Closing Gaps in Global Access to Biologic Medicines: Building Tools to Evaluate Innovations in Biomanufacturing

by

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ABSTRACT

Low-and-Middle Income Countries (LMICs) are experiencing a growing need for safe, effective, and affordable health services, especially medicines. Such trends are in part due to a continued epidemiologic transition from infectious to chronic, non-communicable diseases (NCDs). Today, NCDs account for a large portion of total global disease burden: 70% of deaths as per the World Health Organization (WHO). NCDs are projected to continue to undercut economic productivity and drive up health spending. Many NCDs are effectively treated using biologic therapies; or large molecules produced by, or involving, living cells. Recently, some of these therapies have been included on the WHO Model List of Essential Medicines. However, the molecular, manufacturing, regulatory, and supply chain features of biologics lead to relatively higher costs and complexity compared to small-molecule drugs, with implications on widespread access. As part of the Global Action Plan for the Prevention and Control of NCDs 2013-2020, an 80% target for global availability of affordable essential medicines has been set for all public and private providers. In order to reach this target, there is need to better understand the complex barriers to accessing biologics across the biopharmaceutical value chain.

Current gaps in access indicate the potential need to re-orient the biopharmaceutical system in order to meet future projected healthcare demand in terms of quantity, quality, and affordability. There is also growing uncertainty within the biopharmaceutical ecosystem as to the best use of resources, design of policies, and development of technologies that will have the most cost-effective impact on maximizing the supply of and access to such biologics. This research specifically focuses on the manufacturing component of biologics access, providing an analysis of the benefits and risks across different production networks, with varying number and location of facilities. A cost modeling tool is presented for quantitatively analyzing different manufacturing design options. This is accomplished by comparing the cost of good (COGs) and net present cost (NPC) of different scenarios, using Trastuzumab (a monoclonal antibody drug used to treat HER-2+ breast cancer) as a case study. Finally, future research questions are presented, aimed at better understanding the drivers of variability in manufacturing cost across manufacturing networks, especially when considering differences in product type, locations, regulatory jurisdictions, geopolitical zones, and sociocultural norms.

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In light of changing global health patterns and increasing demand for quality, affordable care, the thesis presents tools that can be generalized for addressing tradeoffs, short-and-long term effects, and intended-and-unintended consequences of investments in global health. It holds the potential for assessing the potential impact of various innovations (policies, technologies, organizational structures and more) on complex, dynamic systems and provide an evidence-base to better inform future areas of research, design of policies, and development of technologies.

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While these small messages do not do justice to the immense support received, I hope they indicate my appreciation and the diversity of resources I had at my disposal in making the thesis a reality. I am eager to delve more deeply into these complex questions and push the boundaries of our current understanding, with the aim of benefitting society by translating knowledge into innovation and eventually real-world impact.

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Overview

Background

The global health landscape is experiencing rapid change, with an epidemiological transition from infectious to chronic, non-communicable diseases (NCDs). NCDs account for approximately 70% of deaths worldwide, 75% of which occur in low-middle income countries (LMICs). Of these, 40% are considered to be "premature", preventable deaths that occur before the age of 70. 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. Leading treatments for many of these chronic diseases are biotherapeutics, with promising clinical outcomes but complex manufacturing, regulatory and supply systems that jeopardize widespread access. This raises questions as to whether the current biopharmaceutical ecosystem is fit-for-purpose and whether health system capacities will be able to meet future projected healthcare needs in terms of quantity, quality, and affordability.

There is uncertainty within the biopharmaceutical ecosystem as to the best use of resources, design of policies, and development of technologies that will have the most cost-effective impact on maximizing the supply of, and access to, such biotherapeutics, especially in LMICs. Evidence-informed tools for addressing tradeoffs, short-and-long term effects, and intended-and-unintended consequences of investments are lacking. In light of growing disease burden, along with a shift towards personalized care and shrinking resources, a decision support tool is presented to inform stakeholders about the influence that innovations (policies, technologies, organizational structures and more) have on the biopharmaceutical ecosystem. This is done through both quantitative and qualitative analysis of economic and other contextual factors.

Central Question

To date, both the manufacturing of and market for biologics has been heavily concentrated in the US, Western Europe, and Japan. Identifying barriers and increasing understanding of this complex system is an important first step towards closing gaps in access to the growing demand for lifesaving therapeutic treatments. This will then allow diverse stakeholders within the biopharmaceutical ecosystem to identify levers most conducive to change and design innovations around them. Access to medicines requires alignment between the sustained supply of high-

quality, safe, and efficacious products and patient demand driven by disease identification and care-seeking behavior. Barriers to the reliable supply of biotherapeutics exist throughout the entire product value chain: drug discovery, clinical development, manufacturing, distribution and global delivery, marketing and reimbursement policy, drug use, and clinical care. Additional barriers arise from the unique economic, regulatory, political, social, and cultural environment of individual local markets. The extent to which these factors influence access vary greatly over context, geographies, and products. The thesis focuses on the upstream component of the value-chain, specifically decision making when considering different manufacturing designs for a particular biologic product.

Historically, the biopharmaceutical industry has concentrated manufacturing of biologic products to several geographic locations, largely in developed countries. This can partly be explained by the opportunities provided by economies of scale to make up for the large capital investment cost required in stainless-steel plants. Manufacturers have also sought to locate these sites in settings that provide conducive economic and regulatory environments, for example through tax breaks and subsidies. More recently, there has been increased interest in establishing manufacturing sites in multiple locations at a time, to lower risk of supply chain interruptions, as well as in frontier markets. This is driven by a host of other factors, such as increased nationalization policies (mandates that require in-country manufacturing to sell in the national market), potential for expansion into emerging markets, national strategies for reducing risks of drug shortages by reducing dependence on external imports, and economic benefits from investing in a local biomanufacturing industry.

The thesis seeks to compare the cost-effectiveness of different manufacturing networks across the spectrum of centralized and distributed models. Analysis of different manufacturing designs is done by comparing the cost of good (COGs) and net present cost (NPC) of different scenarios, using Herceptin (a monoclonal antibody drug used to treat HER-2+ breast cancer) as a case study. A qualitative overview of both cost and non-cost factors is presented to better understand the potential benefits and risks that might emerge when transitioning from a centralized to a distributed manufacturing network. Finally, the thesis points to future research questions aimed at better understanding the drivers of variability in cost-effectiveness across manufacturing networks, especially when considering differences in product type, locations, regulatory jurisdictions, geopolitical zones, and sociocultural norms.

End-to-end solutions across health systems, coordinated among all relevant stakeholders, will be key to overcoming future biologic shortages and closing the widening gap between supply and demand of life-saving or life-extending biotherapeutics. Therefore, better understanding the biopharmaceutical ecosystem is key to generating technically-informed policy options and orienting technological development in ways that will allow decisions makers to more comprehensively assess the impact of different manufacturing models on access.

Methods

Conduct qualitative interviews with experts from the biopharmaceutical industry and global health field, including leaders from multinational companies, start-ups, regulatory agencies, academia and non-profit foundations to determine major cost centers in the value chain of biologics, especially manufacturing and supply chain. Interview questions were designed with a group of advisors, along with preparatory material to help guide the discussion with interviewees. These interviewees were also engaged in verifying the quantitative models that emerged from the research.

Develop a qualitative operations framework for mapping the drivers and barriers to global biologics access, as well as primary costs centers that are most influential in decision making. This was developed as a result of the interviews conducted, national level data (e.g. WHO and World Bank) on prevalence of disease and indicators for medicines access (e.g. imports, financial budgets, shortages, etc.), and extensive literature review. The framework borrows from the WHO Health Systems Building Blocks and other established models used in process manufacturing, supply chain, service delivery, national innovation systems, and public health.

Develop a quantitative economic model to determine the most optimal manufacturing and supply chain design that meet global demand for a given biotherapeutic product, while maintaining high-quality and cost-effectiveness. This will be accomplished in the following steps:
- Developing a baseline, deterministic cost model for the manufacturing of monoclonal antibodies in both stainless steel and disposable systems;
- Performing sensitivity analysis to identify key cost drivers;
- Using probabilistic, Monte Carlo simulation for risk and uncertainty analysis;

- Multi-criteria comparison of manufacturing designs based on cost, product volume, and other variables of interest, as well as technology and policy implications considering a range of social, economic, political, institutional, and environmental factors.

Summary

Chapter 1 starts by presenting trends in global health, outlining the reasons for and demonstrating the behavior of the shift from infectious to chronic diseases, especially in LMICs. It goes further to introduce the role of biologics for various chronic diseases and their unique attributes that make widespread access a challenge. Finally, it focuses the scope of the research to the manufacturing of biologics, a key component to ensuring its sustained supply.

Chapter 2 presents design options faced by biopharmaceutical companies when deciding how to produce a given biologic product. It highlights key differences that can arise across the spectrum from centralized to distributed manufacturing, as well as outlines a qualitative model for calculating the cost of goods (COGs).

Chapter 3 presents a quantitative model for estimating the COGs for the production of monoclonal antibodies, specifying the input variables for each of the cost centers, as well as sensitivity and uncertainty to demonstrate the model's ability to reflect real world and user-specified conditions.

Chapter 4 begins with qualitative analysis of cost and non-cost risks and benefits of shifting from centralized manufacturing (producing total drug volume in one large, stainless steel facility) to a distributed network (producing drugs across 6 facilities, one in each WHO region, with small single-use, disposable bioreactors). The second part of chapter 4 uses Trastuzumab, an effective therapy for HER-2+ breast cancer, as a case study to compare the COGs and net present cost (NPC) for 84 manufacturing scenarios, ranging in location and levels of distribution.

Chapter 5 introduces the importance of incorporating exogenous variables, which may give more insight into the risks that can arise across locations with unique social, economic, and environmental conditions. It also provides a discussion of the results and future potential research directions.

Chapter 1: Introduction

1.1 Trends in Global Health

1.1.1 Changing Global Health Landscape

The health of a country is influenced by population dynamics and is a consequence of social welfare, economic development, environmental factors, and underlying genetic predispositions [1]. Rather than viewing disease in isolation, long-term shifts in mortality and disease patterns reveal that with socioeconomic development, pandemic infections are replaced by chronic, non-communicable and other degenerative diseases [2].

The epidemiologic transition from infectious to chronic, non-communicable diseases (NCDs) is expected to continue due to several complex and interconnected factors [3]. A demographic transition is taking shape, driven by decreasing birth rates and increasing life expectancy. This results in shifting the share of diseases to chronic conditions, such as those associated with older age [4,5]. Development trends accelerated by economic growth coincide with increasing urbanization, changing lifestyles (e.g. food consumption patterns, sedentary behavior, and risks factors such as smoking and alcohol use), and growing purchasing power that leads to increasing expenditure on healthcare [6,7]. Anthropogenic climate change also serves as a signal of unsustainable natural resource extraction, pollution, release of toxic chemicals, and other environmental risks that are exacerbating the shift to NCDs, especially cardiovascular and respiratory conditions [8].

The US, Europe, and Japan were among the first to experience the epidemiologic transition described above. The shift to chronic diseases continues to rise, already accounting for 90% of deaths each year in the US [9]. These trends are starting to take form in low-and-middle countries (LMICs) as well, further imposing pressures on already fragile health systems.

Today, more than 70% of deaths globally are due to NCDs, with LMICs bearing disproportionally higher burden of both infectious and non-communicable chronic diseases [10] This is partly a result of disparities between LMICs and higher-income countries in access to prevention, diagnosis, and care [11] It can also be explained by competing development-related priorities and less stable economic, environmental, political, and social conditions in LMICs [12]. The increase

in mortality due to NCDs is not just higher in LMICs. A disproportionate number of premature (preventable or occurring under the age of 70) NCD-related deaths, are concentrated in these regions [10]

Data from the World Health Organization (WHO) on mortality projections for 2015 and 2030 for LMICs and high-income countries were analyzed to measure disease rates [13]. **Figure 1.1** presents projected changes in mortality disaggregated by cause (infectious or chronic disease) and stratified across World Bank income groups based on gross national income per capita (low-and-middle and high) between 2000 and 2030. During this time, the share of deaths attributed to NCDs in LMICs is projected to substantially increase from 55% in 2000 to 71% in 2030. Data on the rate of change in the total and per capita number of deaths indicate that shifts towards NCDs are expected to concentrate in LMICs, while the number of infectious disease-related deaths will decrease.
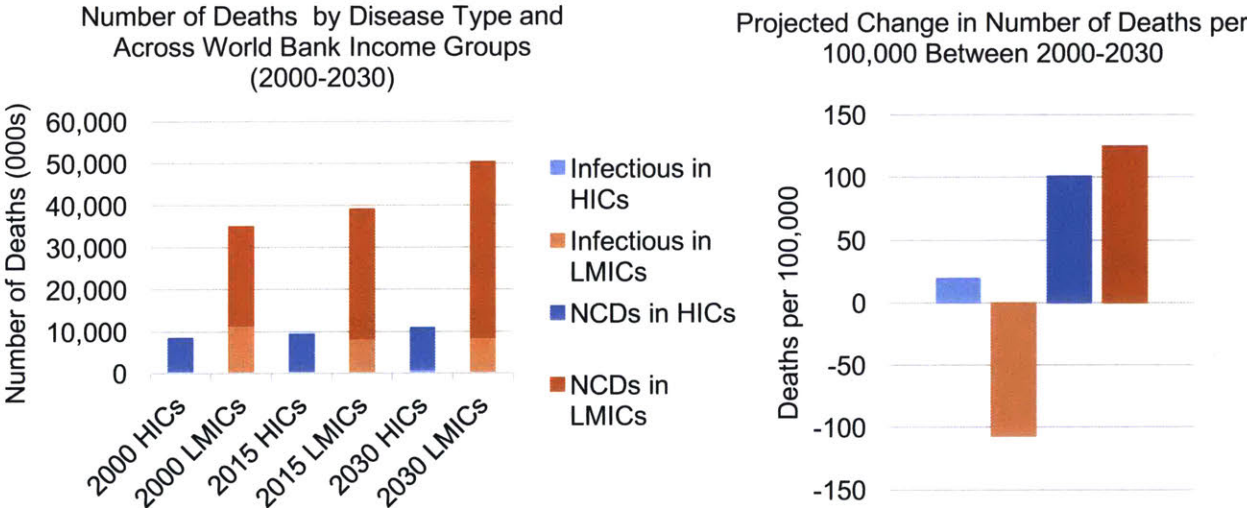
Figure 1.1: Projected change in mortality from 2000-2030, disaggregated by disease type and income group (data derived from WHO Global Health Observatory)

1.1.2 Effects of the Changing Epidemiology

NCDs are a major contributor to social and economic loss, due to both health care cost and reduction in economic productivity. These losses are estimated to total over 7 trillion USD between 2011-2025 in LMICs alone [14]. This has also placed political pressure on different stakeholders to take action to improve health care: governments to provide universal health care (UHC), philanthropy to finance healthcare access programs, pharmaceutical companies to make

life-extending and life-saving medicines more affordable, and patient groups to advocate for the human right to health.

While NCDs become more pervasive in LMICs, infectious pandemics (e.g. Ebola, Zika) continue to be a threat and lead to a double-burden on health systems. This situation is further complicated by the rise of antimicrobial resistance diminishing the effectiveness of once-potent medicines and the chronic nature of many infectious diseases that require life-long management. The chronicity and slow progression of disease can exacerbate costs to both patients and health systems. Given the evolving epidemiology in LMICs, current systems focused on acute, reactive, and episodic care may have difficulty shifting to chronic care models [15]. Innovation will play an important role in attaining the triple aim of access to care, quality of services, and cost-effectiveness of treatment for both patients and the healthcare system [16].

1.1.3 Double Burden of Disease and Global Health Financing

As NCDs continue to increase in LMICs, infectious conditions will still need to be addressed, while the risk of re-emerging epidemics remains. Overcoming the double burden of infectious diseases and NCDs remains a challenge, as health budgets and donor funding continue to be channeled into vertical, disease-specific programs that influence research, policy, and development agendas. Of the $37.4 billion of development assistance for health (DAH) provided to LMICs in 2017, close to 40% was allocated to infectious diseases (primarily HIV, Malaria, and TB), 30% went to maternal, newborn and child health, while less than 3% was allocated for NCDs [17]. **Figures 1.2 and 1.3** map the year-to-year and cumulative DAH, respectively, according to disease area between 1990-2017. Looking holistically at health systems, and recognizing the interdependent nature of risk factors for IDs and NCDs, there is a growing need to coordinate global health assistance and activities for maximum impact on global health and to avoid duplication or cross-purposing of efforts.

Source **Channel** **Health Focus Area**

Philanthropy $67.8 (excluding B&MGF)

B&MGF $29.0

Other Sources $68.5

Other Governments $122.4

Australia $8.7
Canada $14.3
France $21.9
Germany $25.3

United Kingdom $41.8

United States $194.3

Development banks $63.4b

NGOs & foundations $148.6b

Gates Foundation $19.9b

Global Fund $43.3b

Gavi $15.0b

UN agencies $92.5b

Other bilateral aid agencies $50.5b

European Commission $9.6b
Australia $4.6b
Canada $4.9b
France $9.4b
Germany $11.8b
United Kingdom $16.5b

United States $103.9b

HIV/AIDS $141.0

Malaria $27.2

Maternal, Newborn, & Child Health $173.8

NCDs $9.6
Other Infectious Diseases $24.6

Other $96.9

HSS/SWAps $81.3

Tuberculosis $17.5

Unallocable $22.1

Figure 1.2: Flows of development assistance for health (DAH) from source to channel to health focus area in Billions of USD, 1990–2017. Note: HSS = Health systems strengthening, SWAps = Sector-wide approaches, B&MGF = Bill and Melinda Gates Foundation. Source: *Financing Global Health Database 2017.*

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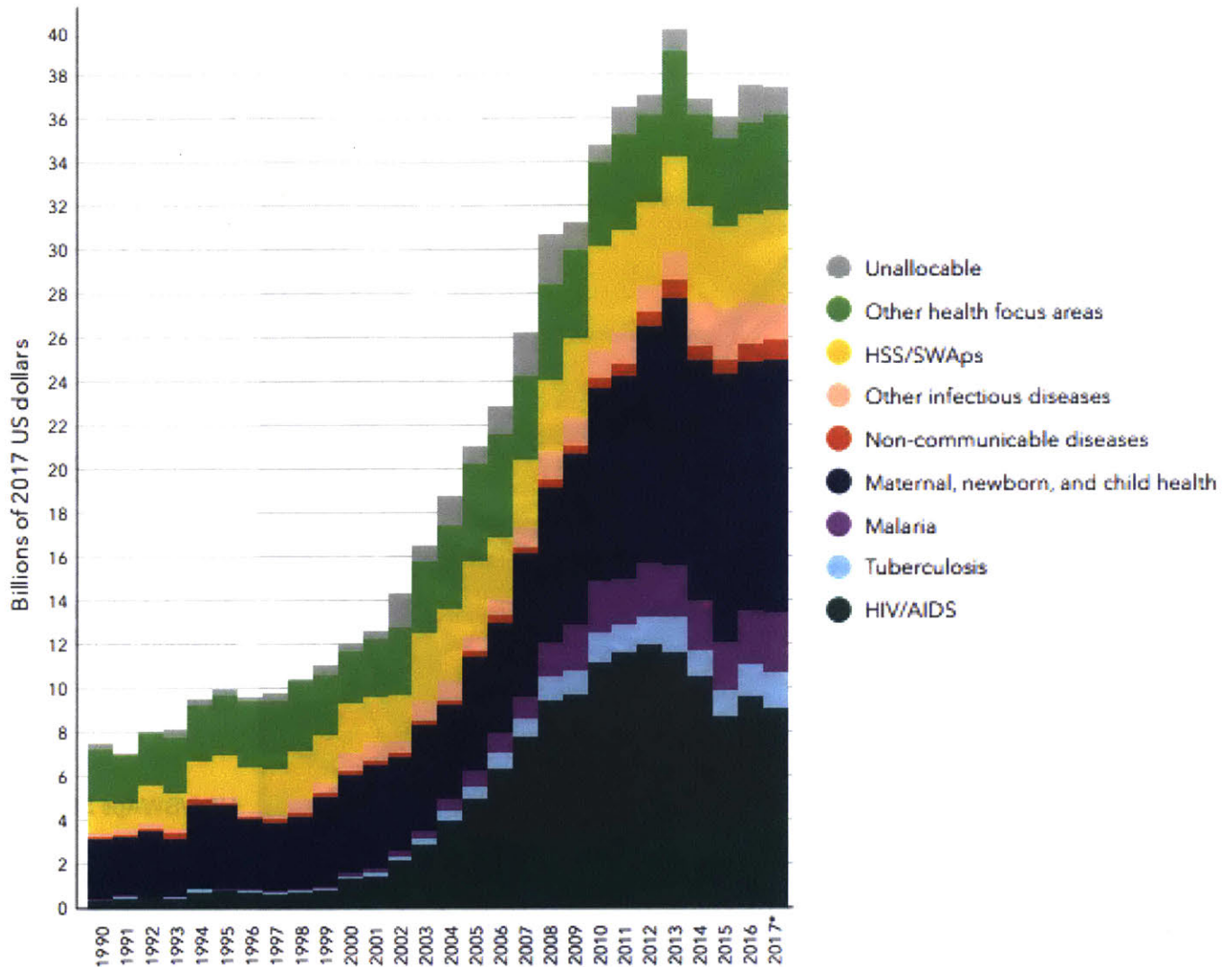
Figure 1.3: DAH by health focus area, cumulative 1990–2017. Note: HSS = Health systems strengthening, SWAps = Sector-wide approaches. Source: *Financing Global Health Database 2017.*

An integrated approach to health systems can help identify the overlaps and parallel activities present across the patient care continuum of prevention, diagnosis, treatment, and management. For example, ID and NCD patients may have similar challenges with compliance during disease management (e.g. diabetes and HIV/AIDS), making training and innovative technologies aimed at improving patient compliance potentially suitable for both. A challenge will be to re-design health care systems to incentivize system-wide improvements and coordination of activities. Health sector reforms that move away from siloed, disease-specific program to cross-sector system-wide investments are needed to enhance the impact of global health investment and build responsive health systems in light of rapidly changing demand [18].

Several synergies can be outlined between NCDs and infectious diseases:

Epidemiology: Both infectious diseases and NCDs have overlapping high-risk populations and risk factors such as rural-to urban migration and low socio-economic levels. Infectious agents have shown to trigger various cancers, most of which disproportionately impact LMICs (e.g. cervical cancer with human papillomavirus, liver cancer with hepatitis B/C viruses, gastric cancer with bacterium Helicobacter pylori, Kaposi's sarcoma with human herpes virus, and Burkitt lymphoma with Epstein–Barr virus, among others) [19]. Patients with NCDs also tend to be more susceptible to infections. For example, diabetics have an increase risk of contracting malaria and TB, while aggravating other chronic diseases like cardiovascular complications. Even though data is limited, the proportion of TB cases attributed to diabetes is 12.9% (250,000 cases) in India and 7.8% (100,000 cases) in China [20]. As the prevalence of diabetes is expected to rapidly increase, the proportion of diabetes-attributed TB cases is also expected to rise. People may have an increased risk of contracting either infectious or non-communicable disease due to changing environmental (e.g. pollution, water quality, air quality) and social (e.g. smoking, alcohol, physical inactivity) risk factors.

Disease management: Many infectious diseases (e.g. HIV) are becoming increasingly chronic in nature, requiring long-term management and care. Alternatively, some chronic diseases can leave patients with a relatively short life expectancy and duration of treatment. Complications such as diabetic ketoacidosis and myocardial infarction even require acute care. Improved surveillance systems to track prevalence of disease, especially of comorbidities between infections and NCDs in LMICs, can reduce preventable death. Prevention programs aimed at promoting healthy livelihoods addressing the full range of risk factors that give rise to diseases, as well as structural changes outside the health sector (e.g. urban planning, sanitation), would help reduce burden of all diseases.

Health service delivery: Opportunities for working at the interface of infectious and chronic diseases can be identified across the value chain- capacity building activities encouraging promotive behavior, prevention and primary care; task shifting for care delivery; digital technologies, telemedicine and other mobile health applications; patient stratification and triage; promoting patient empowerment; promoting conditions conducive to health financing for universal coverage; health technology assessments; rapid on-demand diagnostic tests; overcoming reliance on syringes; overcoming cold-chain and extending shelf-life of drugs; identifying

counterfeit or substandard drugs; last mile delivery of health services; effective forecasting, procurement, and inventory management systems [21, 22, 23].

Regulation: Regulatory capacity, establishing standards, and harmonization across jurisdictions; data quality and integrity; digitization (e-health) and interoperability of health information systems.

Looking more closely into WHO's mortality data, the epidemiological changes can further be characterized across time (2000-2015) and space (183 countries in the WHO database). Generally speaking, the proportion of deaths due to NCDs increases with time, while those attributed to infectious diseases decreases. This is consistent with the data presented in figure 1. Outliers can help draw links between the observed change and known social, economic, or environmental conditions within a country. For example, **Table 1.1** shows that the rate of infectious disease related deaths had the highest increase in South Africa between 2000-2005, with over 135,500 new cases. This can be attributed, in part, to the HIV/AIDS epidemic that peaked during that time. The unexpected increase in infectious disease-related deaths in Russia between 2010-2015 can be explained by the steep rise in the incidence of HIV in the late 1990s, as well as spread of an antimicrobial resistant strain of Tuberculosis [24].

	Infectious Diseases		Chronic Noncommunicable Diseases	
Year	**Largest Decrease**	**Largest Increase**	**Largest Decrease**	**Largest Increase**
2000-2005	India (-111) Ethiopia (-87)	South Africa (135) Mozambique (15)	Germany (-12) Georgia/Netherlands (-4)	India (421) China (385)
2005-2010	India (-319) Nigeria (-219)	North Korea (5) Germany (3)	Russia (-136) Ukraine (-39)	India (575) China (385)
2010-2015	India (-242) South Africa (-86)	Russia (9) Somalia (8)	Russia (-89) Ukraine (-41)	China (936) India (587)

Table 1.1: Countries with the largest increase and decrease in disease burden (1000s of deaths) for both infectious and chronic, non-communicable diseases between each of the following intervals: 2000-2005, 2005-2010, and 2010-2015.

The table also indicates steady and steep increase in NCDs burden for India and China, which is continuing today without indications of slowing down in the near future. As both countries become more industrialized, urbanized, and economically wealthy transportation and mobility systems are making people less physical active, food has become increasingly processed, and pollution is threatening long-term resilience of natural systems and health of individuals. Looking at country-

level changes in disease burden is informative in understanding the degree to which different factors influence population health outcomes.

1.2 WHO Health Systems Framework

1.2.1 Access-to-Medicines as a part of Health Systems

Many complex parts, both within and outside the health sector, interact in a dynamic way to influence health system performance. This makes such systems one of the most complex to understand and act on. In order to identify indicators and strategies for measuring impact, the WHO has developed a useful framework for better understanding the core components needed to achieve responsive and efficient health delivery, while ensuring social and financial risk protection [25]. Namely, the six health system "building blocks" are (i) service delivery, (ii) health workforce, (iii) health information systems, (iv) access to essential medicines, (v) financing, and (vi) leadership/governance. Other conceptual frameworks have outlined more complex relationships between market players (e.g. government, private sector, not-for-profit sector, informal networks, etc.) and across jurisdictions (e.g. global, regional, national, and sub-national).

Rational use of medicines can be understood as selecting an appropriate bundle of medicines that reflect a country's health situations. While standards are usually set at the national level, realities may be different across districts within a country or even across clinical sites. Rational use involves choosing the right medical products that are efficacious, safe, and cost-effective. To translate these principles into practice, the WHO has instituted and published essential medicines lists (EMLs) since 1977, serving as a basis for countries to develop their own national EMLs. These are updated regularly to reflect changing burden of disease and thus relative demand for different drugs. However, identifying a list of essential drugs does not guarantee affordable access, integrity of supply chains, or meeting patient needs. The price of drugs has a major influence on people's ability access to quality care, especially with out-of-pocket (or household income) expenditure accounting for a close to 40% of overall health spending in LMICs [26].

Recognizing the complex nature of medicines access, efforts have been made to embed it within the broader framework of health systems [27]. This allows for better understanding of the levers across the demand and supply side that are most influential to access and where they operate within the system. Several conceptual frameworks for access to medicines are worth noting. The WHO-MSH 2000 "Ferney-Voltaire" framework, building upon the work of Penchansky and

Thomas in the 1980s, focuses attention on barriers at the level of service-delivery by highlighting 4As (availability, accessibility, acceptability and affordability) with quality of products and services as a cross-cutting determinant. A later model developed in 2004 by WHO, the 'equitable access to essential medicines framework", focuses largely on the pharmaceutical and health sector level by highlighting four different dimensions in medicines access: rational selection, affordable prices, sustainable financing, and reliable health and supply systems. In 2010, Frost and Reich looked specifically at medicines access in low-income communities, developing a framework that focuses on a different set of 4As: architecture, availability, affordability, and adoption.

