distribution and scale of cost centers provides a baseline understanding of the complex systems underlying the production and supply within a centralized model. Qualitative analysis of the changes in costs centers imposed by a shift to more distributed models also provides insights on the incentives and risk that may emerge from this newer approach. Recognizing the extent to which biologics value-chains are deeply embedded in local context, we provide a discussion on financial and non-financial drivers and barriers that arise in distributed models, as well as different ways in which innovative technologies and policies can shift the risk-benefit analysis.

Improving technical and operational capabilities is becoming increasingly important, with each company developing strategic plans to meet growing demand by expanding capacity while keeping prices low, quality high, and supply chains reliable. Even more importantly, decisions

[46] Final Concept Paper Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management, ICH Steering Committee, 9 September 2014
[47] WHO Prequalification Programme, Fact sheet N°278, http://www.who.int/mediacentre/factsheets/fs278/en/

made today on expanding capabilities to meet future demand and gain competitive positions in emerging markets will have profound effects on success in the future, outweighing short-term competitive advantages.

These trends will fundamentally reshape the industry. The changes will not be the same for everyone, as multiple successful models across the centralized-distributed spectrum are bound to arise due to different company goals, corporate cultures, market demands, and success factors. In order to expand global access to biologics, while keeping costs low, new avenues need to be explored in order to close the growing gap between demand and supply, especially through strategies that create shared value for all stakeholders.

Approaching such a complex problem will require iterative analysis informed by insights from different vantage points, from producers to patients, in order to address barriers to global access across the system. Another consideration, which goes beyond the scope of this paper, is the extent to which reduction in costs lead to increased access. Understanding the pricing of biologics is complex and difficult to generalize across contexts, while access is influenced by a host of other factors, beyond just supply to providers, such as the ability for patients to access products, cultural stigmas, and other social, political, economic, and environmental factors. Investments in technologies and policies that will decrease costs will likely not lead to linear reductions in price or subsequent linear improvements in access. Therefore, better understanding the dynamics between cost, price, supply, and access is important to apply the findings in this paper into practical, real-world impact.

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APPENDIX - FIGURES

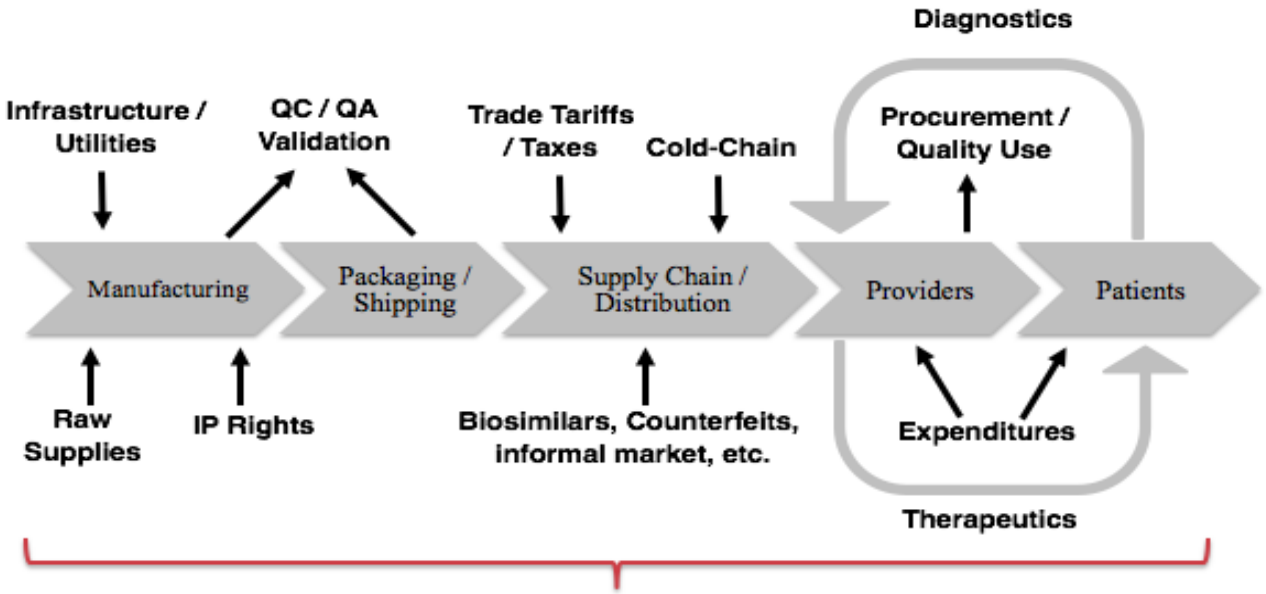

Figure 1: Mapping potential barriers to biologics supply across the value-chain of biomanufacturing, supply, distribution, and patient access.