The framework presented by Bigdeli et. al (2012) seeks to move beyond the linear input-output representation of health services seen until now, rather using system thinking to design a more circular and dynamic model. This new approach gives more recognition to the unique social, political, and economic contexts in which health systems exist, as well as influence from policy actors across the spectrum, from local to international. Particularly, it emphasizes the role of governance in relation to market forces, innovation, transparency, and donor agendas. Rather than seeing medicines as just one building block, it makes medicines access dependent on all six WHO Building Blocks functioning. **Figure 1.4** links both drivers of the epidemiologic change from infectious to chronic disease and components for ensuring responsive health systems to link the discussions of health systems strengthening with changing trends in global health.
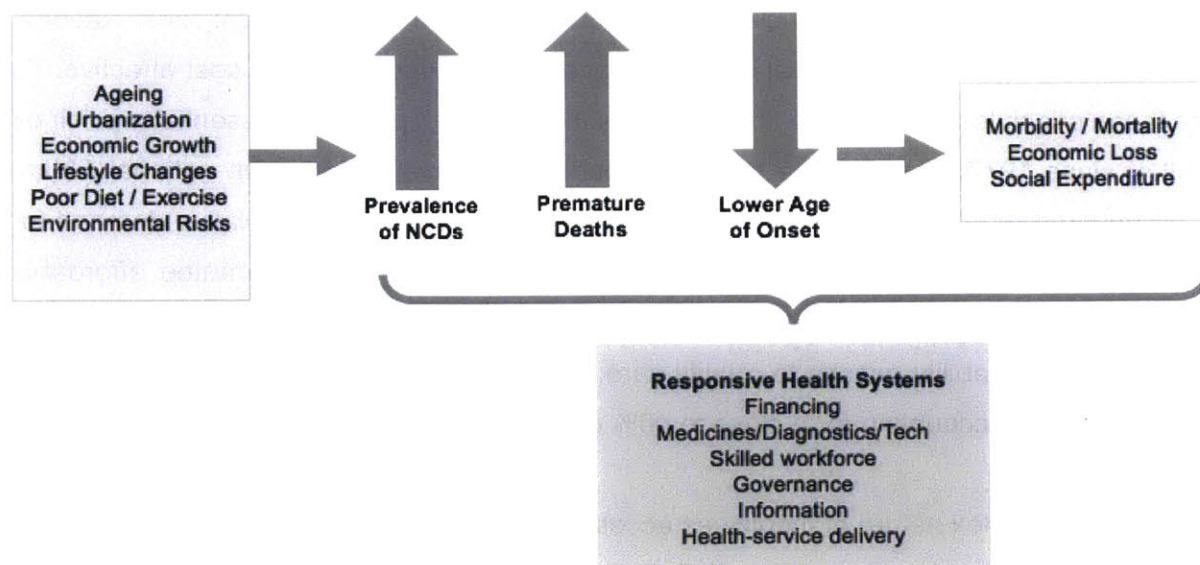
Figure 1.4: Factors affecting global health, their consequences, and building blocks of responsive health systems

1.2.2. Current Access Levels

A core component of any functioning health system is the timely access to safe, effective, and affordable medicines [28]. The access-to-medicines discussion is often part of the broader dialogue on the right to health and universal health coverage (UHC) [29]. The WHO Global Action Plan for the Prevention and Control of NCDs (2013-2020), a follow-up to commitments made in the 2011 General Assembly High Level Meeting on NCD prevention and control, has set an 80% minimum target for availability of affordable essential medicines in both public and private sectors of every country by 2025 [30]. A recent study, analyzing 2008-2015 data from across 30 LMICs on essential medicines to treat NCDs, showed that availability and affordability (less than one full day's wage for a 30-day supply of medicine) in public and private sector providers were, in many countries, below this 80% target [31]. For all countries, regardless of World Bank Income group, median availability of generic therapeutics did not exceed the minimum target for any of the four disease groups (cardiovascular, diabetes, COPD, and CNS) in the public sector, while only cardiovascular medicines reached availability targets in the private sector. None of the measures of median availability of originator brands passed the published targets. Affordability of in-stock medicines were also below targets. In order to provide safe and effective treatments to those who need it, additional challenges within the biopharmaceutical and healthcare ecosystem need to be overcome in order to adequately supply biologics.

1.3 Biopharmaceutical Industry

1.3.1 Small Molecules vs. Biologic Therapies

The above access challenges are particularly difficult with respect to biologic medicines, or "biologics". Biologics are a subset of pharmaceutical drugs that use biologic systems (e.g. microorganisms, animal cells, plant cells, tissues, or enzymes) to produce therapeutics [32]. Historically, the biologics market has been concentrated in the US, Europe, and Japan, though it is growing in other countries. Over the past few decades, platforms have evolved to allow for numerous products, including vaccines, proteins, and cellular and gene therapies. Compared to small molecule drugs, biologic products are more chemically complex, have very large molecular weight, and are comprised of heterogeneous structures as a result of unique post-translational modifications [33]. **Table 1.2** highlights the primary differences between properties of small molecule drugs compared to biologic medicines. These molecular properties, along with distinct R&D, intellectual property, manufacturing, supply chain, and market features, lead to challenges

in ensuring the sustained supply of biotherapeutics. If these challenges are not explicitly addressed, the WHO essential medicine targets may not be reached.

Essential biologic medicines can be used as primary therapeutics or as adjuvants to small-molecule drugs for management or treatment of NCDs. Biologics are key elements of treatment for diabetes and cancer, two of the fastest growing NCDs. Insulin and the anti-cancer monoclonal antibodies such as Trastuzumab, Rituximab, and Bevacizumab are all on the WHO Model List of Essential Medicines, and some groups are advocating for inclusion of more biologics despite their high cost [34]. With the accelerating growth of NCDs expected in LMICs, access to biologics will become an increasingly important issue, as discussed below [35].
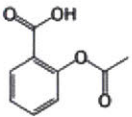
	Small-Molecules		Biologics	
Size / Molecular Weight	Small / Low		Large / High	
Structure	Simple, well-defined		Complex, heterogeneous	
Manufacturing	Chemical synthesis Identical copies	Acetylsalicylic acid (Aspirin)	Cell culture Impossible to ensure identical copy	Trastuzumab (Herceptin)
Stability	Stable		Unstable (temperature, light, etc.)	
Immunogenicity	Mostly not		Yes	
Generics	Common, lower price		Rare, similar price	

Table 1.2: Comparing molecular properties of small-molecule and biologic medicines. Molecular properties influence clinical outcomes, regulation, and supply.

1.3.2 Economics of health care industries

Global spending on medicines is projected to reach 1.8 trillion USD by 2018, an increase of 30% since 2013 with a compound annual growth rate of 4-7% on a constant currency basis [36]. The US market has been and continues to be the largest spender, accounting for one-third of the total with an expected annual growth rate of 5-8%. Growth is expected as a result of health reforms that are increasing demand for medicines, while the pharmaceutical industry experiences a shift from low-cost small-molecule drugs with an extensive generics markets, to high-cost biologics and specialty medicines with a nascent biosimilars market. Biologics comprise an increasing share of the pharmaceutical industry by sale and volume. The global market for biopharmaceuticals is approaching 300 billion USD, growing at about 15% annually, while making up 30% of products [37].

Biomanufacturing, and the industry as a whole, has strong roots in the US, with many companies based in-country due to market size, economic opportunities, relative sociopolitical stability, the presence of a highly educated and skilled workforce, and reliable infrastructure. To maintain their competitive advantage, many small-molecule manufacturers are beginning to explore biologics, raising questions regarding innovation and competition policies in the biopharmaceutical industry [38]. The Biologics Price Competition and Innovation Act passed in 2010, for example, outlines a biosimilar approval pathway modeled after the Hatch–Waxman Act's generic drug approval pathway, but with much more stringent definitions of what "highly similar" means. The complexity in characterizing biologics and demonstrating equivalence will likely limit the competitive, price-reducing potential of biosimilars and continue to impose financial strain on the health system as demand for biologics and other specialty drugs continues to increase. As demand grows, resources shrink, and biomanufacturing capacity wanes, new innovation policies will be important to lower costs, increase efficiency, ease patient administration, and maintain domestic competitive advantage [39].

Despite the prevailing barriers to access, pharmaceutical medicines already constitute a large portion of the US's healthcare budget. Biotherapeutics account for less than 1% of prescriptions filled but nearly 28% of drug spending, with expenditure growing three times faster than for small-molecule drugs [40, 41]. Since biosimilars are not expected to have the price-reducing effects previously observed with small-molecule generics, expenditure on biologics forecasted to account for up to 40% of drug spending by 2020 [42, 43, 44, 45].

1.3.3 Trend Towards Local Production?

Historically, the biomanufacturing industry has concentrated manufacturing of biologic products to several geographic locations, largely in developed countries (i.e. EU, US, and Japan). This allows them 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 closer to markets and in multiple locations at a time to lower risk of interruptions in the supply chain, as well as in emerging markets. This is driven by a host of factors, including economic incentives, increasing nationalization (mandates to manufacture locally to gain market access), and expanding supply to new, emergent markets. While this has brought some products in closer

proximity to markets that currently lack access, the degree to which it has influenced overall access in resources-depleted regions is questionable. 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. Tools are needed to better assess the relative risks, value and tradeoffs of different manufacturing models on both cost and access [46].

1.3.4 Risks and Incentives

The risk-averse nature of the pharmaceutical industry is worsened when looking at biologic therapies, especially vaccines or products for conditions that disproportionally affect LMICs. Compared to small-molecule drugs, biologics often involve longer and more expensive clinical trials, while establishing bioequivalence for biosimilars is more challenging than making generics. In LMICs, there is an additional challenge related to uncertainty in market size and low purchasing power, which can make it unattractive for multi-national companies to serve these patients.

Despite risks associated with R&D investments, pharmaceutical companies are uniquely suited to develop the products necessary to provide care. The industry and regulations around it ensure high quality, safe, and efficacious products that demonstrate positive health benefits compared to no treatment. The industry also takes advantage of economies of scale in order to manufacture products in large enough volumes to meet demand, as well as lower costs of production. However, traditional incentives such as patent protection are not enough for pharmaceutical companies to heavily invest in R&D and manufacturing in LMICs. As little as 16 of the 1400 new medicines developed between 1975 and 1999 were for neglected diseases, amounting to just 10% of R&D specifically for indications unique to LMICs, highlighting the extent of the problem and associated market failure [47, 48]. Therefore, novel financing mechanism need to be designed to better incentivize investments aimed at addressing diseases increasingly concentrated in LMICs. **Table 1.3** highlights major "push" (cost-reducing) and "pull" (demand-creating) policies under consideration for stimulating R&D and the types of risks do they hope to overcome [49, 50].

Both push and pull incentives have mixed positive and negative attributes. For example, while many push incentives such as grants can reduce deterrence pharmaceutical companies have to

R&D investment, it may lead to competition, potential duplication of efforts, and fails to promote sharing of ideas across industry players. Pull incentives, such as advanced purchase commitments can offer the tantalizing opportunity for revenue, but may underestimate actual demand and thus limit production volume in ways that adversely influence health outcomes. These mechanisms can also work synergistically to maximize incentives offered to pharmaceutical companies. Both address different aspects of the risk-adjusted net-profit-value and thus influence company decisions. Push incentives help reduce costs of R&D and manufacturing, while pull incentives help promote revenue. Thus both types of incentives are aimed at maximizing profit and addressing economic uncertainties surrounding investment.

Incentive	Type of Incentive	Risks Addressed
Product development partnerships (e.g. public research funding grants)	Push	Reduce costs of exploratory research, clinical trial, development and manufacturing. Costs can be subsidized by philanthropic agencies, governments, or other generous funders.
Tax breaks and subsidies	Push	Cost savings
Accelerated approval	Push	Expedite time to market and potential reduce clinical trial and regulatory costs.
Open access to research (data, molecular libraries, etc.)	Push	Leverage existing research can lead to cost savings since early development has already been done.
Development assistance (e.g. market guarantees in the form of advanced purchase commitments)	Pull	Ensures that a market exists and some revenue stream will be generated, despite patients no having the purchasing power. These can either be in volume or purchase price, though are not always respected.
Prizes for successful development/approval of therapy	Pull	Immediate monetary reward for putting an approved drug into the market ensures some revenue independent of sales.
Extended market exclusivity	Pull	Extends period for attaining revenue from product before competition.
Priority review vouchers	Pull	Typically reduces review time at the FDA by about 4 months; vouchers have been sold for an average of $200 million each, thus serving as an alternate source of revenue.
Liability limitations, anti-trust waivers	Pull	Reduce potential future costs during post-approval market surveillance.

Table 1.3: Examples of push and pull incentives for reduce risk in health care industries

Both push and pull incentives have mixed positive and negative attributes. For example, while many push incentives such as grants can reduce deterrence pharmaceutical companies have to R&D investment, it may lead to competition, potential duplication of efforts, and fails to promote

sharing of ideas across industry players. Pull incentives, such as advanced purchase commitments can offer the tantalizing opportunity for revenue, but may underestimate actual demand and thus limit production volume in ways that adversely influence health outcomes. These mechanisms can also work synergistically to maximize incentives offered to pharmaceutical companies. Both address different aspects of the risk-adjusted net-profit-value and thus influence company decisions. Push incentives help reduce costs of R&D and manufacturing, while pull incentives help promote revenue. Thus both types of incentives are aimed at maximizing profit and addressing economic uncertainties surrounding investment.

In order to further close gaps in access to medicines for neglected diseases and populations in LMICs, other innovative incentive mechanisms are needed. One approach is to shift away from the fee-for-service approach to a value-based system. This would incentivize performance and increase compensation based on the value generated rather than number of units sold for a given product. Initiatives like the Coalition for Epidemic Preparedness Innovations (CEPI), aimed at proactive response and preparedness through better monitoring and evaluation of risks, are conducting assessments of infectious disease outbreak to more effectively adapt to these difficult-to-predict events. A recent report from the UN High Level Panel on Access to Medicines also emphasizes the importance of better aligning incentives between different stakeholders (e.g. industry, government, patients, and others) in a way that creates shared value and meets minimum expectations of universal health coverage in a way that is both socially and financially sustainable [51].

1.3.5 Increasing Role of Biotherapeutics

New innovations in the biopharmaceutical space offer the tantalizing possibility of patient cures and more effective treatments. According to the Pharmaceutical Research and Manufacturers of America, of the biologic products in the pipeline in 2013, monoclonal antibodies constituted the largest share (37%), followed by vaccines (28%), recombinant proteins (10%), cell therapy (8%), and gene therapy (5%) [52]. However, the complexity and high-cost associated with biologics are prohibitive, limiting their use and making affordable, widespread patient access a growing challenge.

Besides their applications as vaccines, essential biologic medicines can be used as primary therapeutics or as adjuvants to small-molecule drugs for management or treatment of NCDs. Biologics are key elements of treatment for diabetes and cancer, two of the fastest growing NCDs.

Insulin and the anti-cancer monoclonal antibodies such as trastuzumab, rituximab, and bevacizumab are all on the WHO Model List of Essential Medicines, and some groups are advocating for inclusion of more biologics despite their high cost [53]. **Table 1.4** highlights indications for which biologics offer an effective therapy, while small-molecule drugs are not as common or appropriate for long-term management of disease. With the growth of NCDs expected in LMICs, access to biologics will become an increasingly important issue, as discussed below.

Disease	Biologic Therapies	Non-Biologic Therapies	Comments
Stroke / Ischemic Heart Disease	Tissue plasminogen activator (tPA)	Surgery	Mostly dominated by preventive medications & surgical procedures
Diabetes	Insulin (all type I, some type II) Stem-cell derived islet transplantation	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 influences appropriate treatment
COPD	mAbs (mepolizumab)	Bronchodilators O2 therapy Steroids	Other experimental procedures include bronchoscopic lung volume reduction
Arthritis	mAbs (tocilizumab, etanercept, infliximab)	Nonsteroidal anti-Inflammatory drugs	Small molecule options only help address pain and inflammation
Blood disorders (e.g. hemophilia)	Factor VIII, IX Fresh frozen plasma	Clotting agents (desmopressin)	Requires chronic perfusions

Table 1.4: Biologics and non-biologic therapeutic options for different major disease indications.

Case Example: Diabetes

Diabetes, a chronic disease characterized by elevated blood glucose levels, has detrimental impact on morbidity and healthcare cost due to both direct (e.g. medication, glucose testing, inpatient stays, laboratory tests) and indirect (e.g. productivity losses by patients and caregivers, absenteeism, lifestyle changes) costs [54]. Globally, the number of adults over 18 years with diabetes has increased substantively from 108 million in 1980 to 422 million in 2014 [55]. During

the same time period, prevalence has increased from 4.7% to 8.5%, rising more rapidly in LMICs. All type I diabetic and 20-30% of type II diabetic patients require insulin to live with the disease, and increased demand for insulin is expected to follow similar trends to the total number of diabetics globally. Access to insulin continues to be a major challenge to long-term management of diabetes in LMICs. National assessments indicate that 96% of high-income countries but only 23% of low-income countries reported insulin as being "generally available" (present in 50% or more of primary care facilities or pharmacies). Additionally, close to 100% of high-income countries but only 50% of low-income countries reported glucose testing as being "generally available" [55].

The above analysis points to an increase in the projected demand for biotherapeutics in the face of shrinking resources. However, it may be an underestimate of the magnitude of the problem, partly due to the uncertainty associated underdiagnoses of chronic diseases. This means that more people may need biologics than those who seek treatment. According to the Rule of Halves, approximately half of most common NCDs are undetected, half of those detected are not treated, and half of those treated are not effectively controlled [56]. In order to provide high-quality and effective treatments to those who need them, shifts in policymaking, technology development, business models, and the innovation ecosystem are needed to adequately supply biologics in response to observed epidemiologic changes.

1.3.6 Efforts Aimed at Enhancing Access

While biopharmaceutical companies are increasingly investing in industry-led access-to-medicines initiatives in LMICs, most often through donation or price reduction programs, very few high-quality publicly-available evaluations of such programs exist [57]. This section highlights some initiatives aimed at increasing access to medicines, specifically learning from experiences with small-molecules. It does not, however, quantify relative impact on access due to lack of consistent assessment data. While the majority of efforts to date have focused on infectious diseases, vaccinations, and small-molecule drugs, they increasingly include biologics for NCDs.

Pricing: Various pricing strategies have been used by both governments and pharmaceutical companies to promote access [58]. These include caps on prices and out-of-pocket payments by patients, external reference pricing to calibrate prices across markets, value-based pricing according to perceived health outcomes, and therapeutic reference pricing based on efficacy of

treatments. Companies have also adopted tiered or differential pricing, selling a product at different prices based on the customer's purchasing power [59, 60]. For example, the Roche Patient Access Programme in the Philippines has enabled access to Herceptin for more than 30% of patients who may not have received the therapy without the discounted rate [61]. Tiered formularies have also been utilized, in which providers place a drug at a preferred formulary position if they are more favorably priced [62]. Negotiations are also used by companies to gain access to new markets or by payers to drive down prices through competitive bargaining. For example, Brazil negotiated a 65% price decrease for an HIV/AIDS drug manufactured by Merck after the health ministry threatened to locally produce a generic version [63]. The proliferation of other pricing strategies, such as price-volume agreements, along with various reimbursement mechanisms, have also emerged [64].

Bundling: Some companies are experimenting with bundling several drugs as a single product for sale at a lower package price than each individual drug would cost. 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 [65]. A similar concept is the "polypill", combining the active ingredients of several medicines for different indications into a single pill in order to promote both cost-saving and improve health outcomes. Initial studies have shown the potential these multi-drug pills have in preventing and managing cardiovascular diseases, as well as positive benefits by increasing overall access to medicines in LMICs, increasing adherence, and improve cost-effectiveness [66].

TRIPS Flexibilities: Employing trade-related intellectual property (TRIPS) policies provides sovereign rights to governments to compulsorily license pharmaceuticals and invalidate patents in order to enhance drug supply in times of national emergency, producing locally and making medicines available at a lower price [67]. For example, in 2008 the Thai Government issued compulsory licenses to patents on a range of anti-cancer drugs (erlotinib, letrozole, and docetaxel), one of the first countries to do so for NCDs, as it historically had only been used for infectious diseases such as HIV. A 30-fold average reduction in prices led to benefits in the form of cost savings (between $142 and $163 million USD per year) and reaching 19,985 new patients within five years of these drugs entering the public health system [68, 69]. A review study found that 24 unique international compulsory license episodes took place between 1995 and 2011, collectively involving 40 drug patents for 22 unique pharmaceutical products [70].

Biosimilars: The entrance of biosimilar drugs, generic versions of biologic therapies, is expected to increase competition and drive down price, as major innovator biologics go off-patent and lose market exclusivity. The first approved biosimilar in the US, Sandoz's Zarxio, 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 [71]. Zarxio was launched in Europe in 2009, but has only seen a discount price of 20-30% over the subsequent six years compared to the originator drug [72]. This may be due to the complicated biomanufacturing process and quality control systems unique to biologics, as well as fewer competing manufacturers for each molecule compared to small-molecule drugs. Moreover, the extensive regulatory barriers to entry lead to few incentives to lower prices. The complexity of characterizing biologics and demonstrating equivalence, as compared to small molecules, will likely limit the price-reducing potential of biosimilars [73].

Philanthropy and partnerships: Multiple organizations are aiming to increase global access to medicines, particularly in resource-limited, humanitarian, and emergency contexts. For example, the public-private partnership Gavi, supported by the Bill & Melinda Gates Foundation and other donors, accelerates global vaccine access by pooling demand from the world's poorest countries, securing long-term funding and building technical capacity of governments. Between 2011 and 2015, Gavi support helped immunize close to 277 million children in over 60 LMICs to prevent an estimated 4 million deaths [74]. This amounts to an estimated savings on healthcare costs and lost productivity of $18 for every $1 spent on immunization. In 2017, 22 biopharmaceutical companies partnered to launch a multi-stakeholder collaboration with the World Bank Group and Union for International Cancer Control (UICC) called *Access Accelerated*, in order to "catalyze, develop, measure and replicate sustainable programs in low and lower-middle income countries" that address the rise of NCDs.

Given the breadth of initiatives aimed at enhancing access, improved monitoring programs for high-quality data collection would help draw links between the supply, access, quality, and use of medicines and the associated health outcomes. This would be especially useful if done in a coordinated manner given the global nature of pharmaceutical supply chains and to learn from experiences across different contexts. These ongoing efforts, though with some benefits, have not yet been able to meet the 80% global target for availability and affordability of essential medicines, indicating to the need for more work around this topic.

1.4 Biologics Value-Chain

The activities within the biomanufacturing industry can be categorized based on where they stand within the biologics value chain, as seen in **Figure 1.5**. This can include R&D, manufacturing, and supply chain. Other activities are present across the value-chain, including regulation and quality control. Within manufacturing, there are often three principle manufacturing tiers: primary for turning raw material inputs into the drug substance (active pharmaceutical ingredient for small molecule drugs), secondary for turning the drug substance into finished product, and tertiary for fill-and-finish that make sure products are ready to ship. The supply chain involves a host of different components: distribution networks, procurement, tracking and delivery, forecasting demand, optimizing routes, and ensuring product stability at all times.
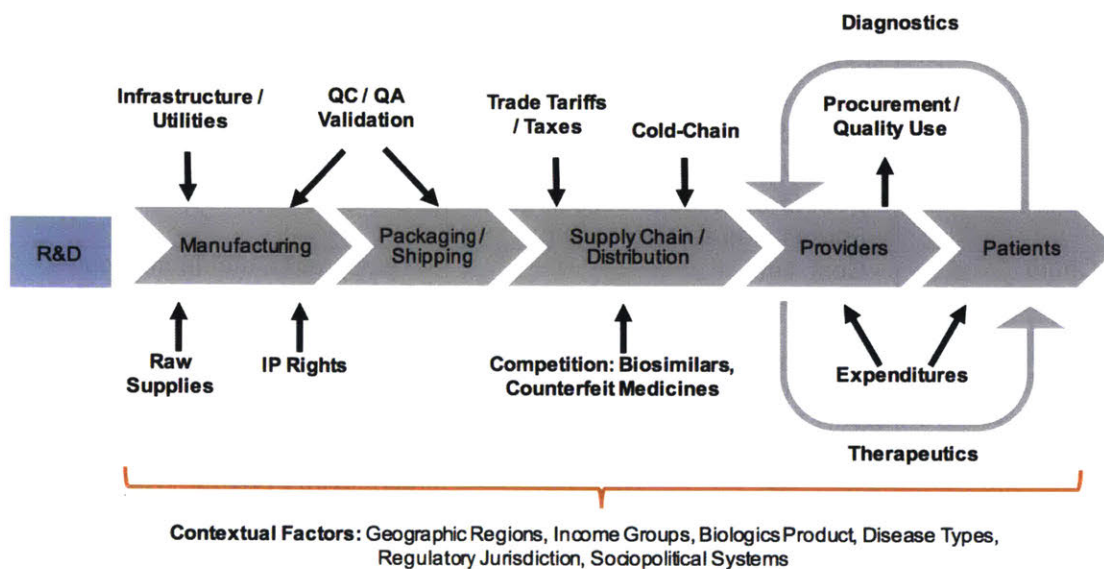
Figure 1.5: Mapping potential barriers to biologics supply across the value-chain

Barriers to sustained access to essential biologic medicines can be looked at from both a supply and demand side. To analyze this further, the supply-side can be divided into major components of the biologics product life cycle – R&D, manufacturing (both drug substance and drug product), and supply chain. The demand-side is divided into stages within the patient care cycle – promotive or preventive action, screening and diagnosis, and medicine use. Systems barriers also arise when mediating between both the demand-side and supply-side components. These include institutional capacities, intellectual property rights, financing, and other economic, regulatory, political, social, and environmental factors of individual local markets. These barriers can arise at

different places along the biologic value chain – an individual patient, local service provider, national health system, and at the interventional level.

1.4.1 Focus on Supply-Side

Biologics Value Chain	Challenges / Barriers	Potential Innovations (Partial List)
Research & Development	- Cost, time of clinical trials, approval, and post-market surveillance - Risk reducing portfolios and shift towards specialty drugs, with monopoly-like IP systems	- Platform technologies for molecular targeting; push (e.g. product development partnerships) and pull (e.g. advanced market commitments) incentives that delink R&D from costs
Manufacturing	- Cost, time - Patent exclusivities - Raw material supply dependencies - Access to cell lines, skilled labor force, and reliable utilities - Limited product yield (g/L) - Facility utilization - Poor forecasting and stock-outs - Formulation and packaging	- Alternate host organisms, manufacturing models and systems - Increased potency of drugs - Regulatory harmonization - Provisions of TRIPS Plus flexibilities for local production or price bargaining - Automation and remote QC/QA - Training programs, apprenticeships, and protocols
Supply Chain	- Cost, time - Cold chain in distribution & storage - Supply chain diversions / disruptions - Last mile accessibility (roads, etc.) - Poor transportation networks	- Temperature-stable molecules - Centralized pooled and tendered procurement processes - Development of national essential medicines lists - Zero mark-up policies - IT-enabled logistics and health information systems - Alternative delivery systems (e.g. drones)

Table 1.5: Mapping barriers across the supply-side of biologics access, as well as potential innovations within the health care ecosystem.

Table 1.5 provides a list of challenges to biologics access drawn from literature, as well as strategies and innovations in place, or proposed for, overcoming them. In this paper, the focus is on the supply-side barriers of biologics, as their complex features make research, development, manufacturing and supply a unique challenge compared to small-molecule drugs, while the demand-side barriers to access are generally the same for all therapies (with the exception of the higher prices of biologics and potential need for administration in a clinical setting). With chronic diseases becoming increasingly frequent in LMICs and "business as usual" not yielding targeted levels of access, overcoming such barriers will require rethinking current assumptions and shifting the biopharmaceutical ecosystem through innovation policy, new regulations, creative business

models, and breakthrough technologies. With an increasing appreciation for the importance of a health systems approach to medicines access, coordination between both demand-side and supply-side components could realign governmental and industrial incentives in a patient-centric fashion [75]. Additionally, the varying healthcare environment in different markets will require context-specific innovations. The extent to which these factors influence access varies over geographies, products, regulatory jurisdictions, and sociopolitical systems in ways that require context-specific innovations.

1.4.2 Focus on Manufacturing

In our analysis, we further focus on costs, risks, and opportunities associated with the manufacturing component of the supply-side of the biologics value-chain. We do not account for R&D investment or reimbursements from sales, nor the downstream supply chain. Whereas average R&D costs are likely to hold true across the industry, the average cost and time from initial research to marketplace is $2.6 Billion and 10 years, the cost of manufacturing along the lifetime of a biologic can be influenced by many factors (e.g. location) [76].

The cost of manufacturing, referred to as the *cost of goods* (COGs) and measured in dollars per gram ($/gram) of finished, accounts for a small percentage of overall cost and market price, but it has been the focus of attention by various actors. The research is particularly concerned with ensuring the production of an adequate volume of biologic product to levels commensurate with growing prevalence of NCDs. It seeks to better understand the costs centers and strategies for reducing costs associated with manufacturing, to ensure sustained supply before addressing demand-side components of access. As the demand for biologics increases, current biomanufacturing capacity is being pressured in ways that will force biopharmaceutical companies to expand existing capacity or increase efficiency of operations [77]. Furthermore, a review done by BioProcess Technology Consultants indicates that the anticipated demand for ~70% of new monoclonal antibody products approved between 2016 and 2020 is expected to be <100 kg per year per product, which can be met with small bioreactor volumes, while for blockbuster biologics the demand can be up to 10 times higher.

Efforts have been made towards reducing COGs, as it will be play an important role in reducing the overall cost increases in light of increased biologics demand. Univercells, funded in part by the Bill & Melinda Gates Foundation, is designing locally-deployable and self-contained

microfacilities that integrate continuous processing with high process intensification. They aim to produce 40 million doses of an inactivated polio vaccine (sIPV) at a manufacturing cost of less than $0.15 per dose [78]. Two initiatives from the US Defense Advanced Research Projects Agency, Pharmacy on Demand (PoD) and Biologically-derived Medicines on Demand (Bio-MOD), aim to develop flexible, aim to miniaturized manufacturing platforms to produce single doses at low costs [79]. There is active research to increase productivity both upstream and downstream, as well as in continuous manufacturing, with the aim to lower COGs to <$10/g [80].

1.5 Decision Sciences

Decision support tools are becoming increasingly used to gain foresight on the consequences of alternative decisions. Systems-based models for multi-criteria decision-making frameworks that incorporate operational, financial, and risk metrics have been employed to better evaluate tradeoffs, identify priorities, and assess uncertainty [81, 82, 83]. Within the biopharmaceutical industry, this can be useful in light of high cost associated with investigational studies of alternative scenarios (e.g. stainless steel versus single use manufacturing systems) and constraints in changing process parameters during late-stage clinical trials and post-approval.