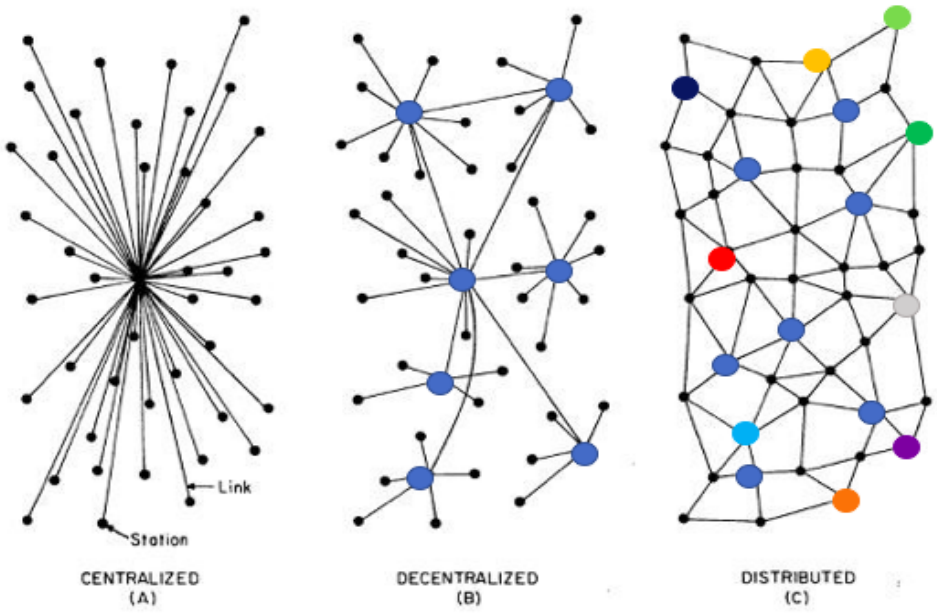

Figure 2: Representation of networks along the centralized-distributed spectrum of biomanufacturing and supply. Adaptation of Paul Baran's On Distributed Communication Networks, RAND Corporation, 1964.

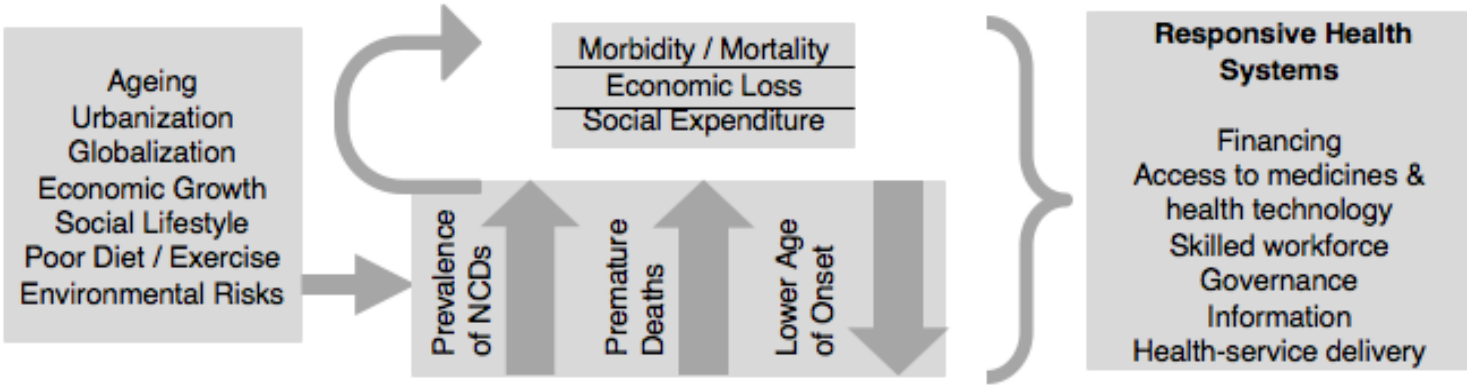

Figure 3: Factors driving changes in global health disease prevalence and requirements for responsive health systems, as described by the WHO Health Systems Framework.