The shift from infectious to chronic diseases has major implications on the design and delivery of health services, as well as social and economic cost. Expanded access to biologics can potentially be met by innovations across the value-chain. However, a great deal of time and effort is spent in healthcare with marginal benefit or improvement in outcomes [84]. This is in part due to the difficulty in quantitatively estimating impact of a policy change or technological innovation on patient access at a population scale. Appropriate and timely decisions are key to effectively prevent, manage, and treat NCDs. However, there is a lack of available data and use of evidence-informed frameworks for designing, monitoring, evaluating, and reporting on interventions aimed at increasing biologics access [85]. Filling such a gap is becoming increasingly important to counteract widening health disparities and the central motivation for this research.

Trial-and-error is not appropriate for testing the impact of policies or innovations on a complex system such as the biopharmaceutical industry. Ad hoc approaches can have wide-ranging unintended effects on the system, often serving as a source of both waste and market failure. For example, IMS Health estimates that in the US healthcare system alone, more than 200 billion USD could be saved through health policies that improve the responsible use of medicines [86].

Models are effective tools that have been employed as a means of observing and analyzing the world around us in a systematic and methodological way. While no model is perfect and none completely reflect the true nature of the system it seeks to represent, they can be powerful tools to test cause-effect relationships.

Cost models identify key cost objects, both financial and non-financial, within the value-chain of a product and are often the main drivers for company decisions. Of interest to this research is a model highlighting the major cost centers throughout the value chain of biologic therapeutics, specifically for manufacturing. It does not account for the upfront R&D investments needed during the discovery phase of drug development, rather focusing on already approved products and costs associated with supplying existing medicines to all who need them. The model can be adjusted to calculate the COGs at different product volumes within predefined bounds of traditional assumptions, taking into account economies of scale (decreasing unit price with increasing production throughput). Using this baseline allows for estimation of changes in cost, production volume, and biomanufacturing capacity when introducing innovations (e.g. policies, technology, organizational structure, etc.) and thus informing the most effective use of resources to maximize patient access.

Better understanding of costs associated with the development of biologics would add value to constructing more realistic models for the COGs of various products. Currently, the industry standard for monoclonal antibody production is approximately $100-150 per gram, but costs have been driven down to less than $100 per gram through a combination of large scale (>10,000L) production capacity and improved titers in the production bioreactor (>1-2 g/L). The Bill & Melinda Gates Foundation determined the target COGs at which combination therapy of 2-3 mAbs for passive immunization would be competitive with pre-exposure prophylaxis (PrEP) for HIV and gain traction as a viable public health intervention. They show that manufacturing processes need to be sufficiently optimized to reduce COGs to approximately $10/g or less [87].

1.6 Broader Applications

Increasing access to medicines, and subsequently to health services more broadly, has a profound impact on closing socioeconomic inequities between and within countries, high-and-low income families, rural-and-urban areas, and stable-and-fragile contexts. Despite a push towards more inclusive health coverage that promotes equity and justice, efficiency-fairness tradeoffs in

the national healthcare system have led to disparities in access in ways that propagate a disproportionate burden of disease, disability, and death.

African Americans have higher rates of mortality than any other racial or ethnic group for eight of the top ten causes of death. They also make up more than one third of all US patients receiving dialysis for kidney failure, despite comprising only 13% of the overall US population [88]. More than 77% of Latino adults are overweight or obese, compared with 67.2% of Whites, with 1-in-4 Latino households seen as food insecure, compared to just 1-in-10 White households. Amongst other factors, obesity has led to the number of Americans diagnosed with diabetes to triple in past three decades, with about 10% (~30 million) of the population living with the chronic condition and 7 million undiagnosed [89, 90]. Along the rural-urban continuum, those living in rural areas tend to have higher rates of heart disease and other chronic conditions, a phenomenon caused by both lower socioeconomic status and access to fewer health care providers [91]. Despite health spending accounting for close to 18% of national Gross Domestic Product (GDP), the most of any country in the world, the US ranks last among 11 wealthy industrial nations in terms of efficiency, equity, and outcomes in the health space, as reported by the Commonwealth Fund [92, 93].

The methodologies used, models developed, and findings from this research can be applicable beyond the scope of this thesis. Given the global nature of the biopharmaceutical ecosystem and growth of chronic disease burden in low-and-middle income countries, the research has application across contexts. Lessons from the research can also be translated to other disciplines and industries experiencing similar pressures to balance supply and demand in the midst of growing uncertainty and shrinking resources. The thesis also has the potential to scan the horizon for emerging issues and breakthrough innovations, testing hypotheses to inform tangible policy decisions, allocation of resources, and appropriate technological change.

Chapter 2: Building a Qualitative Model

2.1 Overview of Biomanufacturing Process

While access to biologic is a systems problem, with attributes spanning both the demand and supply side of medicines, the focus of this research is on manufacturing. Producing biologics is generally more complex, costly, and time-intensive compared to small-molecule drugs. Despite yielding higher profitability and achieving a higher probability of success from phase I clinical trials to approval (approximately 11.5% for biologics compared to 6.5% for small-molecules), operating costs are more expensive and at risk of contamination [94, 95]. Compared to synthetic chemical products, biologics are heterogeneous in nature due to varied post-translational modifications that lead to slightly different products. Therefore, extensive purification steps and rigorous quality control and assurance measures are needed to ensure efficacious and safe drugs for market. Integrating a systematic approach to quality risk management throughout the design and development stage of drug products has been coined as "quality by design" (QbD).

Drug discovery and clinical trials are essential for bringing a drug to market, but the manufacturing process determines the scale to which such a product can be commercialized and made available to patients. For large patient populations, industrial scale manufacturing processes need to be designed to fit product requirements and meet regulatory standards. In doing so, companies consider various options for optimizing quality and cost. Evaluating these options is crucial for biomanufacturing companies to be more competitive. This includes lowering costs and distribution time, as well as reducing risks from the uncertainty in demand and other factors within the biopharmaceutical industry. Identifying which levers are most conducive for achieving optimal time to market, cost, quality, and affordability first requires an understanding of the basic building blocks of the biomanufacturing process.

Within manufacturing, there are three principle components: primary / upstream (turning raw material inputs into the drug substance), secondary / downstream (turning the drug substance into drug product), and tertiary (fill-and-finish). An overview of the upstream and downstream processes can be found in **Figure 2.1**. The supply chain involves a host of different components: distribution networks, procurement, tracking and delivery, forecasting demand, optimizing routes, and ensuring product stability at all times.
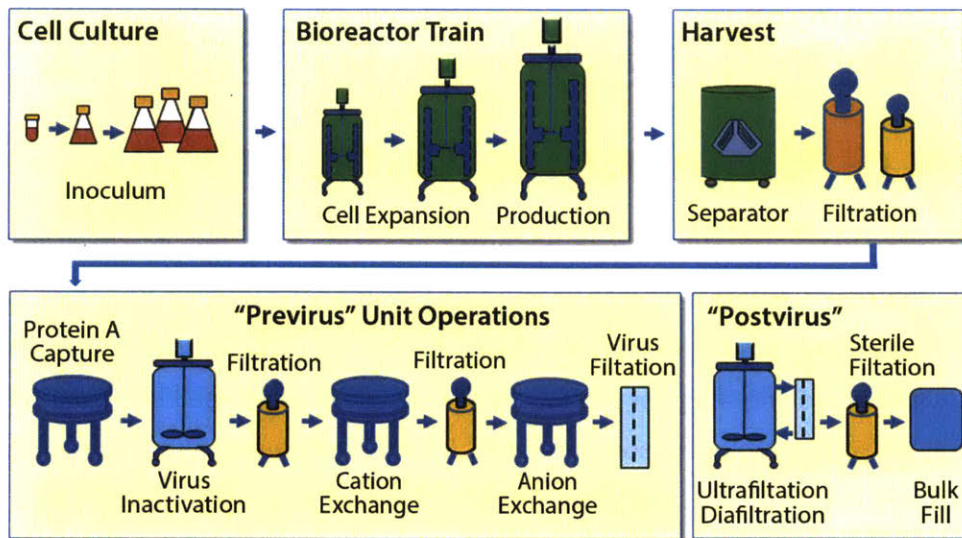
Figure 2.1: Core components of the biomanufacturing process. Source: *Minow B, Rogge P, Thompson K. Implementing a Fully Disposable MAb Manufacturing Facility. BioProcess Int. 10(6) 2012: 48–58.*

2.1.1 History of Biomanufacturing

For millennia, biologic processes in microorganisms have been exploited to make a wide range of products such as food, for example from fermentation (e.g. bread, beer, wine, pickles, cheese) [96]. These systems relied largely on naturally found or "wild" organisms, serving as useful examples for studying underlying mechanisms of microbiology. Since the early 1900s, four eras within biomanufacturing can be highlighted: 1) 1910s: using bacterial monoculture or fungi to produce primary metabolites (e.g., butanol, acetone) and amino acids; 2) 1940s: using mutated bacteria or fungi to produce secondary metabolites (e.g. penicillin, streptomycin); 3) 1980s: using recombinant DNA technology and advanced cell culture to produce large-size biomolecules such as proteins and enzymes (e.g., erythropoietin, insulin, growth hormone, amylase, DNA polymerase); and 4) 2000s: a number of emerging production systems (e.g. stem cells, engineered microorganisms, and more) to allow for an array of new products such human tissues or cells made from regenerative medicine [97]. Approved by the Food & Drug Administration (FDA) in 1982, human insulin produced in genetically modified bacteria by Genentech and Eli Lilly became the first protein therapeutic to be manufactured. This was followed by approval of the first recombinant vaccine for humans as a prophylaxis for Hepatitis B in 1986. Acceleration in the number of products manufactured is in part a result of improved understanding for the underlying mechanisms (genetic and proteomic) of various diseases, more sophisticated production processes, and increased demand for targeted therapies. Over time, advances made through

improvements in both fermentation and purification have enabled more efficient systems to produce higher volumes at lower cost. A summary of the typical steps, based on current manufacturing practice, in the production of monoclonal antibodies is presented below [96].

2.1.2 Upstream Process

Cell Bank

Cells used for production of biologics are derived from a Master Cell Bank (MCB) originally made under proper Good Manufacturing Practices (GMP), which is a process that ensures consistent production of products under tight quality standards. Choice of raw materials is critical, as it may affect future purification steps and overall quality of products. Once identified, the MCB cannot be changed at any time during the development process or while the drug is still on market, unless comparability assessments and regulatory approval is granted for another MCB. Multiple vials of cells are prepared to minimize risks of loss of the original MCB and frozen for future use.

Cell Culture, Fermentation, & Scale-Up

Cells derived from the MCB are placed in successively larger reactors and under conditions that yield greater production efficiency. Different techniques can be used to provide nutrients for growth and extraction of cells, depending on the desired output. These include batch, fed batch, and continuous processes. Output is measured primarily in biomass and percent of live cells. Controls on the environment are essential in order to ensure optimal nutrients, regulating levels of dissolved O_2, temperature, and pH. As biomass accumulates, cells begin to produce product using their cellular machinery and the initial set of starting materials. Risk management strategies are integrated in order to minimize contamination from adventitious agents, avoid high shear that lyses cells (potentially releasing host cell proteins, DNA and other contaminants), and control variation in the raw materials that can negatively affect the quality of the end product.

2.1.3 Downstream Process

Centrifugation and Depth Filtration

This step is used to remove solids from the product through sedimentation by centrifugal force and solid entrapment through depth filters. Controlling for turbidity and filter pressure is important to avoid removing too much or too little of the product, thus minimizing production losses.

Protein A Capture

Affinity chromatography is used to remove impurities and increase concentration of products. Protein A, a surface protein originally found in *Staphylococcus aureus*, serves as an affinity ligand to bind to monoclonal antibodies in the drug substance, while impurities are eluted at low pH and under strictly defined flow rate conditions. This is one of the most expensive components of the biomanufacturing process, while risks arise from potential aggregation of products during elution and contamination from Protein A. Other chromatography steps can be used to further enhance purity of the target product.

pH Control and Viral Inactivation

This step is important for regulatory compliance, inactivating viruses that become unstable in acidic environments. Adding acid to the product after elution lowers the pH and destabilizes any virus, while adding base neutralizes pH. Protein degradation in the product is a risk if pH and time controls are not well regulated.

Ion Exchange Chromatography

Since amino acids can either have a positive, negative, or no charge, proteins have a net charge based on the cumulative charge of their composite amino acids. In this process, products are loaded onto a column with charged beads, with proteins and beads of opposite charge attracting. The product is further eluted with salt to undo the binding, while trace impurities (e.g. DNA, host cell proteins) are removed. Risks arise if impurities are not effectively cleared or if too much is removed and leads to low yield.

Virus Filtration

Additional steps of filtration help remove viruses that may still be present at this stage of the purification process and are a core part of the regulatory process. Filtration is done through narrow pore-size distribution. Integrity and efficacy of the filter needs to be tested and validated.

Ultrafiltration, Diafiltration & Formulation

These steps allow for the addition, removal, or changes in the concentration of excipients, which are products used to formulate the active ingredient in order to stabilize or enhance the final product. Pumping solutions across a membrane under pressure adds appropriate amounts of formulation buffer and allows for the desired protein concentration.

Final Filtration & Freezing

A final step of filtration is used to remove bioburden, the remaining population of viable microorganisms and bacteria that can cause contamination, followed by techniques for stabilizing the protein for shipping and storage such as lyophilization or freeze-drying. Risk mitigation strategies are used to avoid leaching, loss of yield, and decreasing quality of product.

2.1.4 Supply Chain

The supply chain logistics associated with delivering biologics at the right place and right time, while maintaining high quality can be both complex and costly. Labeling, packaging, and shipment processes must also adhere to GMP regulations, while additional controls are needed to avoid agitation, ensure temperature stability, and account for other environmental fluctuations that may compromise the quality of complex protein structures. Depending on the products, supply and delivery can have several intermediary steps such as fill-and-finish (e.g. lyophilization), storage at distribution centers, and multiple tiers of providers and purchasers in the marketplace. For some drugs, maintaining end-to-end cold-chain infrastructure and traceability are important to preserve the quality of the medicine. As demand for biologics increases with time, as well as diversifies across spaces with growing patient populations in LMICs, supply chains will become increasingly complex and costly, leaving biopharmaceutical companies with the challenge of developing strategies for risk-management and cost-containment [98]. The integrity of supply chains is crucial in order for patients to access biologics when they need them, while safeguarding against divergence into informal markets with substandard medicines and avoiding excessive markups that increase prices. Promoting a strong patient-provider relationship can be useful to avoid local aversion to biologic products and to overcome sociocultural barriers to effectively deliver and adhere to long-term treatments for chronic diseases.

2.1.5 Regulatory Landscape

Different regulatory frameworks exist across different jurisdictions, such as the European Medicines Agency in Europe, the FDA in the US, and the Pharmaceuticals and Medical Devices Agency in Japan. Each regulatory agency has oversight for approving medicines within their jurisdiction. However, a challenge has emerged in that countries with increasing demand for biologics lack the regulatory capacity to approve drugs for their markets or use different systems for post-market approval that make it difficult to assess the long-term safety and quality of products [99]. Inconsistency in the requirements, methods, or systems used for drug approval have the potential to slow access to patients and increase burden on biopharmaceutical

companies that need to independently apply for approval in each market. This is also true if a modification is made in the production process.

In an effort to facilitate modifications across the product lifecycle, the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use has proposed a new guideline (ICH Q12) for proactive planning of supply chain adjustments that will allow for more efficient management of changes for biopharmaceutical manufacturers [100]. The WHO Pre-Qualification of Medicines Program promotes access to essential medicines in resource-limited countries by identifying manufacturers and conducting inspections to ensure that they comply with WHO standards of quality, safety, and efficacy. This allows governments, agencies, or other large buyers to purchase medicines from a trusted and reliable source.

2.1.6 Challenges with Biosimilars

In the U.S., the Biologics Price Competition and Innovation Act (BPCIA) defines the abbreviated licensure pathway available for biologics seeking biosimilarity or interchangeability status to a previously FDA-approved reference product. BPCIA was signed into law in 2010 as part of the Affordable Care Act (ACA). As such, abbreviated biologics license applications (aBLAs) are often said to follow the 262(k), or equivalently, the 351(k) pathways; whereas innovator BLAs follow the 262(a) or 351(a) pathways.

Biosimilars must maintain purity and potency of the reference product in addition to demonstrating no clinically meaningful differences. In addition, the BPCIA requires data from various types of studies (e.g. analytical, animal, and clinical) to assess immunogenicity, pharmacokinetics, and pharmacodynamics, thus supporting the claim that a biologic is biosimilar to its reference product. The same mechanism or mechanisms of actions also need to be used by a biosimilar and its reference product [101]. The definition of high similarity is inconsistent across regulatory agencies worldwide, which may add to the difficulty of approving many biosimilars. Demonstrating high similarity is initially done using multiple analytical techniques and tools, though ultimately confirmed through animal and human trials [102]. In comparison to innovator biologics, biosimilars emphasize more analytical data to prove similarity. Often, the manufacturing process will go through multiple iterations until a consistent, highly similar product is produced. Though more analytical data is necessary in the production of a biosimilar, typically, fewer clinical trials are required for approval.

2.2 Design Choices for Biomanufacturing Operations

The design of a biomanufacturing operation is influenced by a number of important factors. These include the type of product, scale of production, location, company culture, costs, production system, and unique product attributes. Foresight into the scale of production is crucial to plan for both current and future demand in ways that maximize net present value of investments and minimize long-term costs. Extensive research has been done to develop multi-criteria decision-making frameworks that incorporate financial and operational factors in order to evaluate different scenarios [81, 82, 83]. While considering design options, two categories are considered in this research: facility options (i.e. design options within a single manufacturing site) and system options (i.e. design options across the network of a company's manufacturing sites for a given product).

2.2.1 Options Within a Facility

Many options arise when planning for, and designing, a biomanufacturing facility. Some of the key ones are presented here:

Size: The size of a manufacturing plant can be thought of in different ways - the physical space occupied (m^3), maximum bioreactor volume (L), and production capacity (kg). The size of a facility may allow for flexibility within the design. Flexible, modular facilities allow for rapid changes in configuration in order to more adequately respond to changes in market demand [103]. 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 Healthcare, for quality assurance and standardization, while assembly take places at the final site. According to GE, these have shown to reduce the time from plant design to production to about 18 months, compared to approximately 3 years for a traditional plant [104]. On average, energy costs also decreased by 15%, waste and environmental footprint is reduced, and capital investment decreased by 25%. Forecasting demand is challenging and adds uncertainty to choosing the appropriate production scale, as this can be influenced by factors such as competition and underestimate in diagnosis. In turn, this can have an impact on capital investment costs and the flexibility to respond to changes in product demand. Furthermore, the volume and number of bioreactors can also be modified to meet different production capacities.

Expression System: Legacy expression systems such as Chinese Hamster Ovary (CHO) cells, yeasts and *Escherichia coli* have all seen improvements in production yield that allow for more efficient production. Depending on the product, certain expression systems may be preferred over others and can influence necessary downstream purification steps. Over the past several decades, CHO cells have been the most widely used cell lines for expressing various products and thus a main driver in the growth of the biotechnology industry. Today, close to 70% of recombinant protein therapeutics produced use CHO cells, given their advantageous attributes compared to other expression systems [105]. This in part because CHO cells are easy to genetically modify, express genes at high levels, enable proper folding and post-translational modifications to ensure active glycoforms, and have low susceptibility to adventitious agents.

Fed Batch-vs.-Continuous Processing: In traditional systems, fed-batch manufacturing allows substrates and other nutrients to be supplied to the bioreactor during cultivation, thus helping maintain conditions for growth, while the products remain in the bioreactor until the end of the run. In continuous processing, integrated systems are used to continuously feed substrates and nutrients, while isolating products. This usually leads to reduced process time, less human error, and more adaptive systems. Simulations of a 10-year product portfolio shows that integrated continuous systems can reduce average cost by 55% compared to conventional batch, assuming process intensification in both upstream and downstream unit operations [106].

Single-vs.-Multi Drug Facility: One of the key objectives for any biomanufacturing company is to maximize capacity utilization. Depending on a product's production cycle, a facility could accommodate one or more products within a given year. If a facility is not used at or close to maximum capacity, costs are distributed over a smaller volume of product, thus increasing the relative production cost of each unit. Other challenges that can arise is the slow turnaround time and potential for contamination when shifting between drugs.

Open-vs.-Closed Systems: Companies like Just Biotherapeutics are innovating biomanufacturing "pods" that can cost-effectively produce low volumes of product in a closed system [107]. These types of pods could potentially become highly-automated, with low-labor requirements. Additionally, they have the possibility of being deployed around the world, requiring only water, electricity, and raw materials.

Bioreactor Type: Traditionally, large stainless steel bioreactors have been the standard in industry with volumes of up to 20,000 liters. However, there is growing use of smaller, single-use or

disposable systems with volumes of up to 3,000 liters. 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) [108, 109]. In these systems, time is saved by expediting cleaning and quality validation steps before initiating the next biomanufacturing campaign, thus also reducing risk of contamination. An study done by BPTC for a typical facility show a 25% lower capital expense for single-use facilities compared to stainless-steel, as well as a 23% decrease in the cost per gram of mAb manufactured [110].

2.2.2 Options Across a System

When designing a system of multiple facilities for a given biologic product, other considerations arise. Some of the most considerable ones are the following:

Location: Historically, the biomanufacturing industry has concentrated manufacturing of biologic products to one or a few geographic locations largely in developed countries, partly as a result of proximity to R&D centers, accessibility to a skilled of labor force and reliable infrastructure. Manufacturers have also aimed to locate these in settings that provide tax break and subsidies, taking advantage of unique laws in certain jurisdictions. 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. Some localization policies put forward by governments mandate 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.

Number: The number of production facilities used to manufacture a product depends on factors such as the demand and the economics of operating parallel plants. In the early years of the biotechnology industry, small markets and the risk-averse nature of manufacturers often led to one, centralized production facility from which medicines were supplied globally, especially in tax-advantaged locations [111]. More recently, there has been increased interest in establishing manufacturing sites in emerging markets, with substantive revenue potential, as well as in multiple locations at a time to lower risk of interruptions in the supply chain and due to growing biologic demand beyond production capacity [112]. This is driven by a host of factors, including economic

incentives, increasing nationalization (mandates to manufacture in market in order to sell in market), and expanding supply to new, emergent markets.

2.2.3 Spectrum of Production Networks

Analyzing design options both within a facility and across a system are often done in conjunction, eventually leading to the network of biomanufacturing production plants. Integrating the operational, economic, and public health components in decision making processes gives better insight into the various production networks that can meet global demand.

Developing an understanding of such systems can be used to compare multiple network options, as well as evaluate the potential impact of emerging manufacturing and supply chain systems on expanding supply. This type of analysis adds an important dimension to be considered, allowing one to compare whether drivers of such change are different depending on the product, regional context, regulatory jurisdiction, geopolitical zone, and sociocultural differences.

Given that the existing biomanufacturing process requires high cost of capital, highly-skilled labor (with increasing need for specialized workers), and reliable infrastructure (e.g. clean water, energy, etc.), a more centralized approach that leverages economies of scale appears to still be favored by manufacturers. 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. Despite this potential promising avenue, there is a gap in publicly available research or data on the potential impact of different production networks (e.g. centralized vs. distributed) of biologics manufacturing on cost and access.

In practice, 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 used for comparing them. This is an initial challenge in comparing models that have fluid boundaries between them, especially as they can be thought of differently even within the biopharmaceutical industry when thinking about manufacturing plants (drug substance), fill-finish-plants (drug product), and the network of suppliers and distributors.

In this context, 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 [113]. 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 [114].

In between these extremes are a diverse range of models that may distribute their 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 activities in its Netherlands site, while building a new production facility in Singapore integrating operations for production of both drug substance and drug product [115]. 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 market [116]. In another case, some manufacturers supplying biologics to small markets, may only have production plants in that country (e.g. Julphar, insulin manufacturer in the 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 [117]. For example, Novo Nordisk set up local production capacity in China in order to better serve the Chinese diabetes market, as well as increase operational efficiency of insulin supply in China and better respond to shifts in market demand [118]. 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 2.2**, 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 drug substance to generate final drug 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.
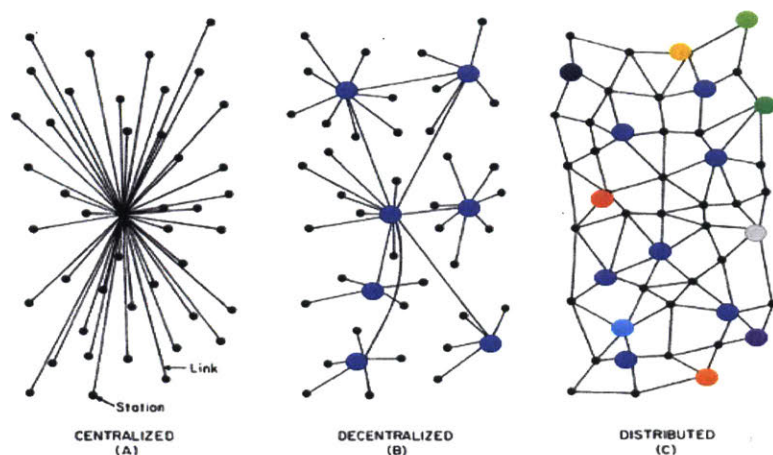
Figure 2.2: Representative networks along the centralized-distributed spectrum of biomanufacturing and supply. Large nodes represent manufacturing sites, while smaller nodes at the periphery perform fill-and-finish or distribution. Different colors could signify multiple manufacturers, while the same color indicates a manufacturer with a network of plants. Adaptation of *Paul Baran's On Distributed Communication Networks, RAND Corporation, 1964.*

Another rendition of different production networks that can arise is seen in **Figure 2.3**. Panel A demonstrates a fully centralized model, with drug substance and drug product made in the same or different facility. Panel B show a de-centralized model, in which a biologic is produced within a specific region to serve that market (the production process is the same for regions A and B, but it is only shown for one to simplify the figure). Panels C and D add complexity to the analysis, as different components (e.g. upstream, downstream, fill-and-finish) can be accomplished in a centralized or de-centralized manner. The use of "centralized", "decentralized" and "distributed" is relative to two systems being compared and can be done looking a global, national, or even local market. In all cases, the aggregate production volume is assumed to meet total demand for the product, as the biopharmaceutical company is still supplying to the same patient population.

Biopharmaceutical Value Chain: **Centralized** Model

Raw Materials
Equipment
Labor
Infrastructure
Utilities

Manufacturing

API Production

Formulation Fill & Finish

Stock

1' Suppliers

2' Suppliers

Transaction
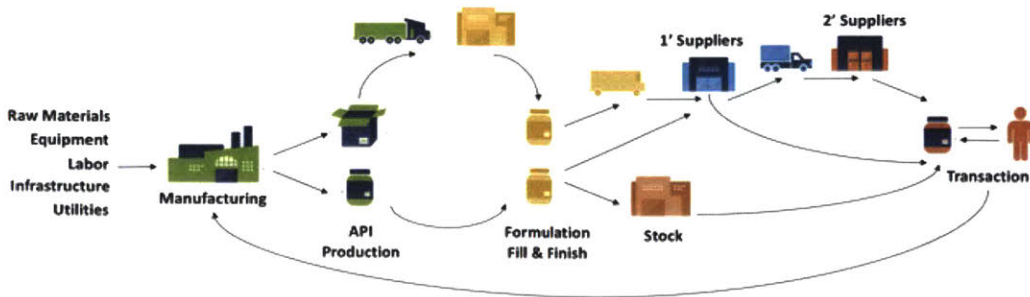
Biopharmaceutical Value Chain: **Distributed** Model

REGION A

Raw Materials
Equipment
Labor
Infrastructure
Utilities

Manufacturing

API Production

Formulation Fill & Finish

Stock

1' Suppliers

2' Suppliers

Transaction

REGION B

Raw Materials
Equipment
Labor
Infrastructure
Utilities

Manufacturing

API Production

Transaction

Biopharmaceutical Value Chain: **Hybrid** Model I

REGION A

Raw Materials
Equipment
Labor
Infrastructure
Utilities

Manufacturing

API Production

Formulation Fill & Finish

Stock

1' Suppliers

2' Suppliers

Transaction

Stock

1' Suppliers

2' Suppliers

Transaction

REGION B

Biopharmaceutical Value Chain: **Hybrid** Model II

Figure 2.3: Comparing different manufacturing and supply networks

2.3 Qualitative Framework

To develop an initial qualitative framework for the cost of biomanufacturing, eleven interviews were conducted with experts from 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 in manufacturing biologics, as well as other competing risks and drivers in choosing one model over another. The information utilized in this thesis 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 analysis leverages knowledge within 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.

2.3.1 Key Cost Centers

The analysis focused on costs, risks, and benefits associated with the manufacturing components of the biologics value-chain. It does 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 - the manufacturing can vary significantly [76]. 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 (e.g. quality compliance, filing). 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 manufacturing process, which itself could 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 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) [96]. 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 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 goods also include materials, which can be further disaggregated into the materials for upstream and downstream processes, as well as those used for fill-and-finish (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 that of the finished product. These tradeoffs can be difficult to assess, for instance, single-dose vials have been shown to have consistently lower wastage rates, although possibly increasing the cost per dose [119].

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 or distribution networks for the company or product. These costs are likely to be less sensitive when comparing between a centralized and distributed systems. 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 [120].

2.3.2 Tradeoffs and Considerations

Innovations in biomanufacturing processes and supply chain have contributed to increasing production yield and end-product quality, while decreasing time to market. Some ways to achieve this include improving hosts used for expression, the lower cost purification methods, use of information technologies and analytics for testing and regulatory oversight, and enhancing operational efficiency by lowering labor costs and increasing plant capacity. In an effort to drive improvements in manufacturing and supply, several new models have emerged. Process improvements like continuous manufacturing, as opposed to batch manufacturing, have the potential to improve scalability and reduce time to market by lowering capital investment and improve quality of products [121]. Similarly, modular factories and single-use systems drive down capital costs compared to the traditional stainless steel systems by lowering investment in infrastructure, reducing production lead time, and reducing resource requirements [122].

Flexible modular systems also make it easier to have multi-product plants, while localizing manufacturing to bring products closer to patients [123]. The shift towards policies that require in-country production to enter in local markets, especially in emerging markets, has been demonstrated by local clinical data requirements in countries such as China, South Korea, Taiwan (accepts data from other Asian countries), Russia, Mexico, India, and Vietnam [124]. Such trends will likely pressure manufacturers to consider moving away from the typical centralized model, with one or few production sites that supply globally, to more distributed models that involves

networks of manufacturers, providers and suppliers. This could, in turn, incentivize more local competitors to manufacture for local patient populations.

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 impeding many people, including within the US and EU, from accessing life-saving-or-extending therapies. This raises questions on how much the biopharmaceutical ecosystem will need to change to address growing demand for biologic medicines.

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. Since bringing a drug to market can take many years, decisions made today on expanding capabilities to meet future demand and gain competitive positions in emerging markets could potentially have profound effects on success in the future, potentially outweighing short-term competitive advantages.

These trends will fundamentally reshape the industry. The changes will not be the same for every company, 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.

This complex problem can be approached through scenario analysis to consider the risks and benefits across different manufacturing options, as well as their implications on global biologics access. **Figure 2.4** presents such a schematic and sets the stage for developing a quantitative model for more detailed analysis of different design options and impacts of different innovations.
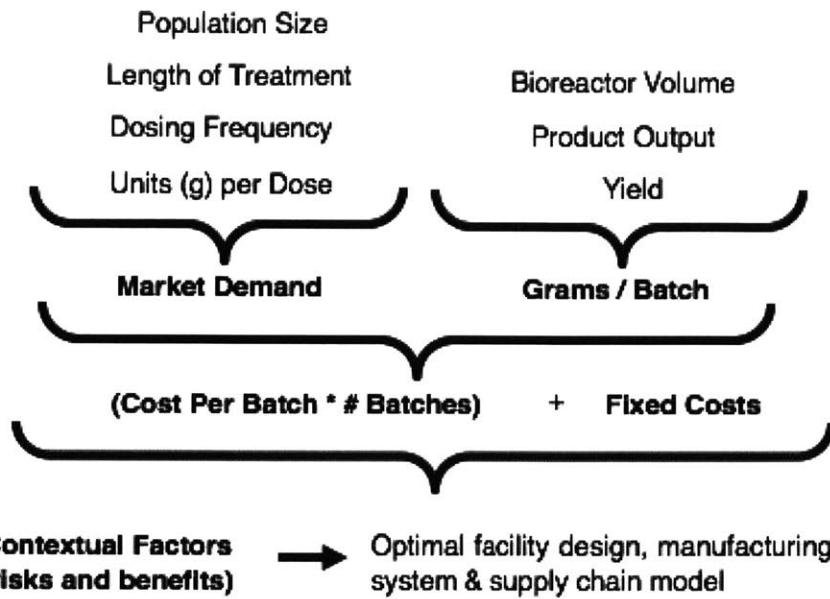
Figure 2.4: Qualitative framework for designing manufacturing systems that minimize cost and meet total demand

Chapter 3: Building a Quantitative Model

When testing the impact of policies or innovations on a complex system such as biologics access, trial-and-error may not be the most cost-or-time effective. Instead, models serve as powerful tools that have been employed as a means of observing and analyzing the world around us in a systematic and methodological way. While no model is perfect and none completely reflect the true nature of the system it seeks to represent, they can be powerful tools for predictive and uncertainty analysis.

Cost models identify key cost objects, both financial and non-financial, within the value-chain of a product and are often the main drivers for company decisions. Of interest to this research is a model highlighting the major cost centers in the supply-side of value chain for biologic therapeutics, specifically the manufacturing. It does not account for the upfront R&D investments needed during the discovery phase of drug development, rather focuses on already approved products and costs associated with supplying existing medicines to all who need them. There is a lack of publically available data on the costs associated with the development of biologics; therefore, there is real value in constructing models that provide a baseline for the *cost of goods* (COGs) of a biologic. In this thesis, the conventional unit used is dollars per gram ($/g).

The model can be adjusted to calculate the COGs at different product volumes, within predefined bounds of traditional assumptions, taking into account economies of scale (decreasing unit price with increasing production throughput). Using this baseline allows for estimation of changes in cost, production volume, and biomanufacturing capacity when introducing innovations (e.g. policies, technology, organizational structure, etc.). Selecting which of the biologic product types are most appropriate to be modeled will depend on a range of factors. These include research interest, availability of data, potential to fill unmet medical need, availability of alternative therapeutic options, molecular and manufacturing understanding, emerging innovations, policy implications, and feasibility of modeling the production process.

3.1 Framework for COGs Model

3.1.1 Methods

The framework described is used for estimating the cost of manufacturing biotherapeutic medicines. It does not take into account R&D cost, nor marketing and sales cost. Data was collected from an extensive literature review of published work on bioprocess economics and financial evaluations of biomanufacturing.

3.1.2 Drug Demand

In the context of this research, drug demand refers to the total volume of a product needed to supply biologic medicines to all those who need it. This gives an estimate for the total amount of product that needs to be manufactured for universal access to quality medicines for all patients globally or within a given region, depending on the user's research question. Often, this is more than the projected market demand because patients with low purchasing power are kept outside of the market and poor diagnosis leads to less people seeking care relative to those who actually need it. 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 fail to maintain health performance targets [56]. To help 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 [125].

Variable	Units	Relevant Equations
# of patients in given geographic area - **P**	P	
Length of prescription (e.g. month) - **L**	L	
# of doses needed for a drug per month (e.g. daily, weekly, monthly) - **D**	D	
Grams per dose of drug (function of age, weight, metabolism, etc.) - **G**	G	
Drug Demand in given geographic area	g	$G*D*L*P$

Table 3.1: Calculating drug demand within a given geographic area

An illustration of this simple, yet versatile calculation is seen in **Figure 1**. In this example, the total 1-month biologic drug demand is modeled for 10,000 patients, considering different dose sizes (ranging between 0.001 to 1 gram per dose) and frequency of dosing regiment (daily, weekly, or monthly). This provides a useful tool for rapidly estimating the total demand for a given therapeutic product, thus informing the process requirements needed to manufacture enough medicine.
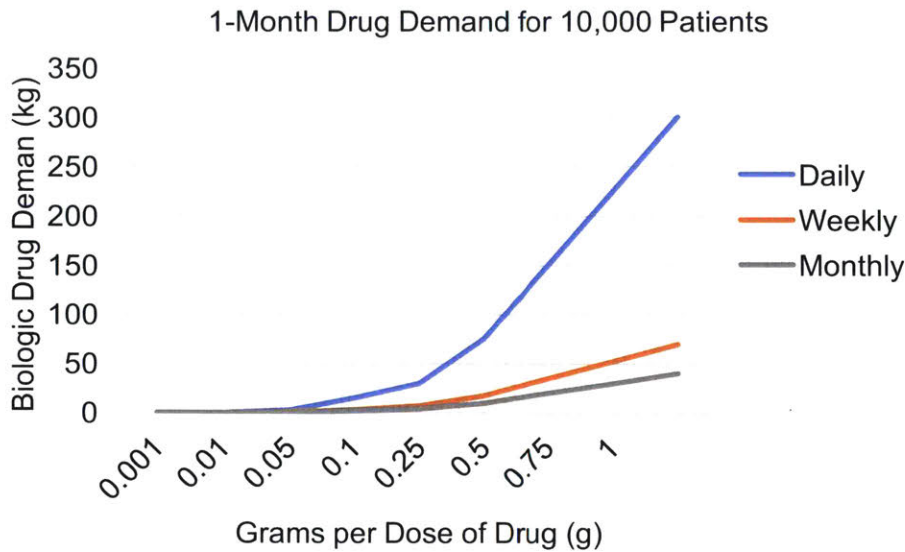
Figure 3.1: Modeling total drug demand as a function of dosing frequency, dose size, and number of patients

3.1.3 Manufacturing Process and Operations

Manufacturing processes and operations describe the manufacturing parameters that go into making a biologic medicine. This includes bioreactor volume, schedules, yield and other process specificities.

Variable	Units	Relevant Equations
Run Duration	days	
Turn Around Time	days	
Idle Time	days	
Process Success Rate	%	
Total Runs per year	Runs	*(365 days – Idle Time) / (Run Duration + Turn Around Time)*
Successful Runs per Year	Runs	*Total Runs per year * Process Success Rate*
Bioreactor Volume	L	
Product Concentration	g/L	
DS Yield	%	
DS to DP Yield	%	
Drug Product per Run	g	*Bioreactor Volume (L) * Product Concentration (g/L) * DS Yield (%) * DS to DP Yield (%)*
Drug Product per Year	g	*Drug product per run (g) * # Successful Runs per Year*

Table 3.2: Calculating quantity of drug produced in a year given specific process operations

These parameters determine the production capacity for the manufacturing plant being modeled, usually at the bioreactor level. Each of the inputs can be modified based on the specific manufacturing process being modeled. The output is a weight value (g) that can be manufactured by a bioreactor per run and per year. Each bioreactor run yields a batch of standard product volume, though some may be contaminated or found to be unfit for use after quality testing.

3.1.4 Capacity Requirement

Calculations for the manufacturing processes and operations can be used to determine the number of batches needed to fulfil drug demand. This helps define the number of bioreactors, bioreactor volume, and number of runs per bioreactor needed within a given time period in order for supply to meet total drug demand. **Figure 3.2** demonstrates the application of a model for calculating the number of batches needed to meet different drug demand quantities (25, 50, 100, and 250 kg), given a one bioreactor plant of various potential volumes (between 500 and 20,000 Liters). These calculations assume a 5 g/L production output and 50% yield, with each input variable easily modifiable based on a reasonable range of values to better understand sensitivity.
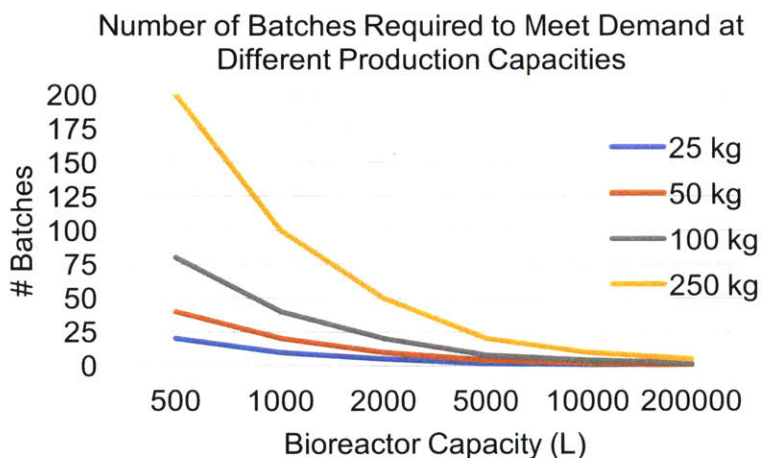
Figure 3.2: Modeling number of batches needed to meet total drug demand as a function of bioreactor capacity (L), titer (g/L), and yield (%)

3.1.5 Cost Centers

These cost centers do not take into account upstream R&D nor downstream supply chain costs. They focus on the drug substance and drug product manufacturing at commercial scale, as seen in **Figure 3.3**.
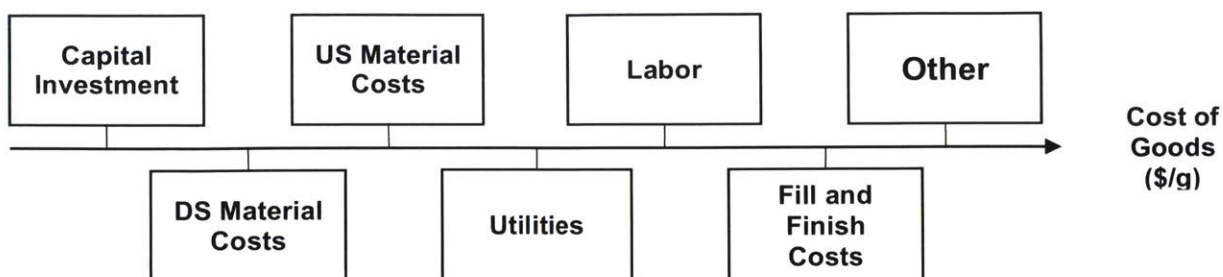
Figure 3.3: Primary cost centers in the manufacturing of mAbs, excluding upstream R&D costs and downstream supply chain

Labor Costs

Variable	Units	Relevant Equations
Bioreactors in facility	#	
Shifts	#	
Administrative/Other	#	5 + (10*shifts)
Engineering	#	5*shifts*number of bioreactors
Material Management	#	5*shifts*number of bioreactors
Manufacturing Operations	#	8*shifts*number of bioreactors
Quality Systems	#	10*shifts*number of bioreactors
FTE	#	Admin/Other + Engineering + Material Management + Manufacturing Operations + Quality Systems
FTE Cost	$	Annual mean salary for FTE
Total Annual Labor Cost	**$**	*FTE * FTE Cost*

Table 3.3: Calculating annual labor cost

Utility Costs

Variable	Units	Relevant Equations
Base Cost per year	$	
Total Runs per year	#	
Cost per run	$	
Total Annual Utilities Cost	**$**	*Base Cost + (Cost per Run * Total # of Runs)*

Table 3.4: Calculating annual utilities cost

Materials Costs

Variable	Units	Relevant Equations
US/DS - raw materials	$	
US/DS - consumables	$	
QC/QA Materials and Other	$	
Cost per run	$	*Raw Materials + Consumables + QC/QA/Other Materials*
Total Runs per year	#	
Annual Materials Cost	**$**	*Cost Per Run * Total Runs per year*

Table 3.5: Calculating annual materials cost

Capital Depreciation

Variable	Units	Relevant Equations
Investment for 1x1000 L Bioreactor	$	
Capital scaled to plant size	$	*Investment for 1x1000L * (Bioreactor Volume / 1000 L) ^ 0.6*
Depreciation period	#	
Annual Maintenance	$	*0.1 * Capital scaled to plant size*
Annual Capital Depreciation	**$**	*(Capital scaled to plant size / Depreciation period) + Annual Maintenance*

Table 3.6: Calculating annual capital cost

Fill and Finish Costs

Variable	Units	
Yield DS to DP	%	
Volume of 1 vial	g	
# of Vials	#	*Drug Product per Year / Volume of Vial*
Cost of Vial (material only)	$	
Process Cost per Vial	$	*(Cost of Vial + Process Cost of Vial) * # of Vials*
F&F Cost	**$**	

Table 3.7: Calculating annual fill and finish cost

Other Costs

Other major cost centers for the supply of the biopharmaceutical products include the following: inventory costs, procurement, shipping, delivery, taxes and tariffs, marketing, and ongoing post-market compliance (e.g. stability testing, patient monitoring, recalls, audit readiness, etc.).

Additional variables of interest, with potential impact on manufacturing cost, include facility utilization rate and drug potency. In the case of capacity utilization, lower utilization will likely lead to the COGs being dominated by fixed costs (including cost of capital), while higher utilization will likely lead to the COGs being dominated by variable, per batch costs. These additional factors influence both the product volume that can be manufactured within a given time period and volume needed to meet population demand. While this list is not exhaustive, it highlights the variables identified as most financially relevant and influential to decision making, as well as those most likely to change as a result of innovations in the biopharmaceutical value chain.

3.1.6 Scaling and Costs

Special considerations should be made when considering the behavior of cost centers at different production scales. While drug demand or the number of facilities may scale a certain way, the cost associated with different components of the value-chain may not change similarly. For example, regardless of the volume of drug manufactured or size of a plant, there will be a minimum critical threshold of employees, materials, and utilities needed to run even the simplest operations. These thresholds set lower bounds on certain parameters. Beyond these minimum values, the cost of materials and utilities scales with the number of runs per bioreactor. In the case of labor costs, the number of employees is a function of both number of shifts and production capacity in the facility (for which the number of bioreactors can be used as a proxy). A proposed model for the total FTE is demonstrated in **Figure 3.4**, with the function easily modifiable within a reasonable range to determine sensitivity. This assumes 10,000 L bioreactors and a specified number of employees associated to different functions. The capital cost already takes into account economies of scale, scaling equipment cost relative to changes in volumetric capacity of bioreactors [126]. Titers also have a large influence on the overall system: cost of the upstream process is inversely proportional to the titer, while cost of the downstream process is linearly proportional to titer.

Number of FTEs and Labor Cost as a Functino of Production Capacity
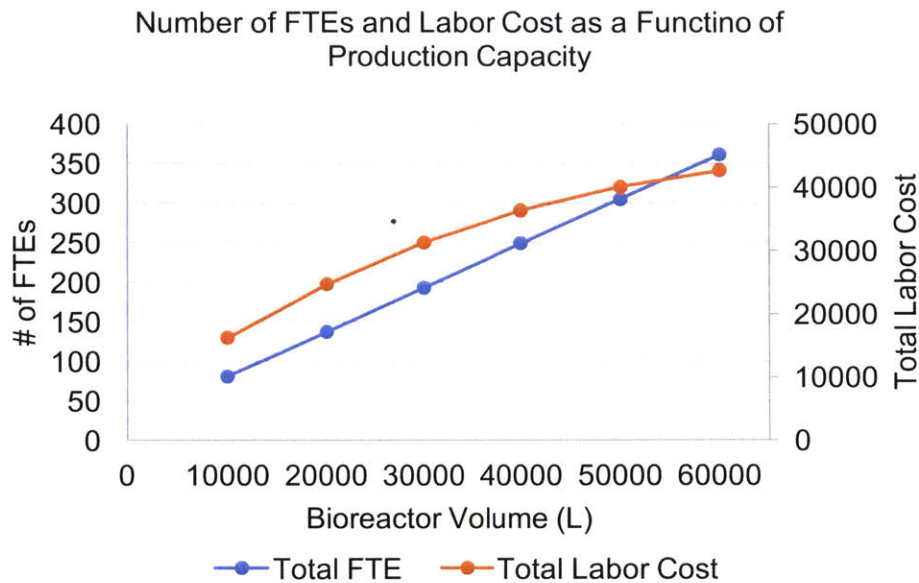
Figure 3.4: Modeling the total number of full time employees (FTEs) and labor cost as a function of production capacity within a biomanufacturing facility. It assumes some job functions scale with the number of bioreactors, while others do not. Additionally, the average annual FTE cost is assumed to decrease 10% during each transition.

3.2 Verification, Validation, & Uncertainty

Verification and validation of the model is important to ensure applicability and robustness in accurately conveying current biomanufacturing processes. Fortunately, elaborate verification and validation methods have been developed to measure uncertainty of a computer-generated model aimed at representing complex relationships in the real-world. These two components are core to the model development process and influenced by the questions the model seeks to answer.

Verification has to do with internal consistency, ensuring that the model correctly functions the way in which it was programmed by the user [127]. It ensures that the model was built correctly, according to the developer's intent. This was done by first outlining specifications for the model before it was built and then ensuring that the final model had those features integrated. Comparing a conceptual model to what is actually being simulated ensures that input parameters and relationships between variables follow a logical structure. Setting bounds on the input variables, based on appropriate and widely accepted values, helps to determine whether the model output is reasonable. To do this, the model was verified by third party reviewers, checking for any errors and confirming that it was built to fulfill the function it was designed for.

Validation has to do with ensuring that the model appropriately reflects the real-world phenomenon after which it is modeled, within a user-determined range of accuracy [127]. It ensures that the model is an accurate representation of the system it is meant to represent. Making appropriate assumptions and using accurate data is the first step in ensuring an acceptable model. For this economic model, a literature review was conducted to ensure a data-informed approach to populating the variables with credible values. Validation is an iterative process that involves comparing the model's input-output relationships to comparable input-output transformations in the real-world system or other published sources. This was done by comparing the outputs of the model with other existing COGs model developed using software such as SimBioPharma and SuperProDesigner, as well as projections shared during the eleven interviews with experts. Modifications can be made in order to minimize errors or discrepancies between the model and real-world output.

Given the evolving nature of the biopharmaceutical ecosystem, verification and validation should be done iteratively, making appropriate changes to input parameters of the baseline cost model for the output to match real-world experience. This will ensure that the model continues to be salient and a useful tool for testing innovations.

Several challenges arise in the verification and validation of economic cost models. One example is identifying and ascertaining different types of uncertainty when conducting assessments. Often, uncertainty can be further categorized as stemming from inaccurate model inputs, numerical approximations, or mathematical assumptions on which the model is based [128]. For the cost models, using an explicit, deterministic approach helps overcome challenges in characterizing uncertainty, as assumptions will be supported by data. Nevertheless, the data varies across sources and is not necessarily a reflection of the specific manufacturing operations of interest. Flexibility and modularity embedded in the baseline model allows for the ability to tweak parameters based on observed conditions. Additionally, necessary precautions need be taken if subsystem data (e.g. purification) is used to predict the behavior of a complete system (e.g. downstream processing) for which performance data is unavailable [128]. Uncertainty can be characterized conceptually, as described thus far, and mathematically through probability functions defining the range of potential values for the input variables if a single point estimate is too simplistic. This involves turning individual parameters into random variables, with pre-defined mean and standard deviation, thus generating a probabilistic distribution of the parameter of interest. Similar uncertainty characterization methods can be used when applying the model to unique scenarios into the future.

3.3 Existing Models and Cost Estimates

Table 3.8 outlines data collected from literature for a typical stainless steel facility, as well as assumptions made when developing the baseline model for monoclonal antibodies.

	Estimate	Explanation	Source	Assumptions in Baseline Model
Process Parameters	Cell concentration at peak: 8.5-9.0 * 10^6 cells / mL for batch and 2.13-2.39 * 10^7 cells / mL for fed-batch	CHO-based batch cultures were tested using different media to compare cell viability and cell concentration. Higher cell concentration correlates with higher titers.	Reinhart [129] Klutz [130]	Cell productivity = 20 pg/cell/day Product concentration = 5 g/L
	5 g/L titer for mammalian cell culture (CHO)	10-fold increase over the past years as a result of process improvements, optimization of media, and cell line development	Thiel [131] Werner [132] Kelly [133]	Run Duration = 15 days
	7-14 days	Typical length of upstream processes for a fed-batch. It takes approximately 7 more days for downstream operations.	Klutz Petrides [134]	Turn around time = 3 days Idle time = 30 days
	70%-80%	Production yield of systems has increased from 40% to at least 80% in the past 10 years	Werner Kelly	Rate of successful batches = 90%
Labor Cost	$58 / hour	Average cost of labor, though this can differ across roles (e.g. managerial, engineering, administrative, legal etc.)	Pollock [135]	Assume average FTE cost of 200,000
	Operating labor = f(utilization)	Demonstrates relative costs of different FTEs, based on their institutional position and utilization of the plant. Managerial and QC/QA labor are equivalent to the operating labor.	Farid [136]	Minimum FTE for basic operations = 55
	$50 million for a 6 x 15,000 L bioreactor plant	For a small-scale plant using disposable, single-use systems the labor is expected to be approximately 60% lower, given the lower number of FTEs needed to run operations.		
Materials Cost	$8 / L $8 / g	Raw material costs for cell culture media, with 75% purification yield. Cost for small-scale, disposable plants is approximately doubled.	Kelly Petrides	Raw Materials = $8/L Consumables = $13.5/g
	$4 / g	Raw materials costs for the downstream purification process of drug substance. Cost for small-scale, disposable plants is approximately doubled.	Kelly	QC/QA/Other = $4/g
	$13.5 / g	Cost for consumables. Assumes Protein A column is used for 60 runs before being switched.	Petrides	

	$35,000 per batch	QA/QC cost per batch	Pollock	
Utilities Cost	$2.5 – 13 million per year	Default value for the annual cost of general utilities per unit floor area was assumed to be $300/m^2. These general utilities do not necessarily account for the additional energy cost for running each batch.	Farid	Baseline $5 million utilities cost per year for operating the plant, plus $10,000 per batch.
Capital Cost	$660-1580 / ft^2 $1765-4220 / L Lang Factor: 3.3-8.1	Determined from data on capital investment costs for 11 antibody facilities using mammalian cell culture. Non-US based facilities cost, on average, 28% less than domestic plants. The factorial method can be used to estimate capital investment by multiplying total equipment purchase cost by the Lang factor.	Farid	Fixed capital investment, with the use of the sixth-tenth rule, that includes building construction, equipment, piping, instrumentation, and utilities installed, as well as design and contractor fees. Assume a 10-year, constant depreciation for estimating depreciation costs. This is based on a 10-year asset lifetime for a manufacturing plant.
	Sixth-tenth Rule, with N = 6/10 as a general rule or ranging between 0.36-1.00 for different bioprocess equipment	Used to estimate capital investment, if the cost of a similar item of different size or capacity is known. The ratio of the capacity of the two objects being compared raised to a power N can help estimate the unknown cost: $C_B = C_A (S_B/S_A)^N$	Remer [137] Tribe	
	$300-500 million for a 6 x 15,000 L bioreactor plant	Cost depends on whether the plant is entirely new or the extension of an old plant, as well as its location. Cost for a disposable plant is expected to be ¼ that of the standard stainless steel plant.	Werner Kelly	
	~$215 million for total direct costs ~$125 million for total indirect costs ~$50 million for contractor fees	These are total, one-time capital costs. Assuming a 4 x 15,000 L train, with production capacity of 2 g/L and yield of ~65%. In the model, it can support 81 batches a year.	Petrides	
Fill & Finish Cost	$10 / vial	Cost of manufacturing drug product, though is influenced by dose and titer	Kelly	$10/vial, split between cost of vial ($1) and process costs ($9)
Other Costs	0.1*capital investment*duration	Maintenance cost	Farid	Maintenance cost integrated in the capital investment.
	0.03*capital investment*duration	Local taxes and insurance	Farid	

Table 3.8: Summary of data collected from literature for operations and costs within a typical stainless steel facility

3.4 Baseline Model & Sensitivity Analysis

3.4.1 Baseline COGs Model

The baseline mode for the production of monoclonal antibodies is a single-product facility with a single 10,000 L bioreactor, with product concentration of 5 g/L and yield of 90%. The base case is static, providing steady-state and time invariant values for discrete event simulations for the manufacture and supply of a specific product. The explicit nature of the models allows all values, both input and output, to be known and modifiable by the user. The model is also deterministic, generating the same output values for a given set of input conditions.

Base Case		
Variable	**Quantity**	**Units**
Process and Operations		
Run Duration	15	days
Turn Around Time	3	days
Idle Time	30	days
Process Success Rate	0.9	fraction
Total Runs per year	18	#
Success Runs per year	16	#
Bioreactor Volume	10000	L
Product Concentration	5	g/L
DS Yield	0.8	fraction
DS to DP Yield	1	fraction
Drug Product / run	**40000**	g
Drug Product / year	**640000**	g

Base Case		
Variable	**Quantity**	**Units**
Labor Cost		
Admin+Other	25	#
Engineering	10	#
Material Management	10	#
Manufacturing Operations	16	#
Quality Systems	20	#
FTE	81	#
FTE Cost	200000	$
Total Annual FTE	**16200000**	**$**
Materials Cost		
US/DS - raw materials	80000	$
US/DS - consumables	540000	$
QA/QC + other Materials	160000	$
Cost per run	780000	$
Total Runs per year	18	#
Annual Materials Cost	**14040000**	**$**
Utility Costs		
Base Cost per year	5000000	$
Total Runs per year	18	#
Cost per run	10000	$
Annual Utilities	**5180000**	**$**
Capital Depreciation		
Investment for 1x1000 L	25000000	$
Capital normalized by plant size	99526793	$
Annual Capital Depreciation	**19905359**	**$**
Fill and Finish Costs		
Yield DS to DP	1	%
Volume of 1 vial	1	g
# of vials	640000	#
Cost of Vial	1	#
Process Cost of Vial	9	#
F&F Cost	**6400000**	**#**

Major Cost Centers	$ (millions)	% of Total
Labor (Annual FTE) Cost	16.20	0.26
Materials Costs	14.04	0.23
Utilities Costs	5.18	0.08
Capital Depreciation	19.91	0.32
Fill and Finish Costs	6.40	0.10
Taxes + Insurance	0.60	0.01
Annual Cost of Production	**62.32**	

Variable	Quantity	Units
Cost of Goods		
Annual Cost of Production	62.32	$ (millions)
Drug Product / year	640000	g
CoGs	**97**	**$ / g**

Table 3.9: Baseline model for the manufacturing of monoclonal antibodies (mAbs)

The relative share of different cost centers is demonstrated in **Figure 3.5**, with capital costs accounting for the greatest share of overall COGs (32%), followed by labor (26%) and materials (23%) costs. The results generated from the baseline model are in the appropriate range and scale compared to published results using this production scale and titer.
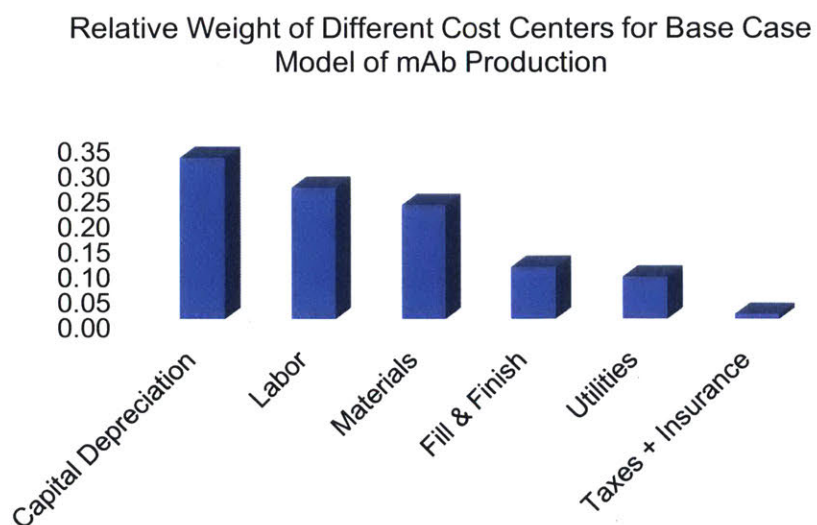
Figure 3.5: Relative proportion of different cost centers in the base case for mAb production

3.4.2 Scenarios: single-variable deterministic sensitivity analysis

Sensitivity analysis is a useful tool to provide a systematic way of examining the effects of deviations in input variables on the output (production volume and COGs). This can be done in a multitude of ways and help validate that the model works properly, as would be expected in the real world. Given the assumption that the base case economic model is for a single-product stainless-steel facility, the deviations are good indicators of batch-to-batch variability of manufactured material. First, a scenarios table was made to indicate the base case, as well as worst and best case values for different input variables of interest based on literature and currently plausible values in industry. This approach fluctuates one input variable at a time, while keeping all others fixed at their baseline values. COGs estimates were made for each of the individual scenarios and compared to the baseline COGs of $97/g of mAb manufactured.