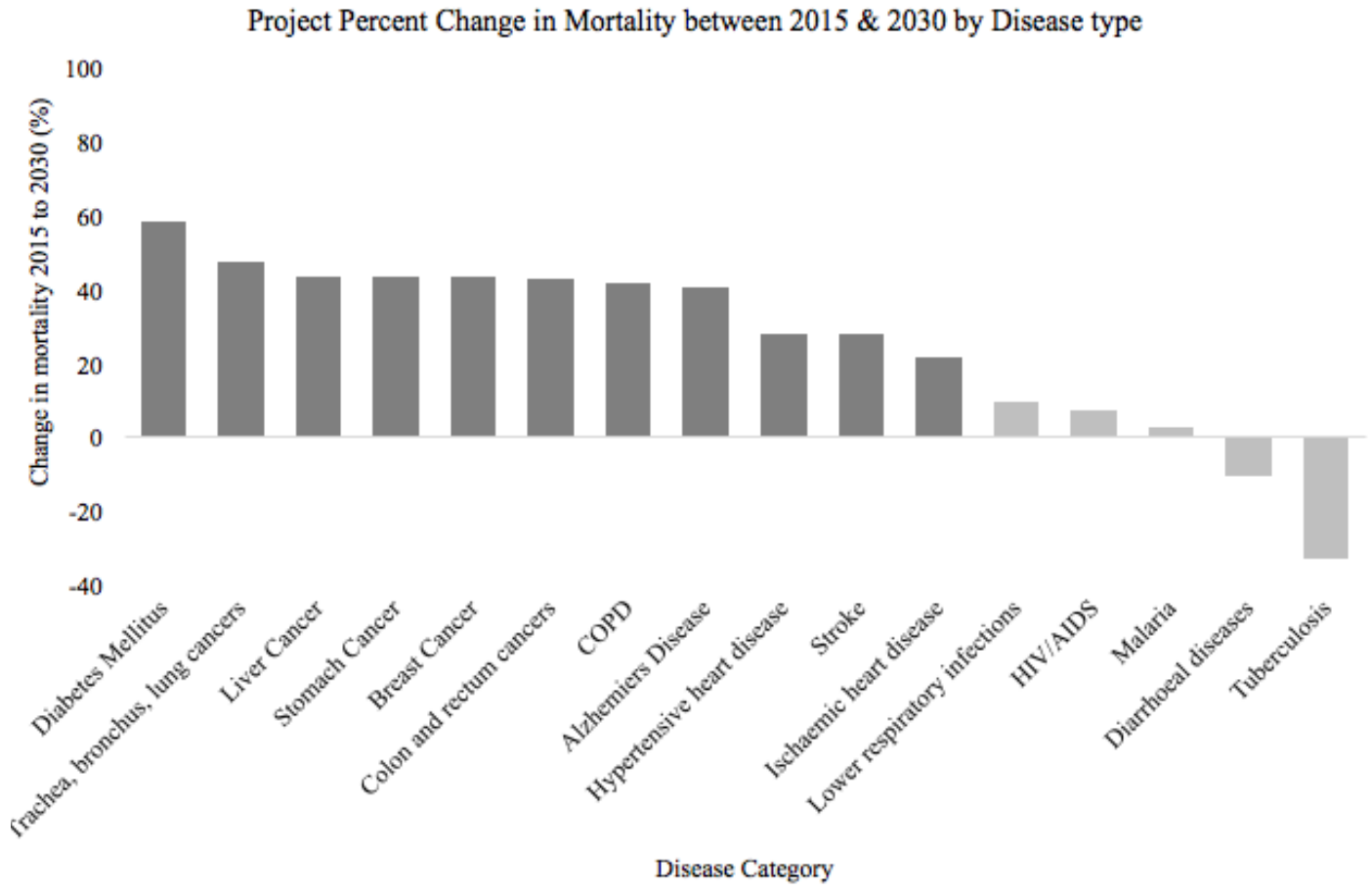

Figure 4: Projected percent change in burden (mortality) for chronic non-communicable diseases (dark grey) and infectious diseases (light grey) from 2015 to 2030, for top