Variable	Units	Worst	Base	Best
Run Duration	days	20	15	10
Turnaround Time	days	6	3	1
Idle Time	days	45	30	15
Process Success Rate	%	75	90	100
Titer	g/L	2	5	8
DS Yield	%	65	80	95
DS to DP Yield	%	85	100	100
Average Wage	$/FTE	250000	200000	150000
Raw Materials	$/L	12	8	4
Consumables	$/g	17	13.5	10
Base Utility Cost	$ (million)	6.5	5	3.5
Investment for 1x1000L	$ (million)	30	25	20

Table 3.10: Worse and best case scenarios for input variables

Tornado plots were then constructed to graphically demonstrate the sensitivity of the annual production volume (**Figure 3.6**) and COGs (**Figure 3.7**), the two major output values, relative to baseline. This was done for each input variable separately, as described in Lim et al [138]. Both figures demonstrate the relatively high impact of titer on both volume and COGs, compared to other factors tested.

Sensitivity of Annual Product Volume to Different Input Variables
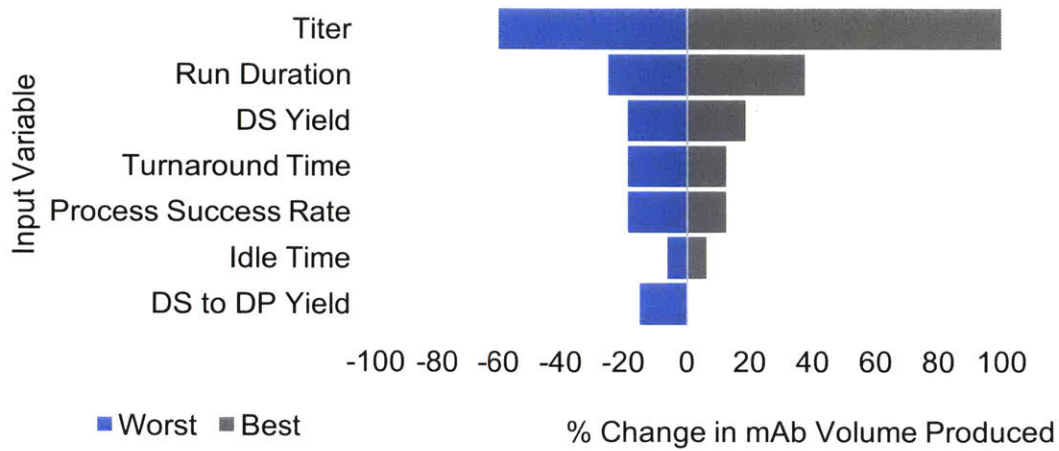
Figure 3.6: Changes in baseline annual product volume for worst and best case scenarios of different input variables

Sensitivity of COGs to Changes in Different Input Variables
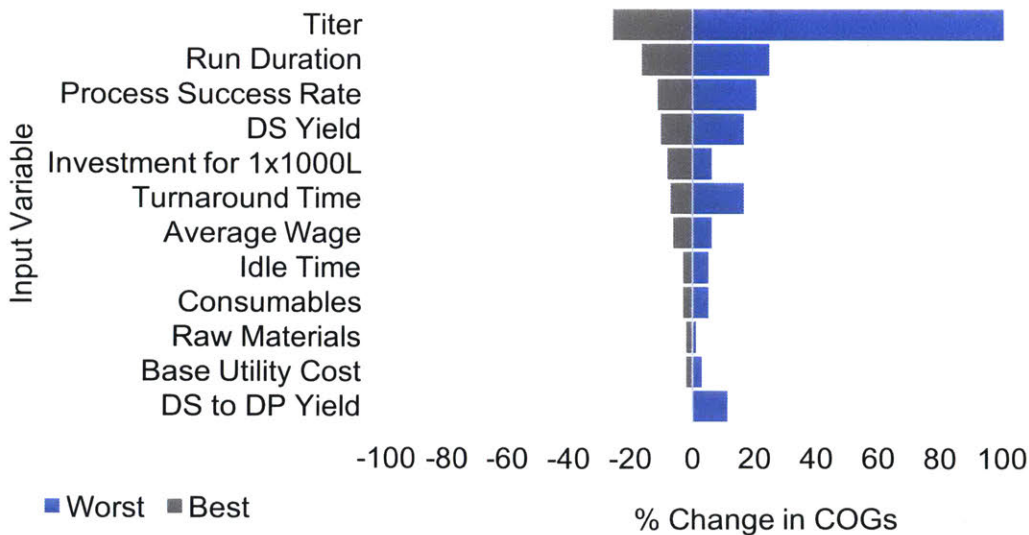
Figure 3.7: Changes in baseline COGs for worst and best case scenarios of different input variables

Sensitivity analysis can also be done by demonstrating the impact of economies of scale. Changes in COGs were modeled when increasing the number of bioreactors in a stainless steel biomanufacturing plant. Each bioreactor is assumed to be 10,000 L, within the normal range for stainless steel plants, while keeping the same baseline conditions as previously defined (titer, run

time, etc.). This ensures that each bioreactor modeled produces the same volume of product. **Figure 3.8** shows changes in the relative weight of the cost centers as the number of bioreactors increases. The percentage of the COGs taken up by materials and fill-and-finish increasing, while that associated with labor and capital cost decreasing.
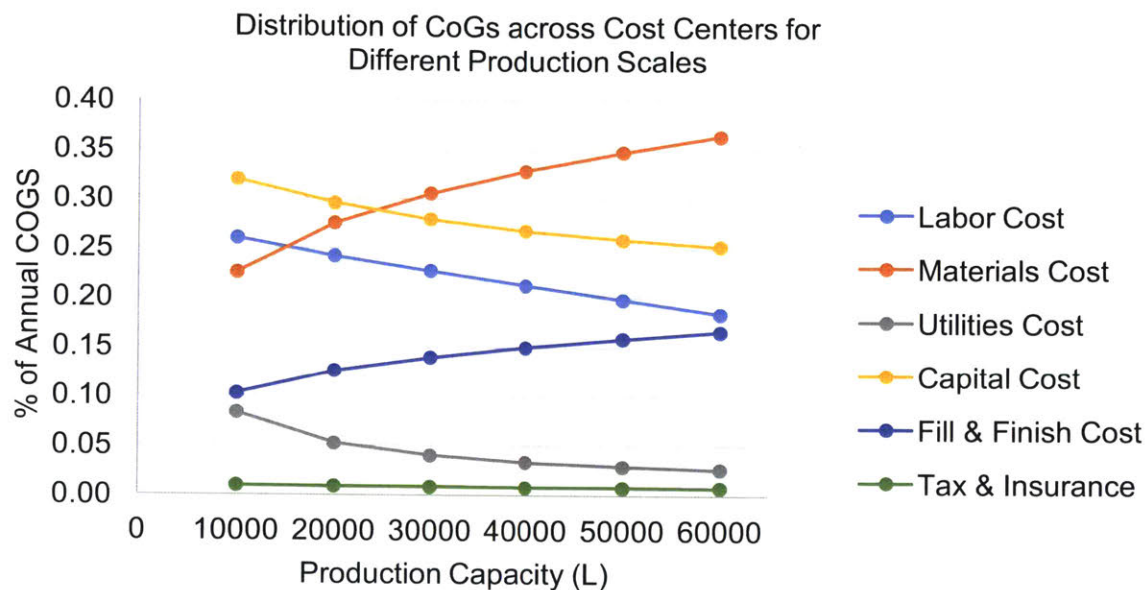
Figure 3.8: Relative proportion of different cost centers as a function of production capacity

The impact of economies of scale on COGs is seen in **Figure 3.9**, with the baseline production cost decreasing from $97/g to $60/g, as the number of bioreactors increases from 1 to 6 and total production output increases from 640 kg to 3840 kg, respectively. These trends are similar to volume-dependent scaling of COGs reported by *Petrides et al.* and others.
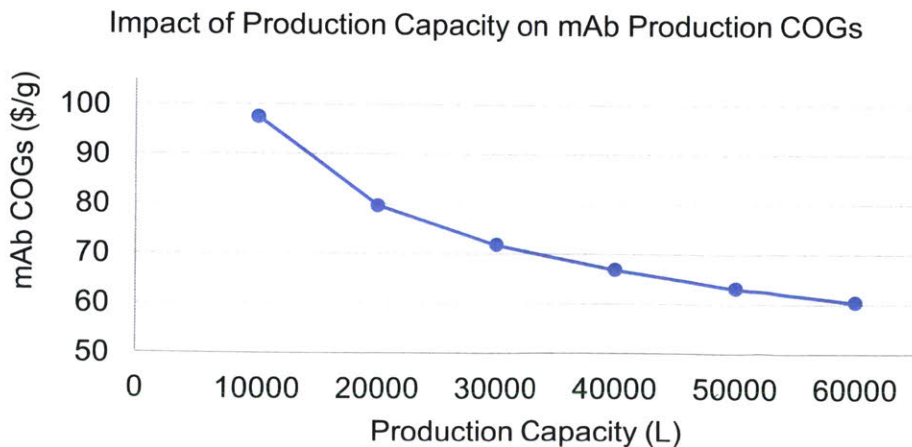
Figure 3.9: COGs for mAbs using baseline model at different production scales

3.4.3 Joint sensitivity analysis

Recognizing that functions within a biomanufacturing systems are interconnected, it can be useful to conduct two-variable sensitivity analysis, especially when variables influence one another. Sensitivity was demonstrated by modeling changes in COGs as a function of both product titer and manufacturing capacity (i.e. bioreactor volume), as seen in **Figure 3.10**.
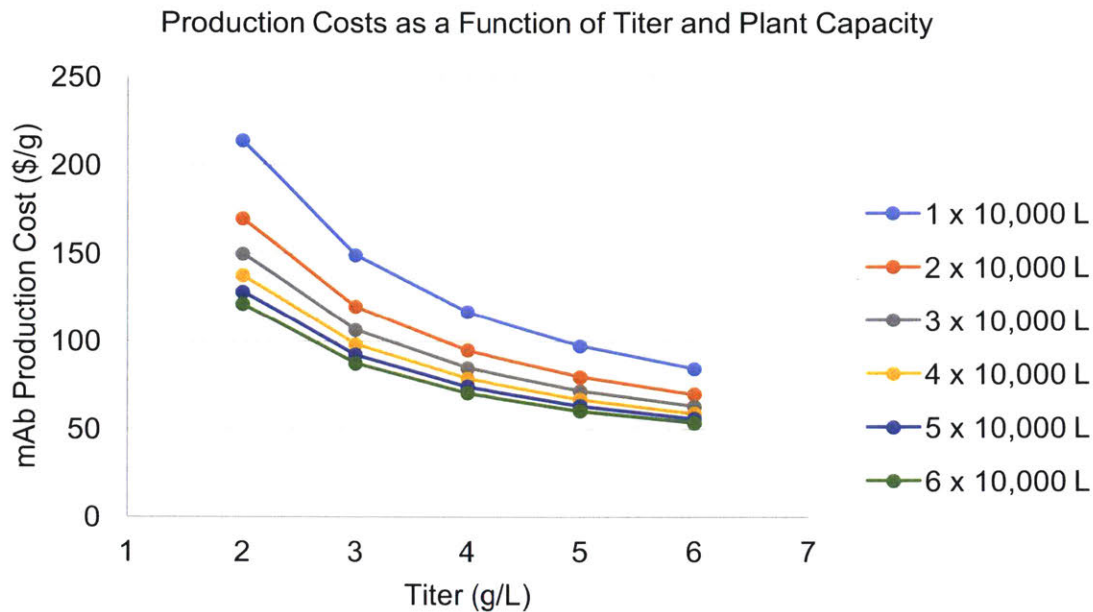
Figure 3.10: COGs for mAb using baseline model at different production scales and titers

3.4.4 Probabilistic analysis

While worst and best case scenario analysis can be useful to model extreme conditions, it may be more realistic to demonstrate uncertainty by taking each input condition as a random variable. In this case, each input becomes a random variable with a pre-defined mean and standard deviation, as well as minimum and maximum cut-off values defined by the best and worse case scenarios, respectively. To demonstrate uncertainty, 1000 samples were generated for each of the following random variables:

- *Operations*: run duration, turnaround and idle time, process success rate, titer, and yield
- *Labor Cost*: number of FTEs, average salary
- *Materials Cost*: raw materials, consumables, QC/QA/Other
- *Utilities Cost*: base cost and cost per run
- *Capital Cost:* initial investment for 1x1000L, maintenance, and depreciation rate
- *Other Costs:* local tax and insurance rates

The samples were used to calculate values for the annual COGs and annual production volume of mAbs for each unique scenario of the baseline, stainless steel model, as seen in the distributions in **Figure 3.11** and **Figure 3.12**.

Distribution for the Cost of Goods of mAb Production
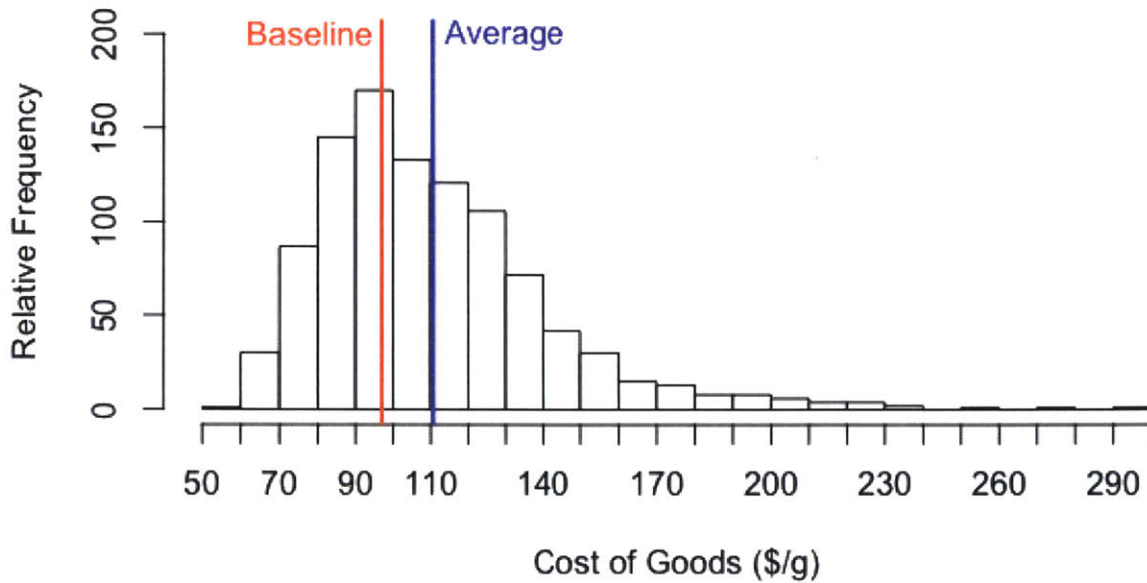
Figure 3.11: Distribution for COGs of 1000 scenarios of the baseline model, with an average of $111/g, standard deviation of $31/g, and 95% CI [108.8,112.6] compared to the baseline COGs of $97/g

Distribution for the Annual Quantity of mAb Production
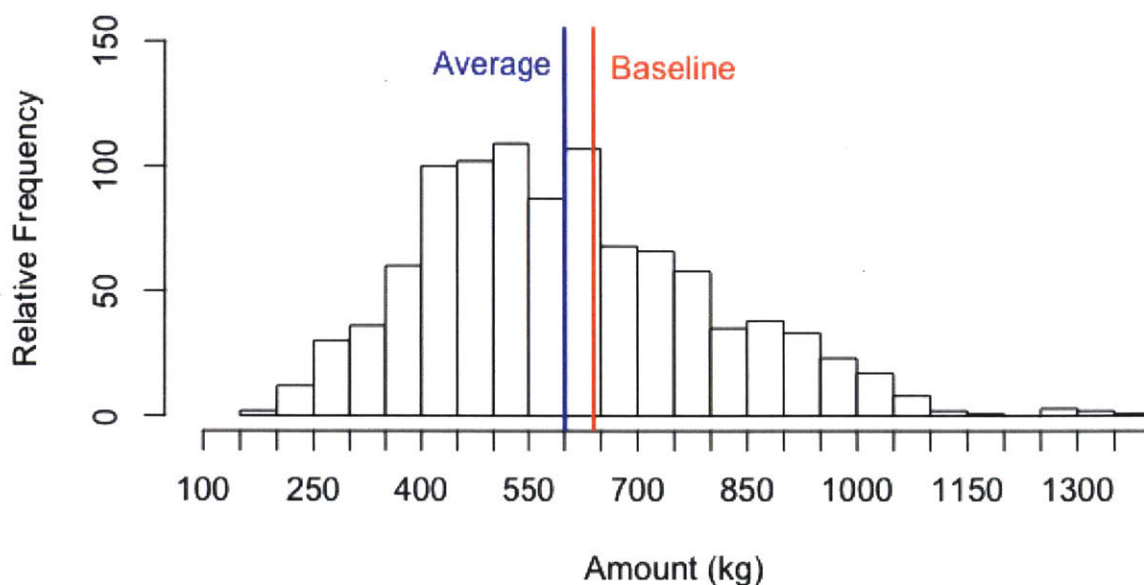
Figure 3.12: Distribution for annual production quantity for 1000 scenarios of the baseline model, with an average of 601 kg, standard deviation of 198 kg, and 95% CI [588.6,613.2] compared to the baseline production volume of 640 kg.

These distributions demonstrate the variability that can arise, even in the baseline model, when input variables take on values within an industry accepted range. In the case of COGs, close to 62% of samples were above the baseline, deterministic value of $97/g, while 61% failed to meet target minimum production volume of 640 kg, which may translate in drug shortage in practice. As previously done, the 1000 scenarios of the baseline model can be used to demonstrate single-variable sensitivity analysis and economies of scale. This was done by plotting COGs as a function of titer and run duration, the most variables for which the COGs are most sensitive to, as seen in **Figure 3.13** and **Figure 3.14**. This further supports the model's ability to account for a range of input values and output realistic values.

Distribution of Scenarios for Baseline COGs Model
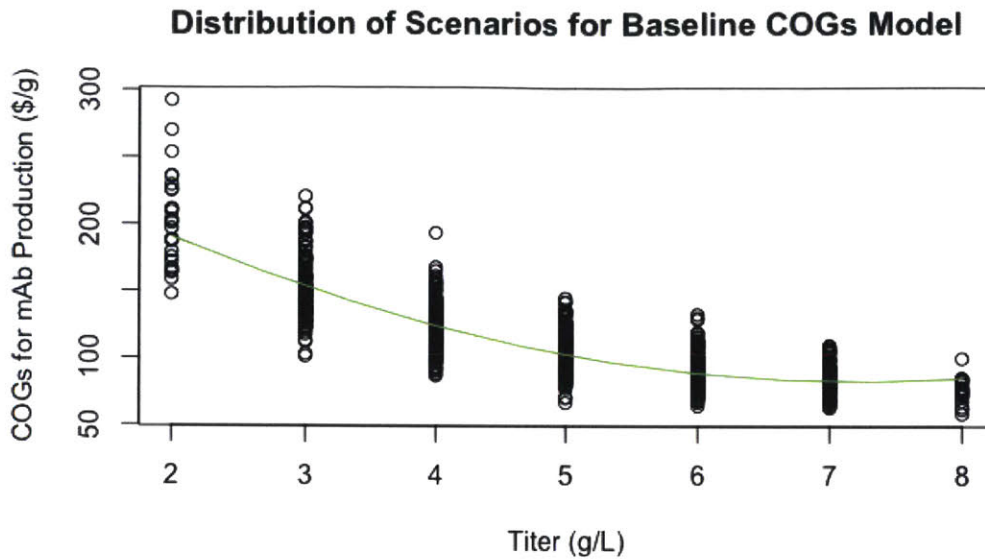
Figure 3.13: Distribution of COGs for 1000 cases as a function of titer

Distribution of Scenarios for Baseline COGs Model
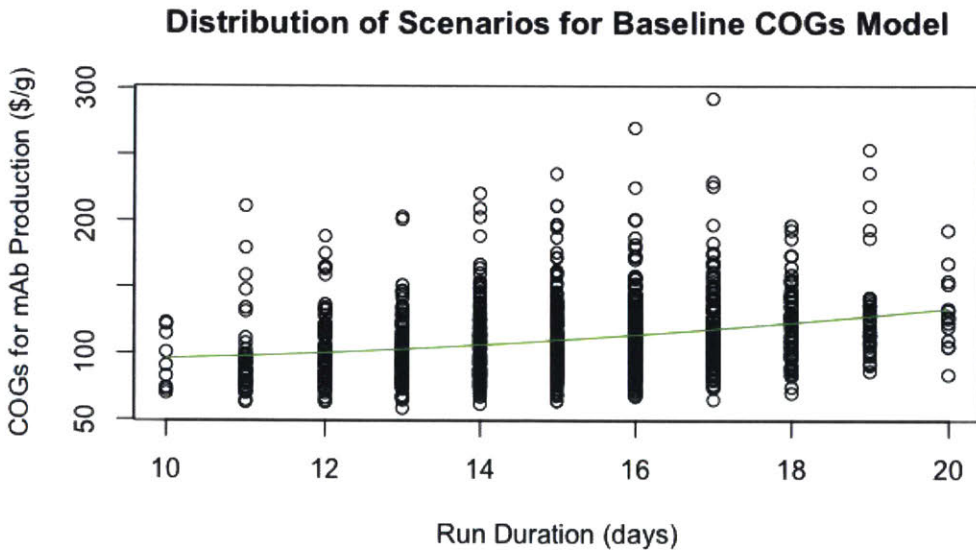
Figure 3.14: Distribution of COGs for 1000 cases as a function of run duration

Incorporating uncertainty into the analysis is better than no uncertainty, as in the base-case deterministic scenario. Probabilistic analysis is useful to generate potential scenarios; however, the shape of the resulting distribution can be influenced by the distributional assumptions. For example, using normal distributions (as demonstrated in this chapter), compared to uncertainty defined by uniform or triangular distributions. Different shapes of uncertainties influence overall performance of the biomanufacturing system being modeled. This can be demonstrated by plotting the COGs relative to realized demand as a percentage of the base-case (640 kg) for 1000

scenarios using uncertainty defined by uniform, triangular, and normal distributions. While there is no significant difference, **figure 3.15** shows how the range of outcomes is larger (thus with more extreme values) when using a uniform or triangular uncertainty distribution. Using the uniform distribution yield the most clustered distribution.
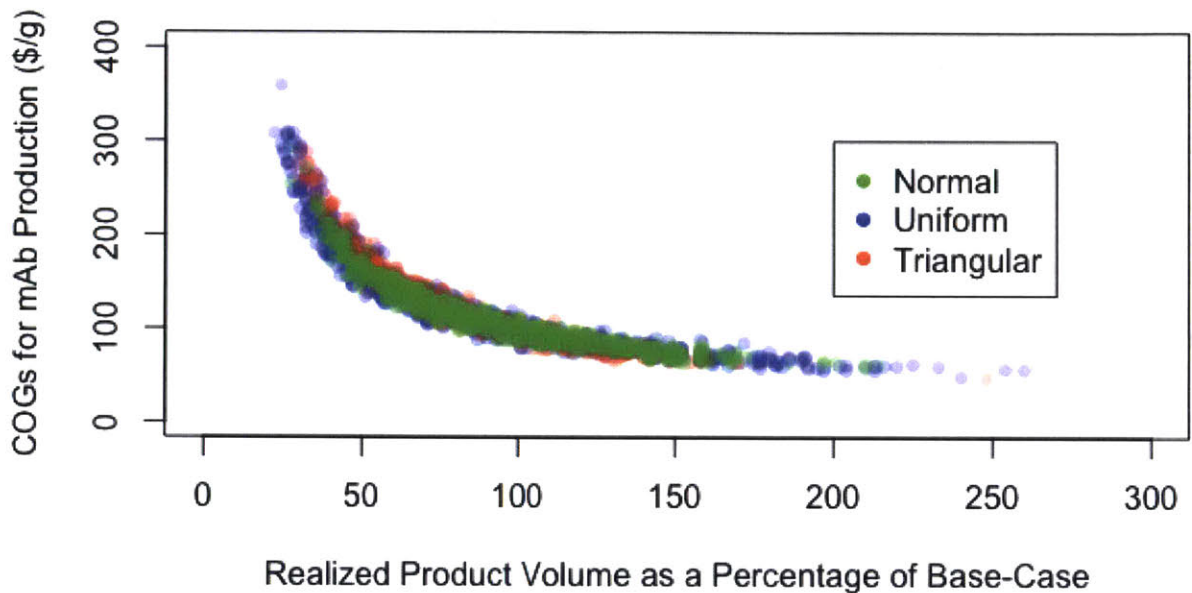
Figure 3.15: Effect of uncertainty function on distribution of COGs relative to the realized product volume as a percentage of the base, deterministic case of 640 kg. This was done using normal, uniform, and triangular uncertainty functions to demonstrate the effect distribution type has on the outcomes.

Chapter 4: Results and Findings

4.1 Using Models to Test Innovations

Understanding the levers influencing production and distribution of biologic medicines, as well as consequences of alternative decisions, are often only recognized in hindsight. More available data could help guide prospective evaluation of the consequences of alternative decisions and reducing the risk of reactive policy changes, misguided investments, or structural reforms that may not be the most optimal. Decision support tools are thus useful in reconciling disparate alternatives, evaluating tradeoffs, and identifying priorities. To address growing health care needs today, and better prepare for future demand, resource allocation needs to account for present supply availability, responsiveness to investments over time, and future trends in science, technology, and innovation policy that have the potential to shift the current biopharmaceutical paradigm.

Decision support tools, especially dynamic models and simulations, also help overcome shortcomings of more common economic models. For example, the use of randomized control trials would be too time-and-resource intensive to implement in practice. The cost of testing policy or technology innovations would be exorbitant, partly as a result of high fixed capital costs and those associated with gaining regulatory approvals for any process changes. Difference-in-difference estimation, measuring pre-and-post states after introducing a change, would also be a challenge due to violating the parallel trends assumptions, with competing regulatory, social, political, and manufacturing conditions across the industry. In each case, the goal is overcoming the fundamental problem of causal inference, in which the outcome of two different inputs on the same system cannot be observed simultaneously. Nevertheless, while these economic tests provide an insight into causal inference, they do not necessarily identify the intervention that will have the most change on the output (e.g. COGs) across a range of input options.

The baseline cost model for the manufacturing of mAbs in a stainless steel manufacturing plant, presented in Chapter 3, can be used to test various innovations (e.g. policies and technologies) to demonstrate system effects, tradeoffs, and impact on COGs. Such an approach can also be used to determine the relative short-and-long term impact of alternative innovations on production volume, facility utilization, and other factors affecting cost. In this research, COGs is used as a proxy for the supply-side component of access. Comparing the relative impact of these changes

allows for cost-benefit analysis and ranking of policies based on their utility in generating cost-savings for manufacturers. The most impactful policy interventions tested can further be optimized to maximize cost savings. This analysis provides insight into which variables in the system are most conducive to enabling change in the output variables when introduced with a hypothetical innovation.

Traditional economic models for causal inference rely heavily on assumptions such as randomization, which are difficult to do in practice at a systems and population scale. Therefore, economic model simulation to perform tradeoff and cost-benefit analysis is most suitable. Employing models to conduct economic evaluations before policy implementation is most useful in promoting efficient allocation of scarce public health resources [139].

4.2 Research Scope

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 [140]. However, to date the biopharmaceutical market has been heavily concentrated in the US, Western Europe, and Japan. Identifying barriers to high-quality, affordable, and reliable biologic drug supply in LMICs, as well as developing innovations to overcome such bottlenecks, is an important first step to ensure that the growing demand for lifesaving treatments is met.

While scaling global supply to biologics requires a multi-pronged approach, the focus of this research is to better understand and analytically model tradeoffs between different production networks, notably across the centralized-distributed spectrum of biomanufacturing. 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 some 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. The recommendation to decentralize production has been made by the World Health Organization for many years as a means to overcoming medicines needs in underserved populations, through with caution against the risk of ineffective local production due to lack of resources or materials [141]. More recently, assessing tradeoffs of locally producing

medicines encompass a broader set of location-specific factors that influence the ability for local production be feasible, internationally competitive, and sustainable. Recognizing the extent to which biologics value-chains are deeply embedded in local context, the context for this research is centered on the unique factors influencing the decision to decentralize biologics production and the relative costs across different productions systems. This research is done with an appreciation for both financial and non-financial drivers and barriers within the biopharmaceutical industry.

4.3 Incentives for Shifting Away from the Current Biopharmaceutical Paradigm

4.3.1 Approach

The analysis below is largely based on secondary research. The growing literature on this topic provides useful insight, though with contradictory information at times. It indicates the importance of spatial factors (social, environmental, economic, and institutional features of places) that influence a country's capacity to endogenously develop and sustain a biopharmaceutical industry. The analysis is also informed by interviews conducted with biopharmaceutical experts, regulators, and NGO representatives during the Fall of 2016 at the Center for Biomedical Innovation, and review of transcripts for comments relevant to the research questions.

Several case studies were also used to draw industry-wide conclusions. These aim to cover a range of geographic contexts and stakeholders, from which findings could be synthesized. While not all case studies converge on similar conclusions, several recurring themes were noted.
- Using Intellectual Property Rights to Stimulate Pharmaceutical Production in Developing Countries: A Reference Guide (UNCTAD) [142]
- Local Production of Pharmaceuticals and Related Technology Transfer in Developing Countries, A series of case studies by the UNCTAD Secretariat [143].
  - o Jordanian Pharmaceutical Manufacturing Co. PLC (JPM), Jordanian Association of Pharmaceutical Manufacturers and Medical Appliances (JAPM) and the World Health Organization (WHO) office in Jordan
  - o Government Pharmaceutical Organization (GPO) of Thailand and WHO Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property (GSPA-PHI)

- Africa Fighting Malaria - the push for local production, costs and benefits – A case study of Uganda's Quality Chemicals (Columbia University) [144]
- WHO and Boston University, Local production: industrial policy and access to medicines- - An Overview of Key Concepts, Issues, and Opportunities for Future Research [145]
- Global Innovation – Lessons Learned from the Novo Nordisk Case in China (Copenhagen Business School) [146]

4.3.2 Defining "Local" Production

The activities within a biomanufacturing industry can be categorized based on where they stand within the biologics value chain. These include drug discovery, clinical development, manufacturing, distribution and global delivery, marketing and reimbursement policy, drug use, and clinical care. Within manufacturing, there are often three principle manufacturing tiers: primary for bringing raw material inputs into the active pharmaceutical ingredient (or drug substance for biologics), secondary for turning the API into finished product, and tertiary when filling the finished product into its final ready-to-ship form. From an operational point-of-view, if any part of the manufacturing process takes place locally, it could be considered as locally-produced. Chapter 2, specifically Figures 2 and 3, outlines different ways of defining "local" production, especially for multinationals that have their headquarters in one place but may have substantive R&D, technical, or manufacturing development in the country of interest. For the purposes of this research, biologics production is deemed "local" when the product is principally manufactured locally, both drug substance and finished product.

4.3.2 Supply-Side Motivations for Localizing Production

Lower costs and tax incentives: Costs such as wages and infrastructure are often lower abroad, particularly in emerging markets, which can reduce the cost of operations for a local manufacturer. However, biomanufacturing remains skill-intensive, making it costlier to find, train, monitor, and retain the right labor. Case studies indicate that heavy investment into education and professional development are needed to maintain a constant supply of engineers to fulfill necessary functions within a biomanufacturing plant. Some regions may lack local talent, therefore potentially increasing upfront costs if implementing the appropriate training. Others can attract manufacturers with well-established educational systems and tax incentives. As one example, Singapore offers both lower wages and a highly-educated workforce, as well as tax incentives, attracting large biotechnology growth over the past few years. Alternatively, companies working in other emerging

markets significantly invest in training programs to build local workforce capacity and promote low attrition.

Closer to market: Proximity between sites of production and local markets may help overcome challenges associated with supply chain logistics, cold-chain, procurements, stock-outs, and cost of inventory. It may also lower time to patients and reduce risks stemming from supply chain dependency.

Market expansion: From a supply-side, biopharmaceutical companies may seek economic incentives from local production, for example, in the form of a new market and revenue stream. With NCDs on the rise in parts of Asia, Africa, and Latin America, large populations are expected to start demanding safe, effective therapies. In BRICs (Brazil, Russia, India, China and South Africa) countries, where socioeconomic level is steadily increasing, purchasing power will also go up and may lead to new market opportunities. Being the first in a new market is important to capture trust and customers before competitors do so.

Mandated or compulsory licensing: In times of national emergency or due to company's abusive use of pricing policies, international trade policies under several conventions have allowed for trade-related intellectual property rights (TRIPS) that provide a pathway for compulsory licensing, allowing governments to locally supply drugs and infringe patents. However, defining when compulsory licensing is appropriate or abused by governments leads to complex negotiations, as well as ethical questions on ensuring the integrity of drug quality. Similar, countries have imposed policies that raise national borders, levying taxes on imported medicines or banning them entirely. Entering the "patent cliff", with many blockbuster drugs going off-patent and introduction of biosimilar competitors, calls for a need to re-examine business models and adjust accordingly. While these actions are aimed at promoting local production, such decisions can have counterintuitive effects if the country does not actually have the capacity to produce safe and efficacious biologics locally. If local production is inefficient, there is the temptation for governments to enact legislation to protect local firms from more efficient, foreign producers. In Tanzania, the government implemented a 10 percent tax levy on imported medicines to keep local producers competitive, and in Nigeria the government banned the importation of many drugs that are also manufactured locally, so much so that local industry now supplies more than 30 percent of medicines in the country.

Cluster enrichment: As described by Michael Porter, "upgrading the cluster" can often be an incentive for local manufacturing, as having a biotechnology cluster can have positive externalities such as knowledge spillovers and enhancing the regulatory capacity of local institutions. Establishing manufacturing capacity can have significant positive externalities on a local economy as well. 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.

Publicity and building trust: Donations have been a major part of the corporate social responsibility portfolio of many biopharmaceutical companies, especially to patients in low-resource settings, as part of humanitarian response efforts, and in post-conflict areas. Despite the intentions associated with giving away drugs to those who need it most, it does little to close systemic gaps in increasing access to biologics and lower prices of drugs. Establishing local manufacturing sites may be seen as a form of publicity and donation, especially if the manufacturer manufactures at-cost or at-loss. There is also value in local presence, allowing to build trust with the rest of the biopharmaceutical and innovation ecosystem, including regulatory institutions, local authorities, suppliers, providers and patients.

4.3.3 Demand-Side Motivations for Localizing Production

From the perspective of a government and its patients, the demand-side motivations are three pronged: public health priority to increase local access to medicines, economic incentives from a local biotechnology industry, and a national security imperative. Tensions arise in developing policies aimed at attaining one or more of these objectives, though they are often aligned. Developing a strong industrial base depends on range of endowments (e.g. reliable utilities, land), skilled labor, political stability, and societal acceptance. However, some countries pass policies aimed at economic protectionism even though they lack capacity for high quality, efficacious medicines production or are affected by chronic political turmoil and regional instability. In 2005, Uganda partnered with Cipla to create Quality Chemicals Industries Limited (QCIL) with the hope of producing affordable anti-retroviral and anti-malarial drugs for the local market. Despite these efforts, investments aimed at localizing production have led to questionable quality standards, inconsistent financing, and persistent issues with local access as a result of an inadequate national procurement and distribution system [147]. This can have negative effects, putting economic incentives in front of people's needs.

There are interesting regional distinctions that can also be made regarding local capacity and competitiveness to maintain a biopharmaceutical industry. Many countries in Asia (e.g. China, India, Thailand) have invested resources and built an environment ripe for biologics development, especially as their patient populations rapidly grow. Latin America has a few unique areas such as Brazil and Cuba that have developed into emerging centers for biologics manufacturing, though for different reasons. The former is due to economic policies aimed at increasing the economy and better responding to public health needs, as high prices for biologics became an impediment to medicines access. For Cuba, its isolation from the rest of the world and trade embargos imposed by many countries forced it to develop the capacities and know-how for local production. Many countries in Africa, however, have protracted issues that prevent them from developing biotechnology clusters and ecosystem appropriate for local biologics production. These include, amongst others, lack of technical expertise (e.g. access to know-how for designing and running GMP-compliant facilities), financial constraints (e.g. access to consistent investment capital, reliance on aid and foreign debt), and infrastructure requirements (e.g. poor utilities, undeveloped supportive industries), along with issues such as political instability and corruption [148].

From a national security perspective, localizing production of biologics (e.g. vaccines) is important to reduce reliance on imported medicines and to promote faster response to national emergencies. For example, a study conducted on insulin trade estimated that 50 million people globally lack sustained access to insulin, three countries account for exporting 85-96% of global insulin (primarily to other high income countries), and that from 2004-2014 approximately 60 countries had no local production and imported from only one exporter, making them vulnerable to disruptions in the supply chain [149]. From an industrial and economic perspective, governments are increasingly passing policies that mandate in-country production for in-country marketing in order to promote local economic growth, or provide subsidies to incentivize companies to manufacture within their borders.

A main challenge with accomplishing local production is technology transfer and know-how. 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, therefore, 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. A potential incentive, however, may be the diversification of risks through local

production. If one facility breaks down, another would be able to fill the gap, assuming that the second plant is able to meet the demand and that it has been approved to do so from a regulatory standpoint.

4.3.4 Spatial Factors Influencing Location Selection

A range of different factors have been defined in literature for their influence on the capacity for and competitiveness in sustaining biopharmaceutical production in a non-traditional market (e.g. low-and-middle income countries). Of relevance, the location-allocation problem offers a logical and analytical approach for comparing tradeoffs when choosing the location of new manufacturing facilities [150]. Traditionally, such problems have focused on minimizing transportation cost from facilities to customers and satisfying customer demand, but have more recently been expanded to consider a broader set of variables. Various other definitions and frameworks have been proposed, as the type and importance of different factors depends largely on the stakeholder's perspective. In this research, the focus is on risk factors and conditions most conducive for the manufacturer, the entity making and supplying the biologics.

A compilation of relevant variables, seen in **Table 4.1**, are grouped into four overarching categories: social, economic, built-and-natural environment, and institutional/political. While there is no deterministic list of factors that define whether or not local production will be successful, given the complexity of their interactions and unique local environments, there are ways to categorize them in meaningful ways. Some variables are considered go/no-go given their level of influence on a manufacturer's decision. For example, if a government mandates local production for a given product, there is no other choice than to manufacture locally if patients are to have access to the product. A second tier of variables, largely economic (e.g. tax incentives, market potential) tend to have more influence than some of the social factors that influence quality of life. The severity of risks associated with environmental factors of a place (e.g. risk of natural disaster) may be too high, in some context, even with economic incentives.

Providing a qualitative ranking of different factors within each category could be useful to guide which factors should be optimized when guiding decision-making. However, these may differ depending on the company culture, type of product, risk-aversion, and pre-existing infrastructure, amongst other factors. Companies may also have multiple motives when deciding on the type and location of manufacturing networks, making multiple factors linked and thus increasing risk [151]. For example, these can include political stability, global competition, clarity of corporate

government regulations, and other economic-related factors, each of which can have several sub-factors to help rank competitiveness between locations [152]. With available data, optimizing tools such as integer goal programming have been used to compare risks across locations and solve the location-allocation problem described above. While these are difficult to generalize, providing a framework is a useful starting point for appropriately considering relevant factors in the early stages of the decision making process in biomanufacturing, especially since choices made during clinical stages can lead to substantive capital investment and long-term obligations on the way a product is manufactured.

Social	Economic	Natural/Built Environment	Institutional
Working conditions and quality of life	Tax Incentives and other subsidies	Disaster Risks (climate, biologic, chemical, etc.)	Legal and regulatory framework
Safety and community	Cost of capital and materials, economies of scale	Transportation networks (air, road, rail, water)	Patent protection and licensures
Cost of living	Depreciation of assets and competition	Utilities (water, power, connectivity, etc.)	Technology transfer mechanisms
Education and training	Skilled workforce, constant supply of talent	Infrastructure	Political stability
Knowledge spillovers	Proximity to market	Waste disposal and ecological footprint	Networks – research centers, universities, etc.

Table 4.1: Range of spatial and factors influencing strategic manufacturing decisions

4.4 Consequences of Shifting from Centralized to Distributed Production

4.4.1 Approach

A qualitative thought experiment was conducted to determine how major cost centers identified in Chapter 2 would be impacted when shifting from a traditional, centralized manufacturing model to one that is more distributed. **Figure 4.1** and **Table 4.2** outline the expected consequences of a shift to a distributed model relative to the centralized, baseline reference model, as determined from literature and interviews conducted. In this scenario, a centralized model with one stainless steel, high-volume production facility is compared to six smaller production facilities, one for each of the WHO regions. Both production networks have the same total aggregate output of mAb product. In this scenario analysis, the following assumptions were made:

- The traditional, centralized model is comprised of a large plant with stainless steel bioreactors, while the distributed model is made up of smaller plants with single-use and disposable bioreactors;
- Comparing across sites contrasts one high-volume stainless steel plant to one small, single-use and flexible factory;
- Comparing across networks contrasts one high volume central manufacturing plant with the sum of six (one per region) small, single-use factories that are needed to satisfy the same production output;
- Geographic differentiation between production networks being compared, such that small, modular factories are likely to be used when distributing production while large plants are used in the case of centralized production

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.

Cost Centers

R&D	Cost of Capital	Cost of Regulation	IP Protection	Taxes & Trades
	Cost of Operations	Cost of Inventory	Shipping & Delivery /	Sales & Marketing

Other Risks / Benefits

Time to Product	Capacity Utilization	Reliability of Utilities	Risk of Error
Tax Incentives	Sales	Waste / Footprint	

Legend
- Strength
- Similar
- Weakness
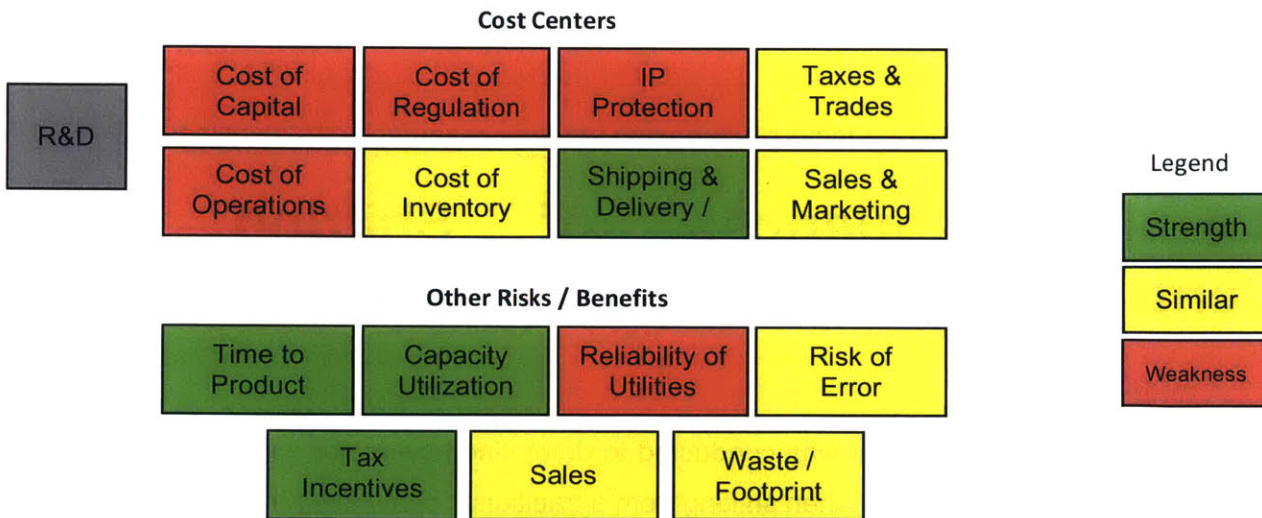
Figure 4.1: Expected change in cost centers and other non-cost variables when comparing a centralized model with a decentralized system, each producing the same total product volume

Variable	1:1 site comparison	1:1 capacity comparison	Comments
Cost Centers: higher (-), lower (+), or no change (0) compared to centralized model			
Cost of capital	+	-	May depend on the type and number of distributed sites
Cost of operations and goods	+	-	Lower wage but may need more training, access to raw materials may be challenging
Packaging	0	-	Scale with number of sites
Shipping	+	+	Lower distance but may incur raw material supply costs
Tariffs/trade taxes	+	+	Overall less export/import, local productions likely favored
Regional delivery / storage	+	+	Closer proximity to sites
Local delivery / storage	+	+	Closer proximity to sites
Sales / marketing	0	0	Expect balancing of increased exposure and competition
IP / trade secrets	0	-	Great exposure to knowledge and tech transfer in more sites interested in growing their biotech industry
Regulatory compliance	0	-	Scale with sites, given different requirements in different regulatory jurisdictions, especially if implementing process changes
Other Risks/Benefits: better (+), worse (-), or no change (0) compared to centralized model			
Capacity / Output	-	0	Aggregate capacity is equivalent
Time to manufacture	+	-	Installation and start-up time is shorter per site, but may not be for all sites combined
Ease of changing products	+	+	Single-use facilities allow rapid turnaround between products
Risk of utilities	0	-	Higher risk in non-traditional contexts

Tax incentives / subsidies	0	+	Likely incentivized by local government and authorities
Access to market	-	+	Close to end-market, potential for more exposure and growth
Risk of regulatory non-compliance	0	-	Scales with number of sites, especially cross-site coordination
Risk of contamination	0	0	Assumed constant for each production scenario

Table 4.2: Qualitative analysis of switching from a centralized to distributed manufacturing model

4.4.2 Analysis of Trends

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

Cost of Capital & COGs: While the capital cost of a 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 [153]. 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 [154].

Labor: Wages are often lower abroad, particularly in emerging markets, which can reduce the cost of operations for a distributed manufacturer. However, biomanufacturing 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 appropriate training. As one example, Singapore offers both lower wages and a highly-educated workforce, attracting large biotechnology growth over the past few years. Alternatively, governments or companies in emerging markets may need to invest in training programs to build local workforce capacity and incentivize low job attrition. 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 need to be duplicated at each site.

Cost of Regulation: Each facility and manufacturing process must be qualified and validated, such that costs 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, as well as experience delays in 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 access to subsidies or other financial incentives, especially if benefitting local economy and labor, the tradeoffs may be more difficult to discern.

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 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, given the importance of integrating knowledge of cold chains throughout the entire value-chain [98]. Distributed systems likely reduce total shipping, as products are prepared closer to markets. Estimating changes in storage costs is more difficult since this 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.

4.4.3 Contextual Considerations

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 [155].

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: While the local economy may not be a driver for selecting the location of a manufacturing facility, doing so may have significant positive externalities on its surrounding

ecosystem. 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 companies 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.

4.5 Case Study: Trastuzumab

Breast cancer is the most prevalent cancer in women, with 1.7 million cases diagnosed globally in 2012 [156]. While the highest incidence rates are found in Western Europe and North America, survival rates in most LMICs are lower than in high income countries [157]. An estimated 15% to 20% of breast cancers are classified as human epidermal growth factor receptor 2 (HER-2) positive, requiring aggressive clinical treatment [158]. Anti-HER2 monoclonal antibodies (e.g. Trastuzumab) have been shown to decrease rates of recurrence by up to 50% and breast cancer mortality by up to 30%, compared to traditional chemotherapy alone [159]. By 2030, the number of women diagnosed with breast cancer each year is expected to nearly double to 3.2 million cases, and along with it HER-2+ patients who could be eligible for life-extending biologic treatment [157]. A survey of oncologists in the US, Brazil, Mexico, Russia, and Turkey showed that the greatest barriers to accessing Trastuzumab were availability, cost to the patient, patient comorbidities, and insurance coverage [160]. In Brazil, for example, only 6% of patients with HER-2+ breast cancer receive Trastuzumab in the public system compared to 56% in the private sector, also highlighting gaps in access within countries [161].

Figure 4.2 shows the substantive increase in the projected number of deaths due to breast cancer between 2015 and 2030, approximately 561,000 to 805,000. More than 85% of this increase is concentrated in low-and-middle income countries. Recognizing the important role Trastuzumab plays in the clinical treatment of HER-2+ breast cancer, as well as increasing occurrence in LMICs, it is a useful and timely case study for determining which production network would both maximize access and minimize cost. Given that the supply-side component of biologics access

is central to this research, the case study will use the cost model developed in Chapter 3 to compare different scenarios of production.

Projected Change in Total Number of Deaths due to Breast Cancer from 2015 to 2030
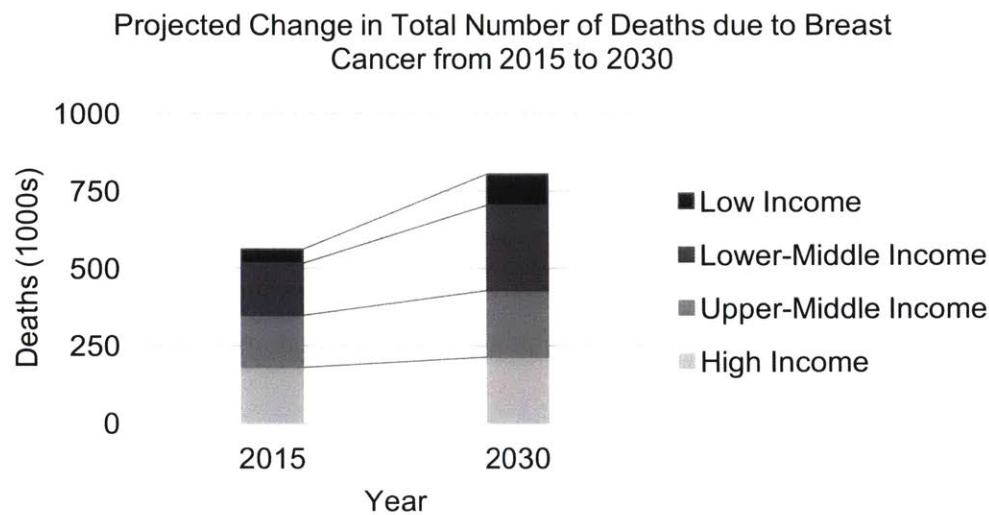
Figure 4.2: Projected change in the number of breast cancer deaths disaggregated across World Bank income groups

4.5.1 Forecasting Demand

Estimating market size is important for multiple reasons. From the perspective of a biopharmaceutical company, the market size gives an indication of the potential revenue flow and biomanufacturing capacity needed to supply safe, efficacious drugs to patients in a sustained manner. While market size can refer to the total number of HER-2+ patients, this is often an over-estimation because patients can be divided into smaller patient classifications based on genotypic features that make targeted therapy more effective. Additionally, patients with low purchasing power are often kept outside of the market and poor diagnosis leads to less people seeking care relative to those who actually need it. Nevertheless, estimating market size is crucial for both determining biomanufacturing capacity needed to meet product volume requirements and for financial forecasts.

In this case, the dual objective of maximizing access and minimizing costs, leads to determining the entire HER-2+ population as relevant for calculating demand. An interactive, user interface was developed to determine demand for Trastuzumab, allowing the user to change assumptions for the average patient weight, dose size, treatment length, and percent of HER-2+ breast cancer patients. Standard assumptions for the input values were made to project a demand of 10.92

g/patient/year and total demand of 3712.8 kg for all HER-2+ patients to receive the biologic drug during a one-year therapy, as seen in **Figure 4.3**.

Predicting herceptin demand, based on mortality rates between 2000-2015

Data Generation

Average Weight (kg):

Dose Size (mg/kg):

Treatment Length (weeks):

% of Her2+ Patients:

Created by:

Center for Biomedical Innovation - BioAccess Program

MIT | BIO
Center for Biomedical Innovation | ACCESS
A Global Health Initiative

Forecasting Trastuzumab Drug Demand

Patient Pool	1,700,000
x	
Length of Treatment	52 weeks
x	
Dosing Frequency	Weekly
x	
Units (g) per Dose	0.003 g/kg
x	
Patient Weight	70 kg/patient
% HER-2+ Patients	20%

Patient Population   x   **% Diagnosed***

Diagnosed Population   x   **% Seeking Care***

Assume 100% for maximum total

**10.92 g/patient/year
3712.8 kg total per year**

Figure 4.3: Graphical user interface and tool for projecting Trastuzumab demand, with each input variable tunable to fit specific scenarios

4.5.2 Capacity Requirement

As described in Chapter 4, different process parameters can be modified to yield a range of production volumes. In each scenario, the calculations are made for one year of operations. In this case, similar starting parameters as those used to construct the baseline, stainless-steel facility COGs model are assumed: production titer of 5 g/L, 80% yield, and standard volume of 10,000 L bioreactors. In a single-facility production system (the typical centralized model) all products are manufactured at a single site and supplied globally. In a multi-facility production

system, manufacturing is split across the number of sites within the network, with each site making products for the region in which it is located. The relative product volume manufactured at each site can either be split evenly at each site, correspond to the estimated demand in the regions in which the sites are located geographically, or any other combination of production levels that the user chooses.

Additionally, single-use, disposable systems are considered, scaling the COGs for each scenario of the base case by a random number in the uniform range between 0.45 and 1.00. The bounds were chosen as a result of potential cost savings demonstrated in the range of 32% (Jacquemart et al.) to 55% (Walther et al.) [162, 106]. This is especially important as single-use, disposable and flexible factories are increasingly considered as the number of biologic products in market increases. Data on the number of deaths due to breast cancer in 2015 for each of the six WHO regions, as seen in **Figure 4.4**, can be used to determine the relative demand of Trastuzumab across different regions and thus inform the production capacity needed.
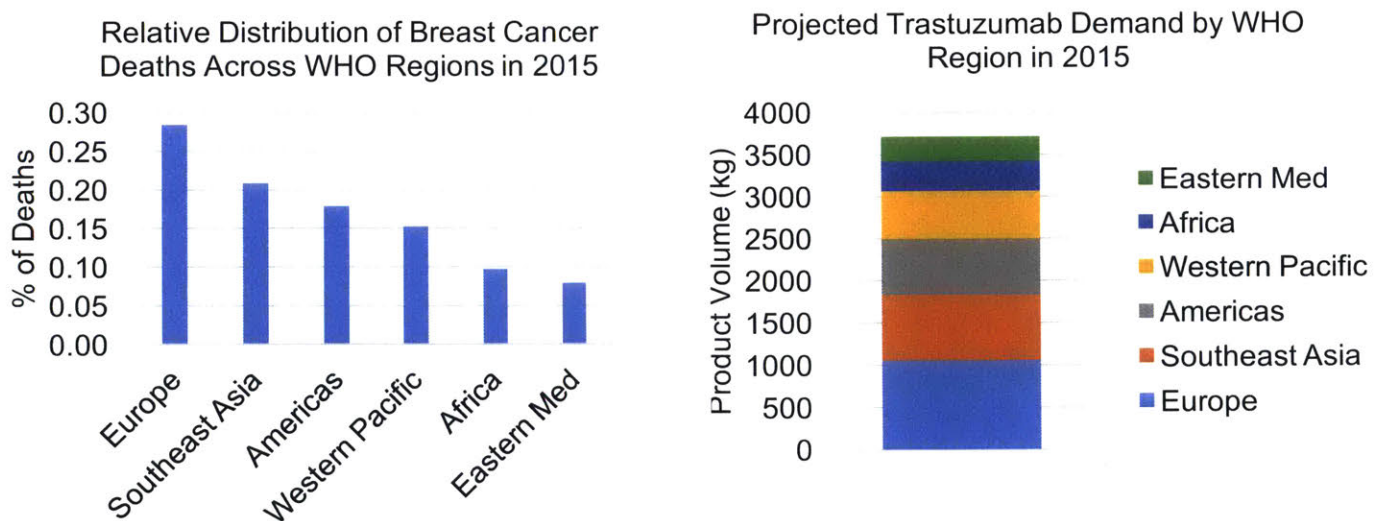
Figure 4.4: Distribution of breast cancer deaths and Trastuzumab demand across WHO regions

4.5.3 Real Options

Multiple scenarios of production networks can be used to meet global Trastuzumab demand. These include centralized (manufacturing all products at one site), decentralized (manufacturing products across multiple sites within the same region), and distributed (manufacturing products across many sites located in various regions). The table below outlines the scenarios that were considered in this case study in order to compare the relative COGs across the centralized-

distributed spectrum of production. The difference between the production volume used in the model (3840 kg) and the projected demand (3712 kg) does not impact the comparative analysis across scenarios and can be indicative of surplus kept in stock in case of shortages.