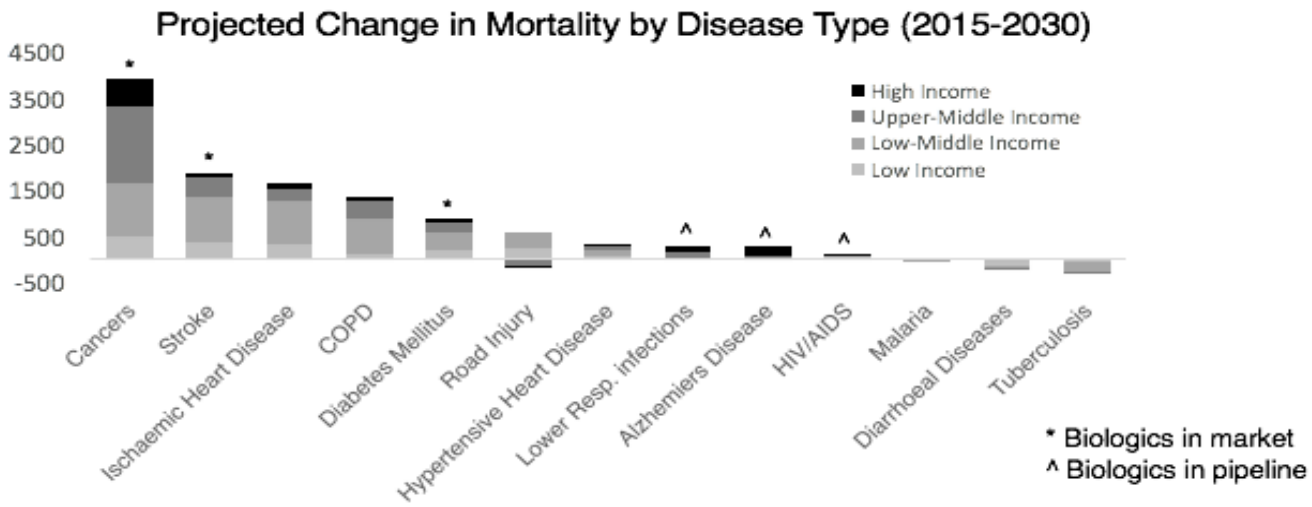

Figure 5: Projected change in mortality from 2015-2030, disaggregated by disease and income group (data derived from WHO Global Health Observatory).

Disease	**Biologic Therapies**	**Non-Biologic Therapies**	**Comments**
Stroke / Ischemic Heart Disease	Tissue plasminogen activator (tPaA)	Surgery	Mostly dominated by preventive medications & surgical procedures
Diabetes	Insulin (all type I, some type II)	Glucose-reducing medications kidney/pancreas transplant	Multiple types of insulin products Other costs such as glucose testing.
Cancers	Immunotherapy (MAb, cytokines, CAR-T, vaccines), stem cell transplant	Radiation Chemotherapy Surgery	Classification of tumors and orphan drug designations
COPD	Aerosolized biologics	Bronchodilator O2 therapy Steroids	
Arthritis	Biologics / biosimilar (e.g. tocilizumab, infliximab)		
Blood disorders (e.g. hemophilia)	Only option	n/a	Blood is a biologic product, no synthetic options

Table 1: Biologics and non-biologic therapeutic options for different major disease indications.

Effects of adopting a de-centralized model compared to traditional centralized system:

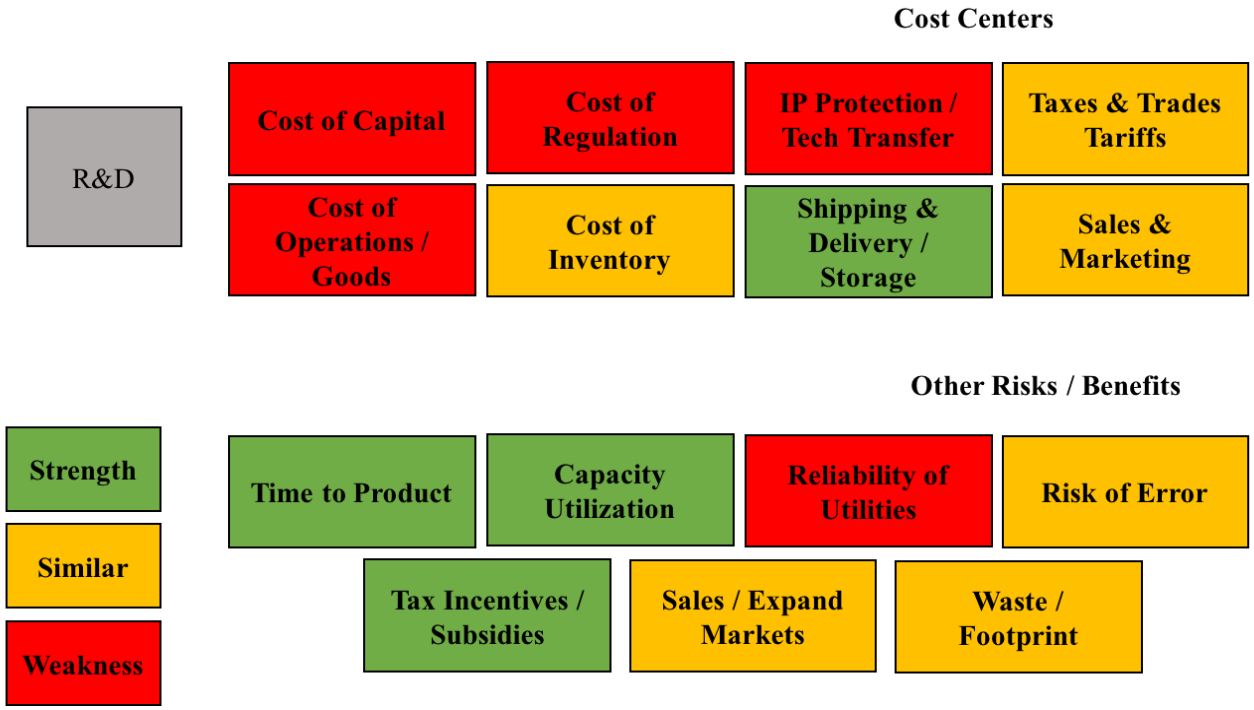

Figure 6: Expected change in cost centers and other non-cost variables when comparing a centralized model with a decentralized system, each producing the same total product volume.

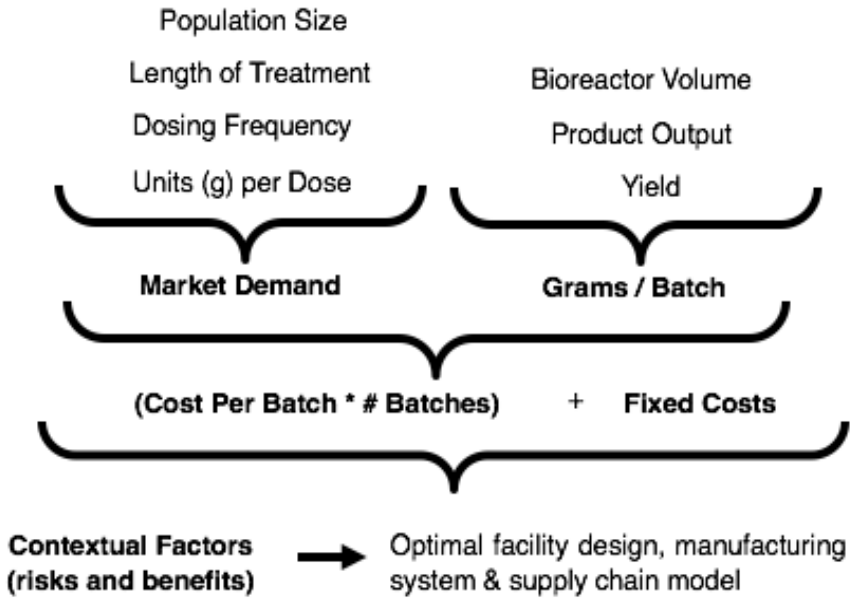

Figure 7: Qualitative framework for designing manufacturing and supply models that minimize costs and meet total demand.