Scenario ID	# Sites	# Bioreactors / Site	Volume ('000s L) / Bioreactor	Total Product Volume (kg)	Location
Centralized – all products manufactured at one site					
A1	1	6	10	3840	Europe
A2	1	6	10	3840	Southeast Asia
A3	1	6	10	3840	Americas
A4	1	6	10	3840	Western Pacific
A5	1	6	10	3840	Africa
A6	1	6	10	3840	Eastern Mediterranean
Decentralized – all products manufactured within one region (stainless steel systems)					
B1	[1,2,3,4,5,6]	[6,3,2,3,2,1]	[10,10,10,5,6,6]	3840 each	Europe
B2	[1,2,3,4,5,6]	[6,3,2,3,2,1]	[10,10,10,5,6,6]	3840 each	Southeast Asia
B3	[1,2,3,4,5,6]	[6,3,2,3,2,1]	[10,10,10,5,6,6]	3840 each	Americas
B4	[1,2,3,4,5,6]	[6,3,2,3,2,1]	[10,10,10,5,6,6]	3840 each	Western Pacific
B5	[1,2,3,4,5,6]	[6,3,2,3,2,1]	[10,10,10,5,6,6]	3840 each	Africa
B6	[1,2,3,4,5,6]	[6,3,2,3,2,1]	[10,10,10,5,6,6]	3840 each	Eastern Mediterranean
Decentralized – all products manufactured within one region (single-use systems)					
B7	[1,2,3,4,5,6]	[20,10,10,5,6,5]	[3,3,2,3,2,2]	3840 each	Europe
B8	[1,2,3,4,5,6]	[20,10,10,5,6,5]	[3,3,2,3,2,2]	3840 each	Southeast Asia
B9	[1,2,3,4,5,6]	[20,10,10,5,6,5]	[3,3,2,3,2,2]	3840 each	Americas
B10	[1,2,3,4,5,6]	[20,10,10,5,6,5]	[3,3,2,3,2,2]	3840 each	Western Pacific
B11	[1,2,3,4,5,6]	[20,10,10,5,6,5]	[3,3,2,3,2,2]	3840 each	Africa
B12	[1,2,3,4,5,6]	[20,10,10,5,6,5]	[3,3,2,3,2,2]	3840 each	Eastern Mediterranean
Distributed –products manufactured across regions (stainless steel systems)					
C1	2	[4,3]	[8,9]	[2048, 1728]	[EU+Ams+Emd, Sea+Wep+Afr]
C2	3	[1,3,3]	[10,9,7]	[640,1728,1344]	[Ams, EU+Emd+Afr, Wep+Sea]
C3	6	[2,2,1,1,2,1]	[8,6,10,10,3,5]	[1024,768,640,640,384,320]	1 country in each region
Distributed –products manufactured across regions (single-use systems)					
C4	2	[16,9]	[2,3]	[2048, 1728]	[EU+Ams+Emd, Sea+Wep+Afr]
C5	3	[5,9,7]	[2,3,3]	[640,1728,1344]	[Ams, EU+Emd+Afr, Wep+Sea]
C6	6	[8,4,5,5,2,1]	[2,3,2,2,3,5]	[1024,768,640,640,384,320]	1 country in each region

Table 4.3: Overview of scenarios for production networks to meet global Trastuzumab demand

4.5.4 Location Selection

In order to perform the analysis of the above stated scenarios, information is needed to distinguish production across different regions. Within each region, some countries are more likely to have a mature and competitive biomanufacturing ecosystem than others, or would be more economically appealing for the production to take place in. One way to determine the most appropriate location is by co-localizing manufacturing sites with countries that have the highest burden of breast cancer. For example, in the Americas the most strategic site would be the USA followed by Brazil, Argentina and Mexico. This ensures that production take place closest to the patient, and potentially simplifies supply chain management. Alternatively, manufacturing sites could be selected based on locations with pre-existing mammalian cell culture capacity, since those areas are likely to have the most available infrastructure for ensuring successful manufacturing. **Figure 4.5** demonstrates changes in cell culture capacity between 2012 and 2018, with the US accounting for approximate 50% of the total capacity, while Europe covers another 25% and other regions make up the last 25%.
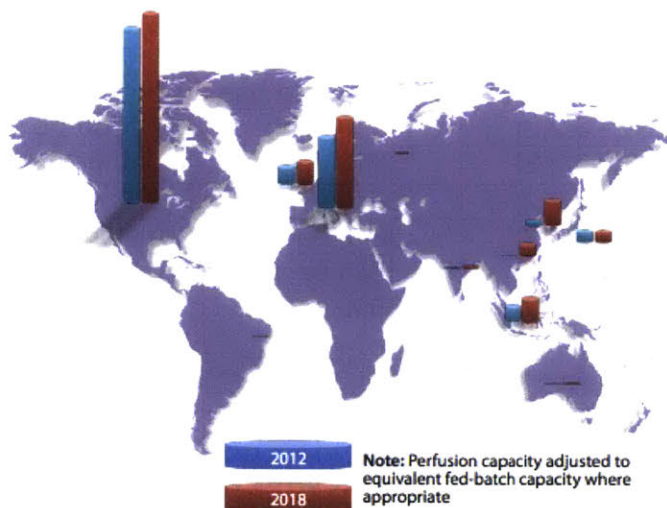
Figure 4.5: Global distribution of cell culture capacity in 2012 and 2018, from *BioProcess Technology Consultants*

Using either approach when considering manufacturing location will likely yield similar results, as countries with the largest burden of breast cancer are often more economically developed and thus likely to also have a biomanufacturing industry. While this observation is interesting to note, it should not limit the scope of locations considered. Likely locations for biomanufacturing within each WHO region are presented in **Table 4.4** below.

WHO Region	Country	# of Deaths (000s) in 2015 [13]	Cell Culture Capacity (000s L) in 2018 [123, 163]
Americas	US / Canada	53.1	1963
	Brazil	18.4	4
	Argentina	6.6	
	Mexico	6.4	
Europe	Russia	28.7	7
	Germany	19.8	~900*
	France	14.1	
	UK / Ireland	14.1	241
South-East Asia	India	76.4	35
	Indonesia	21.3	~5*
	Singapore/Malaysia	3.4	264
Eastern Mediterranean	Pakistan	17.9	~5*
	Egypt	7.4	
	Iran	2.5	
Western Pacific	China	49.0	125
	Japan	14.2	115
	South Korea	2.2	270
	Australia	3.2	3
Africa	Nigeria	14.9	<5*
	Ethiopia	7.7	
	South Africa	4.9	

Table 4.4: Most likely countries for locating biomanufacturing production sites within each WHO region, *estimated from available data from *BioProcess Technology Consultants* and the *12th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production*

Information on how cost centers change with location, with the US serving as a baseline, is important to effectively compare the baseline COGs for mAb production across different scenarios. As discussed in Chapter 3, the costs centers most influential on overall COGs are capital, labor, and material costs. When comparing different sites, the focus will be on changes in capital and labor costs only, as materials costs can be difficult to determine, especially when there are multiple suppliers, potential need for raw material supply chains, and since prices can change with volume of purchases. The COGs model is versatile enough such that the input variables can be easily changed depending on the specific country being analyzed. While it is difficult to generalize conditions across an entire country or region, some estimates are provided by Andrew Sinclair, which have been extrapolated to cover all scenarios, as seen in **Table 4.5** [164]. This will

allow to demonstrate applicability of the model to this case study and its potential to compare options with different conditions.

Region	FTE Cost	Capital Cost
Europe (UK)	0.8	1
Southeast Asia (Singapore)	0.55	0.85
Americas (USA)	1	1
Western Pacific (China)	0.40	0.75
Africa (South Africa)	0.25	0.70
Eastern Mediterranean (Pakistan)	0.50	0.50

Table 4.5: Relative value of different input variables across regions, using the US as the baseline

4.5.5 COGs Analysis

As previously mentioned, the COGs is used as a metric for comparing the relative cost-effectiveness of different manufacturing scenarios. For each scenario, 1,000 trials were generated to allow for a more realistic evaluation of COGs distribution. **Figure 4.6** compares the distributions for COGs in the centralized model, scaling the base case to meet total demand and adding region-specific factors for the labor and capital cost. For all cases, the average COGs is lower than the baseline model since six times more product by volume (on average) is being manufactured. The substantive overlap between the probability curves indicate that the difference across sites is small, while the large range demonstrates the impact small shifts in initial conditions can have on overall COGs. It also points the importance of better understanding local conditions, for both variables considered endogenously in the model, as well as those exogenous to it, as they can shift curves in ways that lead to significant differences in COGs across scenarios.
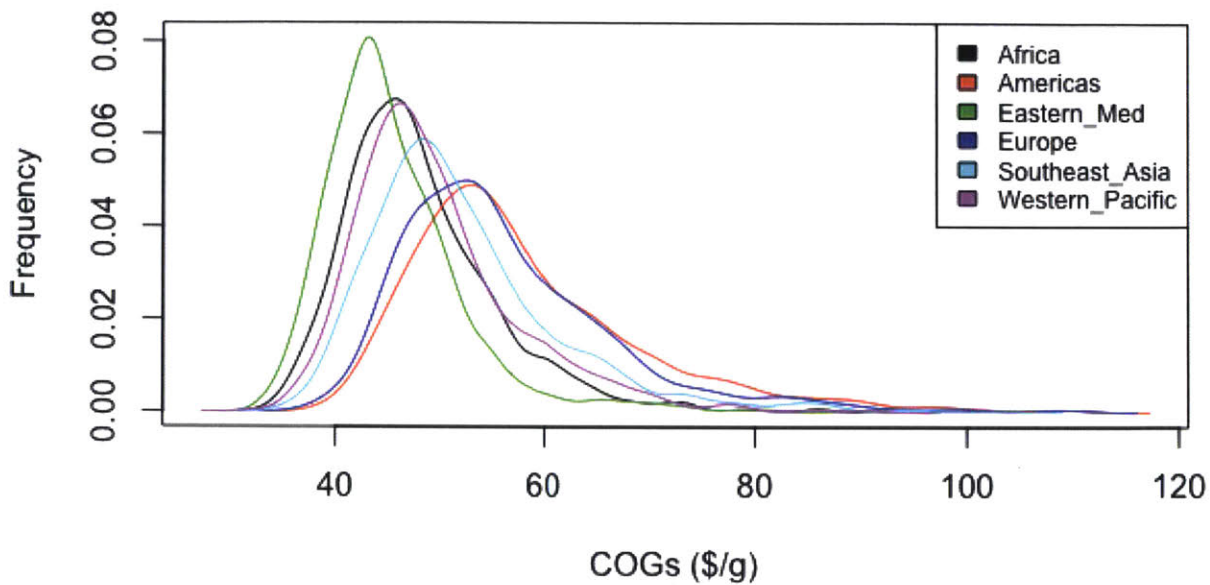
Distribution of COGs in Centralized Case

Figure 4.6: Distribution of COGs for centralized production of mAbs in each of the six WHO regions (scenarios A1 to A6)

In the decentralized case, the distribution of COGs for mAbs production was modeled for 1, 2, 3, 4, 5, and 6 sites within each region separately. **Figure 4.7** compares the distribution for COGs for the decentralized model in each region, for both stainless steel (solid lines) and single-use (dotted lines) manufacturing systems. In this scenario, an assumption is that the product volume is evenly split between production sites within a region. In each case, average COGs increases with the number of sites, as predicted during the qualitative analysis earlier in this section. Compared to the stainless steel scenarios, the average COGs is lower for the single-use production networks. This is expected, as the single-use case was derived by scaling stainless steel scenarios by a random number within the uniform distribution between 0.55 and 1.00, as previously described.

Decentralized Case - Africa

Decentralized Case - Americas

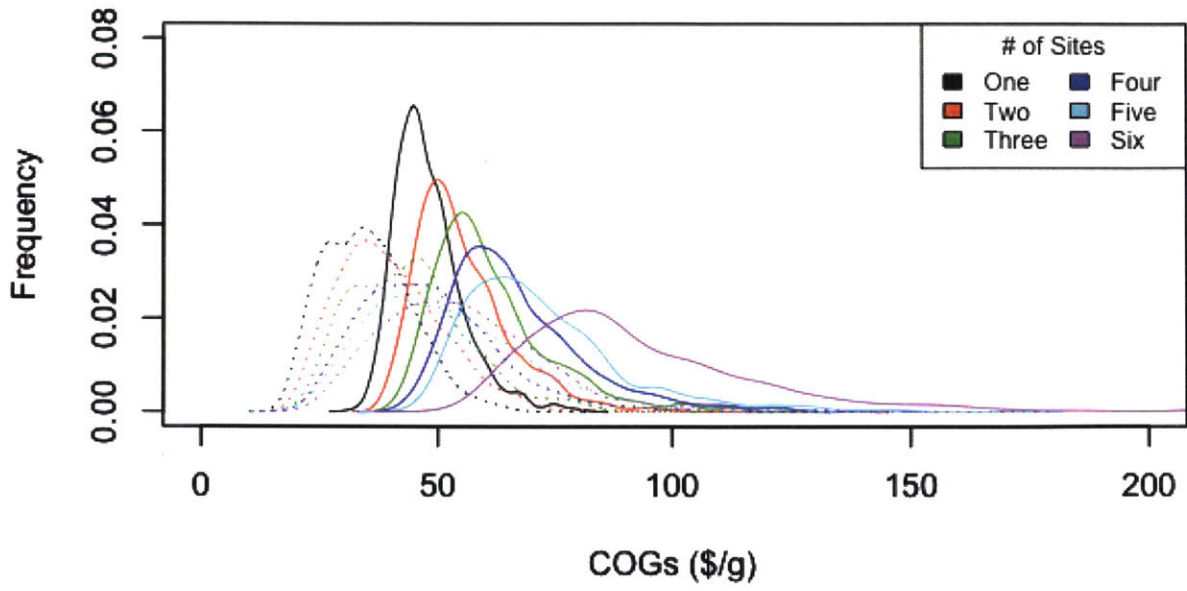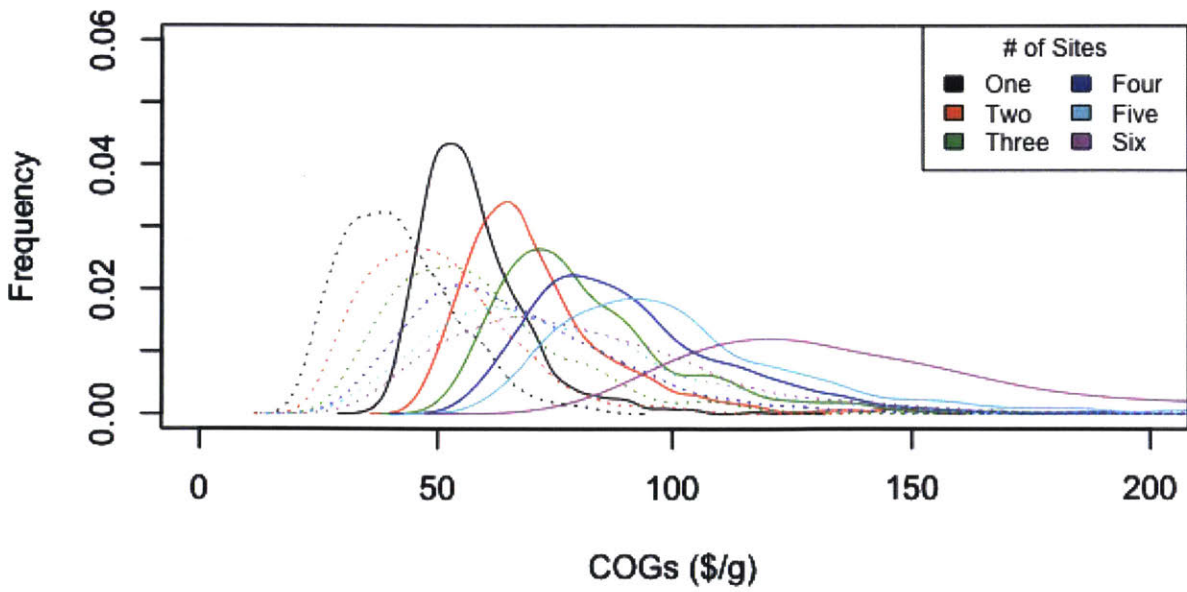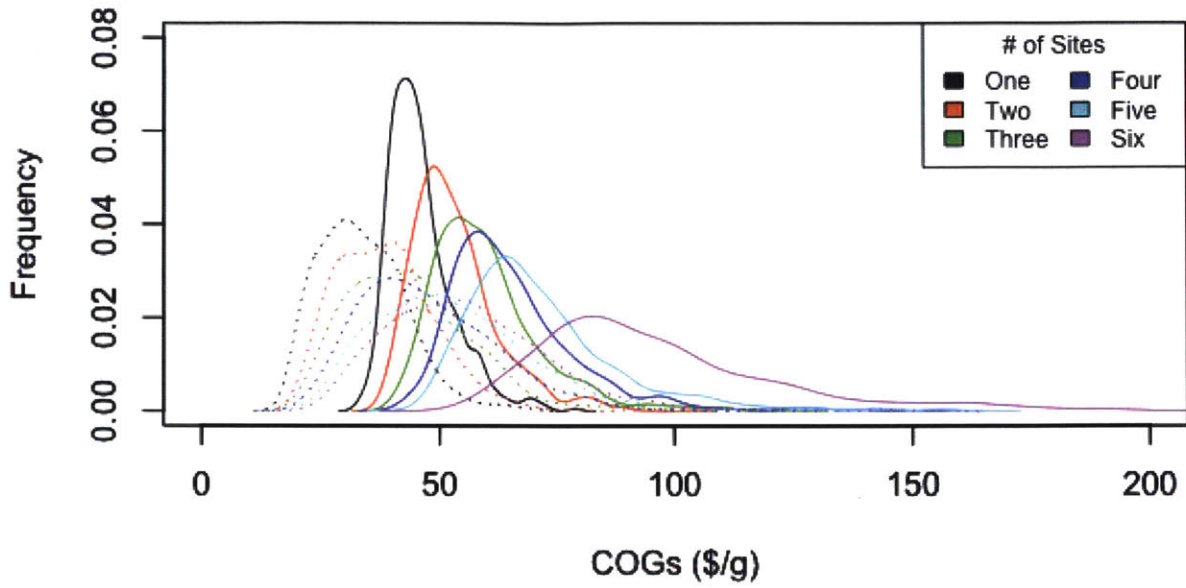## Decentralized Case - Eastern Mediterranean

Decentralized Case - Europe
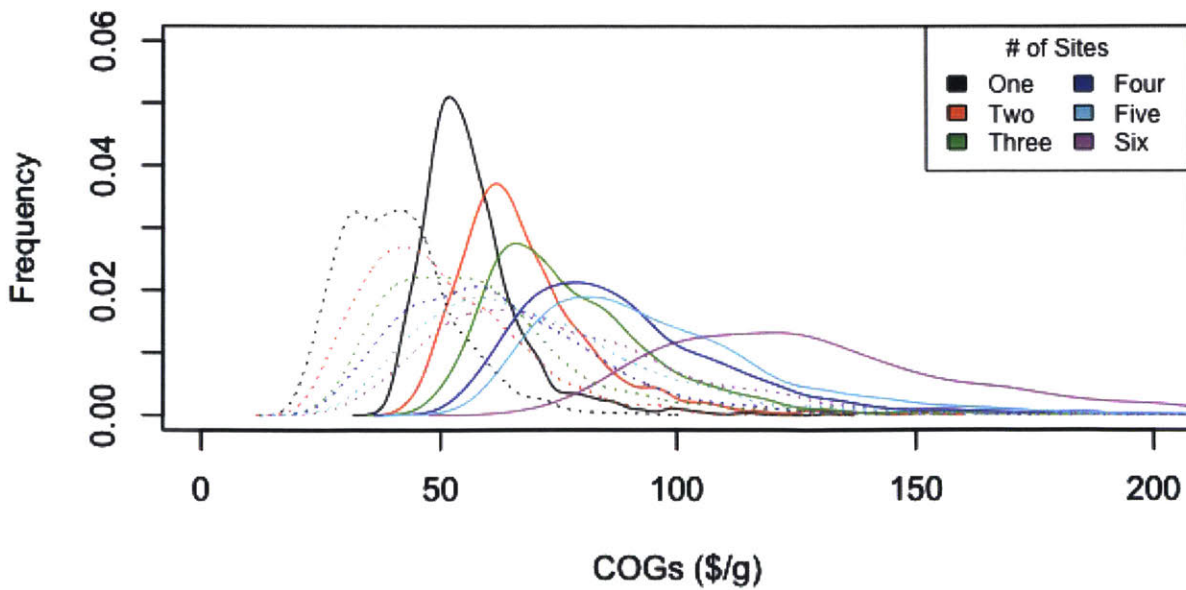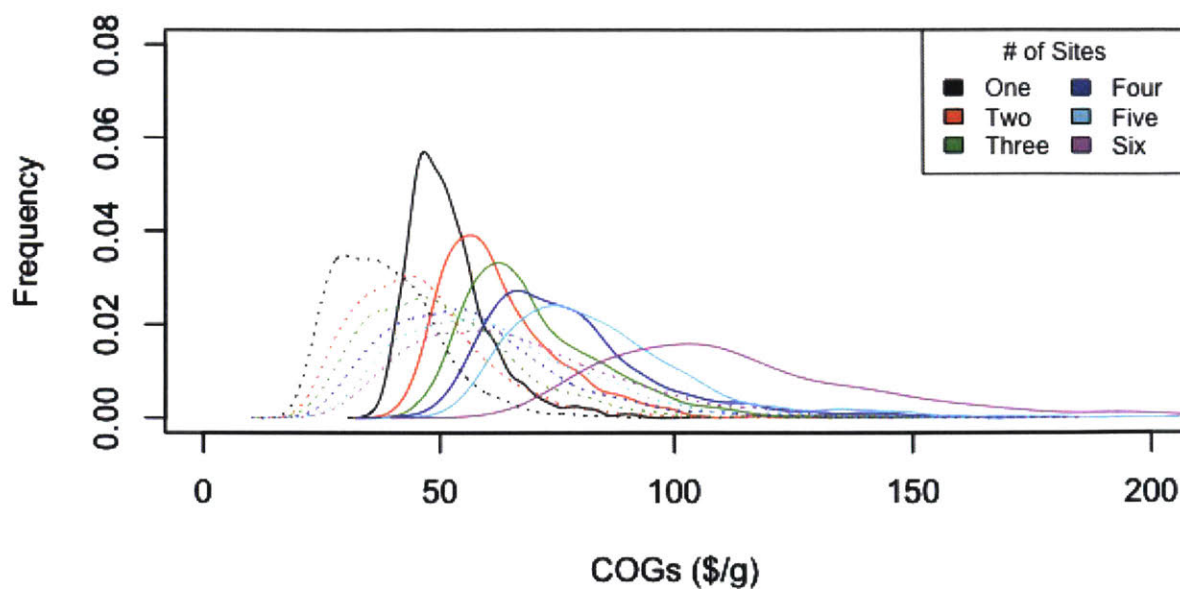
Figure 4.7: Distribution of COGs for decentralized production of mAbs in each of the six WHO regions (scenarios B1 to B12). The solid and dotted lines indicate stainless steel and single-use systems, respectively.

For the distributed model, COGs for mAbs production was modeled for several scenarios. In the first case, production of Trastuzumab takes place in the US (supply to the EU, Americas, and Eastern Mediterranean), as well as in China (supplying to Southeast Asia, Western Pacific, and Africa). In the second scenario, three sites of production supply biologics: USA (supplying the Americas), UK (supplying Europe, Eastern Mediterranean, and Africa), and China (supplying Southeast Asia and Western Pacific). In the last scenario, production is split over six sites, each serving their respective region. **Figure 4.8** compares the distribution for COGs in the distributed model, ranging from low (2 sites), medium (3 sites), and high (6 sites). In these scenarios, the amount of product manufactured at each site is proportional to the breast cancer burden in the market they supply to. While the average COGs increases with the numbers of sites, as previously demonstrated, there are conditions during which a more distributed system can be as, or more, cost-effective than the centralized case, especially in the single-use case. This analysis does not account for the potential economic incentives (e.g. tax breaks and subsidies) that may come from localizing production, or other context-specific conditions that may influence the analysis.
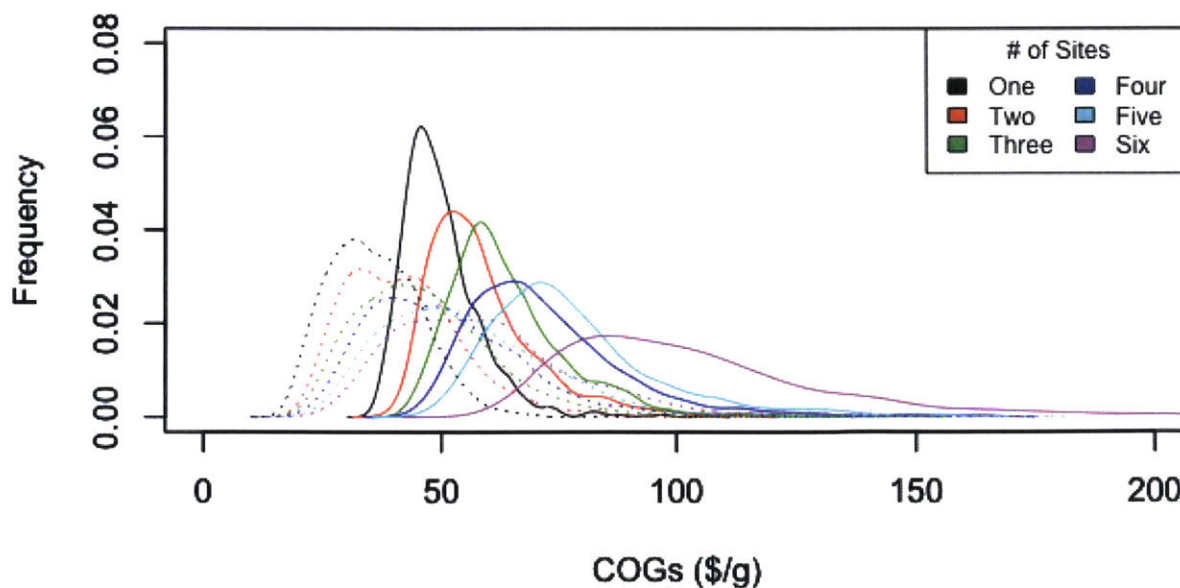
COGs at Different Degrees of Distribution

Figure 4.8: Distribution of COGs for distributed production of mAbs across the six WHO regions (scenarios C1 to C6). The solid and dotted lines indicate stainless steel and single-use systems, respectively.

4.5.6 NPV Analysis

The use of net present value (NPV) estimation is a powerful tool to evaluate the relative value of different options. NPV calculations involve discounting all future cash flows (both in- and out-flow) during the lifetime of a project, based on a given discount rate [165]. This is most commonly mathematically defined in the following way: $NPV = \sum_{t=0}^{n} \frac{NCF_T}{(1+R)^T}$, where NPV = net present value; NCF_t = net cash flow generated by project in year t; and r = discount rate. In this project, the goal is to minimize cost rather than maximize profits, as we make no assumption on the revenues and thus only have costs to forecast. This form of calculation is called Net Present Cost (NPC), which gives the present value of all future costs of the project. An important factor in calculating NPC is the discount rate, whose effect on the eventually valuation of a project can be seen in **Figure 4.9**. In this case, the project is a manufacturing facility producing mAbs, estimated to have a lifetime of 10 years with a depreciation rate of 10%.
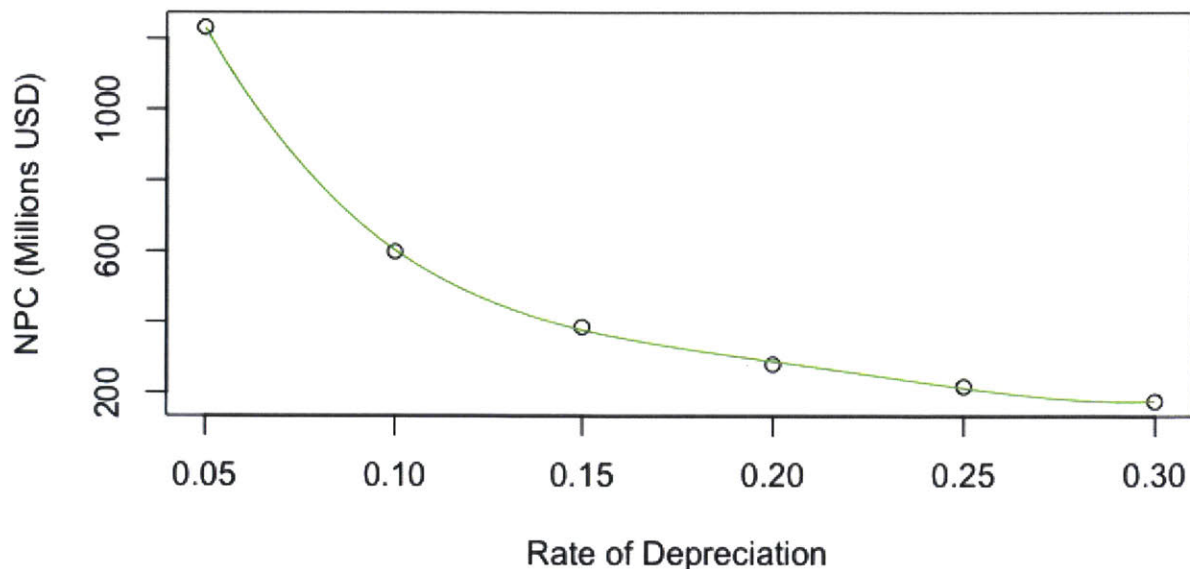
Figure 4.9: Net present cost for different rates of depreciation

Calculating the NPC values allows the evaluation of the cost-effectiveness of a project and having multiple scenarios to test (e.g. as those defined in table 3) compares across options. NPC values were calculated in millions of USD for all 1,000 simulations of each of centralized (**Figure 4.10**) and distributed (**Figure 4.12**) scenarios. For the de-centralized scenarios, only the average is presented over a range of one to six sites (**Figure 4.11**).

Net Present Cost Distribution for Centralized Case
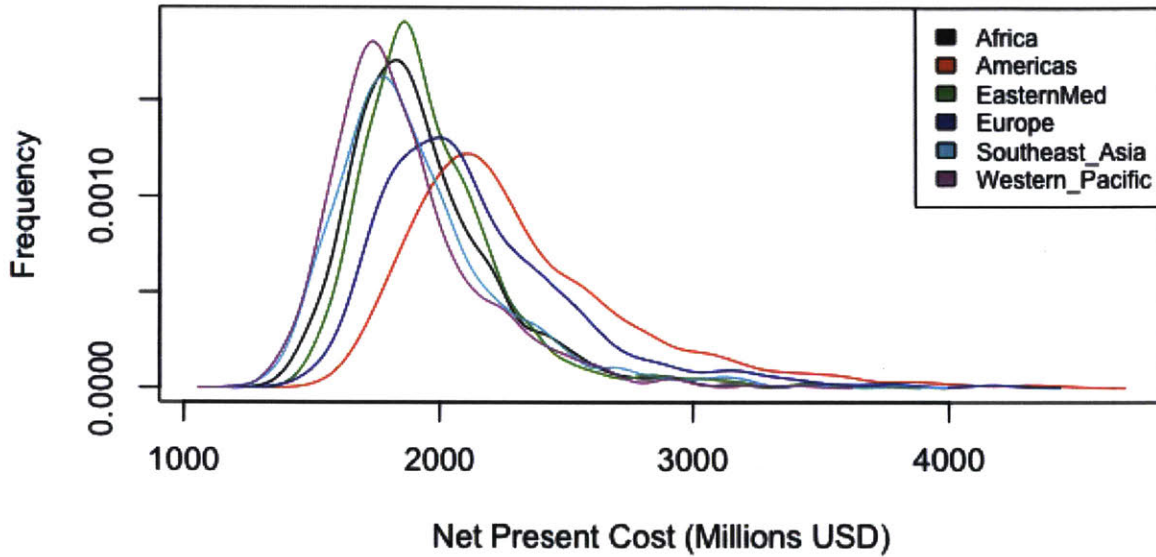
Figure 4.10: Distribution of NPC values for the centralized production of mAbs in each of the six WHO regions (scenarios A1 to A6)

Changes in NPC with Degree of Distribution Within Regions
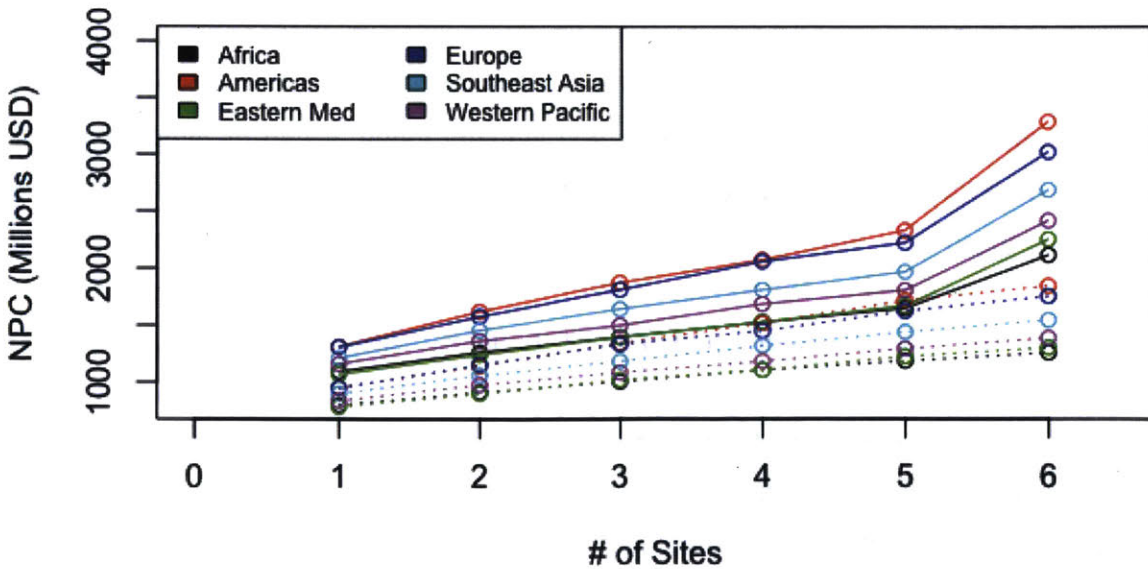
Figure 4.11: Average NPC values for decentralized production of mAbs in each of the six WHO regions (scenarios B1 to B12). The solid and dotted lines indicate stainless steel and single-use systems, respectively.

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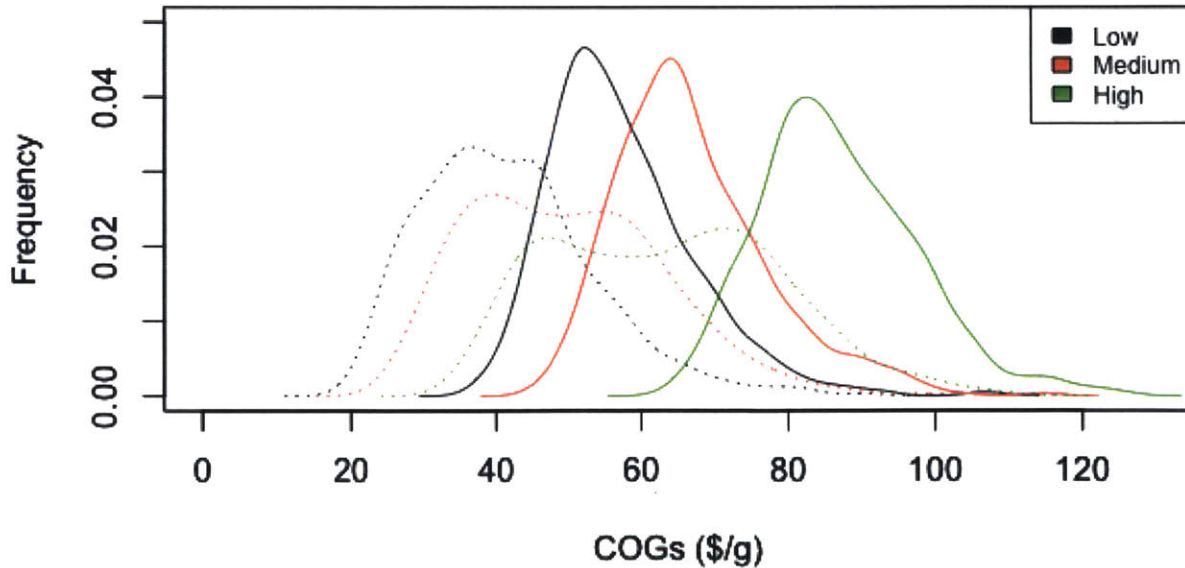## Net Present Cost at Different Degrees of Distribution
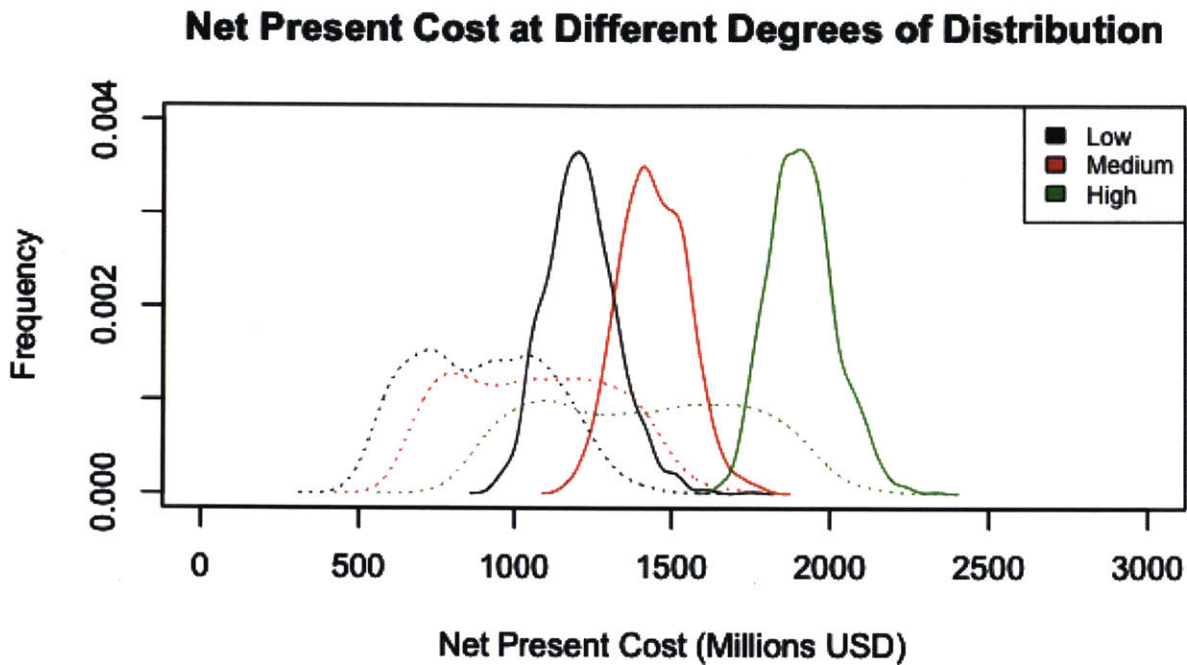
Figure 4.12: Distribution of NPV values for distributed production of mAbs across the six WHO regions (scenarios C1 to C6). The solid and dotted lines indicate stainless steel and single-use systems, respectively.

4.5.7 Analysis of Trends

The results presented above point to several interesting conclusions. First, the cost modeling tool developed in this research can be used to generate estimates for the COGs for manufacturing mAbs commensurate to those found in literature and industry today. It can be easily tuned to account for a broad range of different assumptions and user-defined specifications, increasing its applicability in modeling real world scenarios. Uncertainty analysis are useful to determine variations observed as a result of risk endogenous to the variables, notably those that make up the major cost centers (capital, labor, materials, fill & finish, utilities, and taxes/insurance). However, a limitation of the model is that it does not account for the risk exogenous to the systems, notably those that can arise from unique geographic location, regulatory jurisdictions, and other time-dependent risks such as probability of disasters, war, and variations in currency (e.g. inflation). Nevertheless, the tool remains useful in comparing the magnitude and variability of manufacturing costs associated with different production networks. An overview of the NPC estimates for the 84 scenarios analyzed is seen in **Figure 4.13**.

Net Present Cost for Various Manufacturing Scenarios
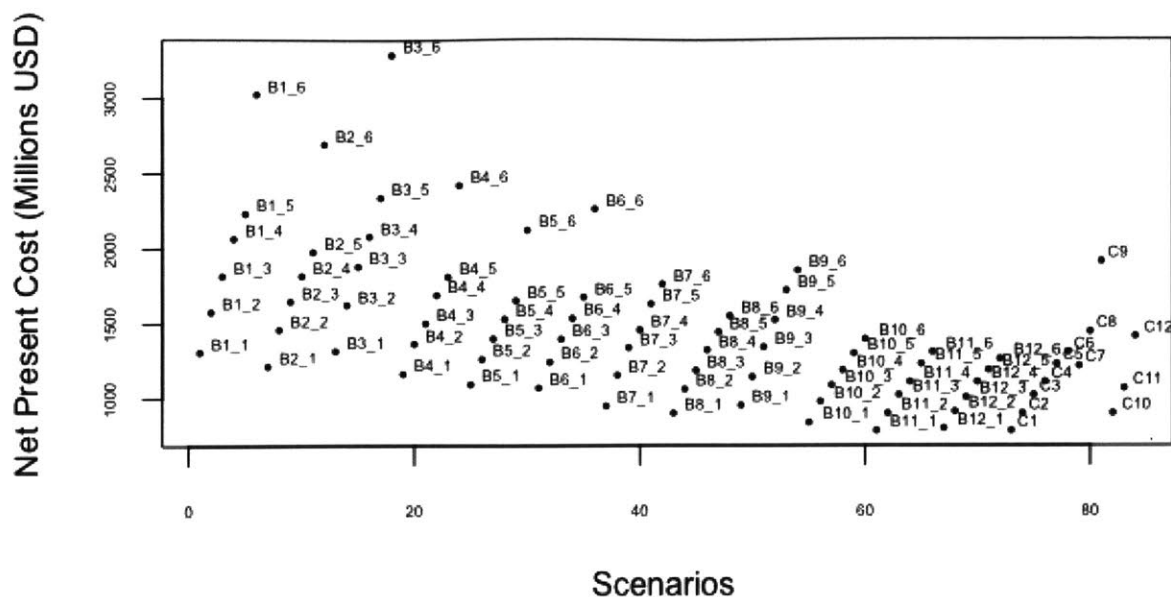
Figure 4.13: Variation in the NPC for various manufacturing scenarios of mAb production

A driving factor for the variation in the NPC of the different scenarios is the weights used for contrasting labor and capital costs across different regions. In most cases, the NPC increases with the number of sites, for both stainless steel and single use systems. However, comparing across systems, the distribution for the NPC indicates that shifting from a centralized, stainless steel facility to a distributed, single-use production network can can be equivalent. This means that the cost savings gained from switching to single-use, disposable systems are similar to the cost incurred when increasing manufacturing across multiple sites. A difference is seen in the range of the COGs and NPC values, demonstrating potential higher risk associated with the distributed production network. From a manufacturer's perspective, the average NPC is lowest (minimizing costs) in the following scenarios: centralized production in regions with the lower labor and capital costs and low to medium level of distribution. This means that it may be more economically viable to design the production of mAbs across multiple sites if they are distributed across several regions rather than all within the same region.

The potential for centralized, stainless steel production systems and distributed, single-use systems to have an equivalent NPC (demonstrated by the overlap in probability curves) means that other factors, exogenous to the variable are needed to inform the level of risk and inform the decision-maker's choice over which manufacturing model would be optimal to meet targets. While

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the baseline costs may be similar, one scenario may have advantages over the other (e.g. close to patient populations in the distributed case), which could be a deciding factors in choosing the optimal design for both minimizing costs and maximizing access.

Chapter 5: Discussion and Future Research

5.1 Discussion

5.1.1 Incorporating Risks Exogenous to the System

As with any modeling tool, the outputs are only estimates of the real world system being observed. In the COGs model presented in Chapter 3 and subsequent result in Chapter 4, uncertainty is incorporated by generating random normal distributions for input variables, within user-designated bounds set by worse and best case scenarios. The use of probability distributions allows us to add a stochastic dimension to the risk analysis, rather than assuming only a few possible values for each input variables. In future iterations of the model, a broader range of probability distributions could be used to more accurately model the random behavior of different variables. The 1,000 iterations of the random variables used in the model gave rise to the 1,000 unique scenarios in each of the 84 cases modeled. As with typical Monte Carlo simulations, it allows for a range of outcomes, each with probabilistic likelihood of happening, providing a powerful tool compared to deterministic, single-output models.

Despite the uncertainty analysis performed on the model, it remains limited to the normal operations within a biopharmaceutical facility and only accounts for variations in variables endogenous to the system. An extension of the model and future direction of this research will be to incorporate variables exogenous to the system, which may have catastrophic impact on manufacturing operations in ways that lead to significant and unexpected costs. For example, this include modeling the impact of events with hard to predict probabilities, such as a cybersecurity attack or earthquake that disrupt production. Incorporating these exogenous factors is especially interesting when comparing the number and location of manufacturing sites, as different locations will have unique underlying risks. As alluded to in Chapter 4, the substantive overlap in the probability curves for the COGs and NPC of different manufacturing scenarios point to the need for incorporating a broader range of factors that can better differentiate risks across options in a time-dependent manner. For example, this includes attributes of individual locations (e.g. risk of natural disaster), communities in which facilities are located (e.g. risk of war), and global patterns (e.g. changes in inflation).

For each of the manufacturing locations considered in Chapter 4, **Table 5.1** presents an estimate for the export and investments risk, as provided by Credendo's country-level risk assessment as of April 2018 [166].

	PR: Short Term	PR: Medium/Long Term	PR: Special transactions	Commercial Risk	Political Violence Risk	EGA Risk	CITR Risk
US	1	1	1	A	1	1	1
Canada	1	1	1	A	1	1	1
Brazil	2	5	3	C	2	3	5
Argentina	4	5	4	C	2	4	5
Mexico	2	3	2	B	3	2	3
Russia	3	4	3	C	4	5	4
Germany	1	1	1	A	1	1	1
France	1	1	1	B	1	1	1
UK	1	1	1	C	1	1	1
Ireland	1	1	1	A	1	1	1
India	2	3	2	B	4	3	3
Indonesia	2	3	2	B	3	4	3
Singapore	1	1	1	A	1	1	1
Malaysia	1	3	2	B	2	2	3
Pakistan	4	6	5	C	6	5	6
Egypt	4	6	5	C	5	5	6
Iran	5	5	5	C	6	6	5
China	1	2	1	C	3	5	2
Japan	1	1	1	B	2	1	1
South Korea	1	1	1	A	3	1	1
Australia	1	1	1	A	1	1	1
Nigeria	6	6	6	C	6	6	6
Ethiopia	6	6	6	C	6	5	6
South Africa	3	4	3	C	3	4	4

*PR = political risk
*EGA = Expropriation and Government Action
*CITR = Currency Inconvertibility and Transfer Restriction Risk

Table 5.1: Ranking countries based on export and direct investment risks

In this analysis, export risks are those related to domestic and international sales of goods, especially debtor default and political risk. Political risk includes events such as political unrest and risk of war, revolution, natural disaster, and arbitrary government action. Short-term political risk measures likelihood of risk during a one-year horizon, while medium/long-term political risk looks beyond one year. These measures are based on a range of quantitative indicators, such as those reflecting a country's growth potential. Classification is done using a 1-7 scale, with larger number reflecting greater intensity of risks within the specific country. Commercial risk, measured on a categorical scale (A, B, C), assesses risk caused by macro-economic trends, such as

volatility in exchange rates and corruption, affecting all companies and transactions within a country. In this classification, "A" represents a lower-than-average risk, while "B" is normal and "C" indicates a larger-than-average risk. Next in the model, indicators for direct investments provide insight into risks related to investments abroad. These are determined by three main criteria: political violence risk (all violent acts undertaken with a political objective, including terrorism), expropriation risk (discriminatory measures taken by a host government that deprives an investor from adequate compensation), and currency inconvertibility or transfer restriction risk (the inability to convert or transfer funds from an investment out of a host country). These indicators also use a 1 (worse) to 7 (best) classification.

Of particular interest are catastrophic events as a result of natural disasters (e.g. earthquakes, tsunamis, floods), as they can have detrimental impact even in economically and politically stable contexts. This can be especially problematic when there is only a single manufacturer and supplier, interrupting supply chains and thus exacerbating the risk of drug shortages [167]. A future direction of the research could include mapping current supply chains for specific products to better understand and forecast susceptibility to future drug shortages The WorldRiskIndex, created by the United Nations University Institute for Environment and Human Security, provides a measure for the risk of disasters as a consequence of extreme natural events for 171 countries. The world risk index is a composite score determined by the product of exposure and vulnerability [168]. Exposure is a metric that includes an estimate for the percentage of the population exposed to hazards from earthquakes and other types of disasters (as determined by the UNEP Global Risk Data Platform) and exposure to emerging risks such as effects of climate change (e.g. sea level rise). Vulnerability is the sum of three factors (each equally weighed): susceptibility (probability of suffering damage in the event of a disaster), adaption capacity (ability to build resilience within society), and coping capacity (aimed at reducing negative effects of disasters). The world map in **Figure 5.1** demonstrates average country-level risk index between 2012-2016, with the specific countries of interest presented in **Table 5.2**.
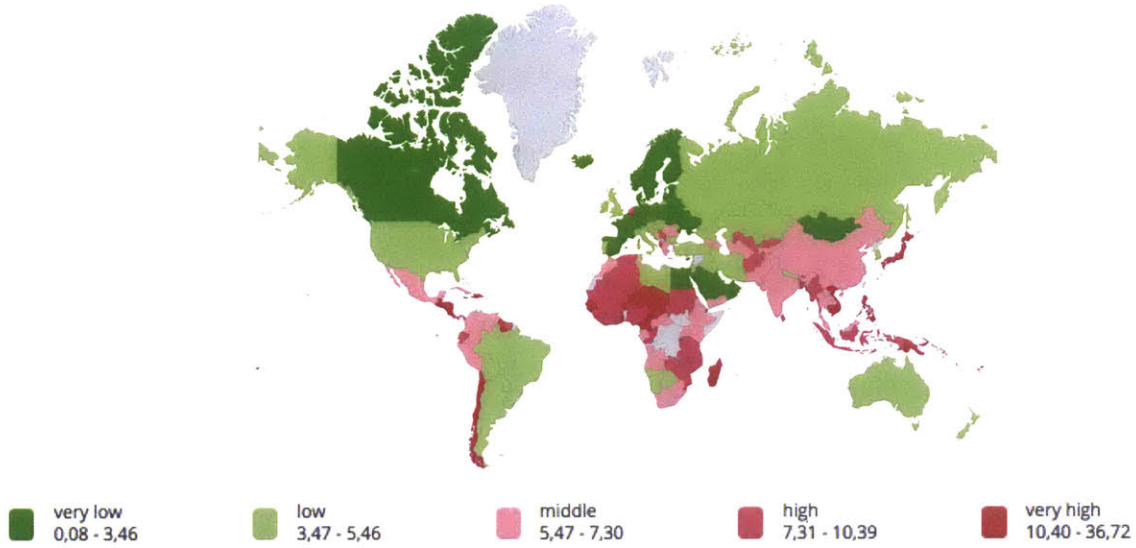
Figure 5.1: Mapping average risk of natural disasters across the global (2012-2016). Source: *The WorldRiskReport 2016*

	Risk	Exposure	Vulnerability	Susceptibility	Lack of coping capacities	Lack of adaptive capacities
US	4	12	32	17	49	30
Canada	3	10	31	15	46	31
Brazil	4	10	44	25	67	41
Argentina	4	10	39	21	60	35
Mexico	6	14	45	24	72	40
Russia	4	9	40	21	59	40
Germany	3	11	27	15	38	29
France	3	9	29	16	43	29
UK	4	12	31	16	47	30
Ireland	5	15	31	16	46	31
India	7	12	59	38	80	57
Indonesia	10	19	54	32	81	49
Singapore	2	8	30	14	49	27
Malaysia	6	15	44	20	68	45
Pakistan	7	11	63	37	87	64
Egypt	2	5	49	22	77	48
Iran	5	10	48	19	80	44
China	7	14	47	26	70	45
Japan	13	46	29	17	38	33
South Korea	5	15	32	15	47	36
Australia	4	15	28	15	42	27
Nigeria	8	12	68	54	88	62
Ethiopia	7	11	67	57	82	63
South Africa	6	12	47	30	69	40

Table 5.2: Ranking countries based on exposure and vulnerability to natural disasters

In addition to political, financial, and environmental risks, indicators have been developed to determine the competitiveness of different national economies. The Global Competitiveness Index (GCI), developed by the World Economic Forum, tracks the performance of close to 140 countries based on their competitiveness, productivity, and economic stability. This is done through an elaborate and multidimensional framework covering 12 pillars: institutions, infrastructure, macroeconomic environment, heath and primary education, higher education and training, goods market efficiency, labor market efficiency, financial market development, technological readiness, market size, business sophistication, and innovation [169]. Most of the data is derived from a survey sent to CEOs around the globe, complemented with census data, which is then normalized to maintain a relative range of scores between 1 (best) and 7 (worse) across countries. The relative scores of a subset of indicators relevant to decision making in biomanufacturing are shown in **Table 5.3**.

	IP protection	Burden of gov't regulation	Quality of overall infrastructure	Quality of the education system	Availability of research and training services	Effect of taxation on incentives to invest	Prevalence of trade barriers
US	2	4	2	3	2	4	3
Canada	2	4	3	3	2	4	4
Brazil	4	6	5	5	5	6	4
Argentina	4	6	5	5	3	6	5
Mexico	4	5	4	5	4	5	4
Russia	5	5	4	4	3	5	4
Germany	2	4	2	3	2	4	3
France	2	5	2	4	2	5	4
UK	2	4	3	3	2	3	3
Ireland	2	3	3	3	2	3	3
India	3	4	4	3	3	3	3
Indonesia	4	4	4	4	3	4	4
Singapore	2	2	2	2	2	2	2
Malaysia	3	3	3	3	2	3	3
Pakistan	5	5	5	4	4	5	4
Egypt	5	4	5	6	5	5	4
Iran	5	5	4	5	4	5	4
China	4	4	3	4	4	4	4
Japan	2	4	2	4	3	4	4
South Korea	2	4	2	4	3	4	4
Australia	2	5	3	3	2	5	3
Nigeria	5	5	6	5	4	4	3
Ethiopia	4	4	5	4	4	4	4
South Africa	2	5	4	6	3	4	3

Table 5.3: Ranking countries based on indicators within the Global Competitiveness Index

While numerous metrics have been built with the aim of better understanding the relative impact of social, economic, and environmental factors unique to specific locations, none are entirely exhaustive or provide a deterministic insight into the potential risks that may arise. Nevertheless, the three indices presented above shed light on the type of data that could be used to complement the cost model developed for mAb production. It is interesting to note that the scenarios with the highest COGs calculated in Chapter 4, those concentrated in high-income countries, also tend to be least exposed to political, economic, and environment risks. This adds complexity between financial and non-financial components of the model when forecasting long-term value. Future work will focus on incorporating a broader set of variables, especially those exogenous to the cost model, in order to forecast NPC and risks in a more realistic way.

5.1.2 Technology and Policy Foresight in Biomanufacturing

Better understanding the factors influencing manufacturing cost for biologics, especially when comparing differences across the centralized-distributed spectrum of production, provides insights into decision making. A centralized system is more cost-effective under the current state of the industry. Given that biopharmaceutical business models are driven primarily by volume, gains from economies of scale are most evident in the centralized model. Nevertheless, the results demonstrate that distributed models under certain conditions can also be competitive, especially when both subsidies and expanded market access are provided. To better forecast future levers that may influence global biologics supply, there is value in also reviewing rapidly changing innovations in biotechnology, innovative financing, operational designs, and regulations.

Calling for innovation alone, however, does not necessarily translate to impact. Innovation can come in many forms – pricing strategy, technological change, policy and regulatory reform, organizational re-design, new business models, institutional strengthening, among others. For example, push (e.g. grants) and pull (e.g. advanced market commitments from large purchases) financial incentives can help reduce risk and cost in R&D, while ongoing process (e.g. high-titer mAb production) and production improvements (e.g. single-use and disposable technologies) have the potential to reduce manufacturing costs, footprint, and time to market [170, 121]. Other innovations in operational management such as distributed manufacturing, subsidies based on access levels, and emerging technologies could allow the treatment of previously neglected populations. Other examples of innovations aimed at increasing biologics access can be found across the biologics manufacture value chain (e.g. temperature-stable protein therapeutics,

alternate host organisms, regulatory harmonization) and patient care continuum (e.g. improved diagnostic capacities, mobile health applications).

The extent to which these innovations impact access will be influenced by a range of factors - their applicability in local contexts, interoperability with existing health infrastructure, resource availability, and alignment of incentives across stakeholders. Research on the effectiveness of previous initiatives and development of novel ones to meet unmet medical needs are important to build an evidence-base that can better inform the allocation of resources and technology development towards context-specific innovations that can promote sustained access. Finally, sustained access will require transdisciplinary collaboration between different stakeholder groups such as industry, government, philanthropy, academia, and patients. Aligning incentives through multi-stakeholder collaborations and partnerships are needed to promote more equitable access to NCDs. For example, the WHO Collaborating Center in Pharmaceutical Policy at Boston University conducts health and pharmaceutical policy analyses to inform WHO's Essential Drugs and Medicines Program. Similarly, the Center for Biomedical Innovation at MIT has recently launched the BioAccess program, specifically aimed at fostering collaboration between academia, industry and regulatory bodies to better understand and overcome barriers to biologics access across the value-chain from a health-systems perspective.

With increased demand and pharmaceutical competition, there is increased pressure to improve efficiency, enable increased flexibility in production systems, and lower costs while still maintaining quality [29]. Better understanding the factors most likely to enable an environment ripe for innovation and informing the most effective allocation of limited resources is especially important. Increasing the scale of 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 production models:

- Increasing efficiency across manufacturing - lower resource use, less energy/waste, maximizing capacity utilization
- Improving production processes - alternate host organisms, reducing purification steps
- Innovating manufacturing systems - single use technology, continuous manufacturing, modular designs, automation/digitization

- Improving product – specifying target product profiles in a context specific way, temperature stability, improved shelf-life, increased potency
- Regulation - harmonizing regulatory standards across jurisdictions and facilitating process changes over multiple sites, real-time quality control
- Technology transfer - with increasing trends towards nationalization (in-country, for country), facilitating sharing of knowledge and process

5.1.3 Future of Distributed Manufacturing

A large focus in biomanufacturing continues to be on traditional 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 to be more favorable for distributed production networks of biologics production. It is important to note, however, that many of the innovations 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 in Chapter 2, have the potential to act as key drivers to overcome barriers to distributed manufacturing models: disposable single-use systems, small-scale and modular factories, and continuous manufacturing.

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 more likely if such treatments were to be made more accessible. While a distributed model may be the only viable option, global supply may not be the foremost priority as these medicines are still very resource-intensive, expensive, and address needs of a small proportion of patients. One the other hand, therapies such as mAbs and protein therapies, with declining COGs and increasing demand, could be more suitable for distributed systems, especially if that can increase access while keeping costs low.

5.2 Future Research

A major outcome of this research was the development of a quantitative cost model for the manufacturing of monoclonal antibodies. The next steps of the research will be to develop similar manufacturing models for a range of other major classes of biologic products: protein from

recombinant DNA (e.g. insulin), blood product (e.g. factor VIII fibrin stabilizing factor), vaccine (e.g. human papillomavirus), *ex vivo* cell therapy (e.g. CAR-T), and gene therapy (e.g. voretigene neparvovec). These are especially interesting candidates for further exploration given the increasing burden of diabetes, auto-immune disease, and other chronic conditions for which they are used. Many of these therapies are also the only ones that can effectively prolong life, for example insulin for type I diabetics and factor VIII for hemophilia patients. Furthermore, these cost models can become more effective decision support tools by incorporating dynamic forecasting of demand, regulatory requirements across a product lifecycle, business models, and financing mechanisms, while maintaining the capability of incorporating user-defined specifications.

Additionally, system dynamic models incorporating both financial (e.g. cost) and non-financial (e.g. behavior) components could be developed for other components of the biologics value chain. These include the medicines supply chain and patient demand (e.g. screening, diagnosis, and seeking care), serving as important components to build a more holistic model linking both the supply and demand side components of access. Supply chain modeling could be done using publically available trade data, as well as mapping tools such as ArcGIS and developing algorithms that can simulate changes in disease burden, medicines procurement, shipment, storage and quality of product across the supply chain. Eventually, this could enable the use of analytics to identify most at-risk patients in a population, triage them across a network of diagnostic centers based on resource availability and patient need, and specify the type and volume of biologics needed across the health network to ensure timely and sustained delivery. As seen in **Figure 5.2**, the use of operations research and systems design can be applied to better synchronize supply and demand side components of biologics access in a temporally and spatially relevant manner.
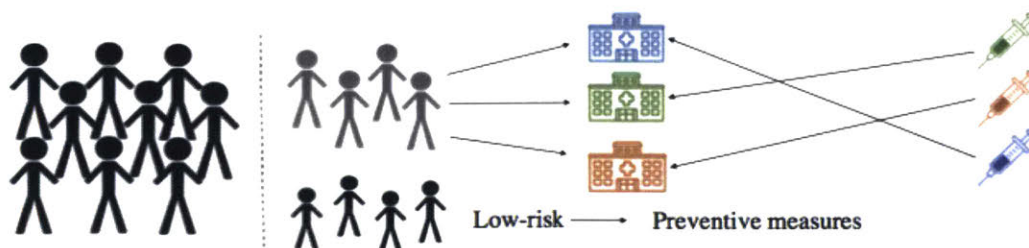

Figure 5.2: Aligning patient triage across a diagnostic network and biologic supply to ensure sustained access

Another area of future research will be to use the cost model to test a broader range of innovations. These include, but are not limited to the following:

- Emerging manufacturing, supply, and quality-assurance technologies
  - How will digitization and automation influence the biologics ecosystem and how will it differ for various types?
  - How impactful are process enhancements such as alternative host organisms, disposable technologies, and high-throughput-screening
- Regulations and Policies
  - How can regulatory coherence (upstream, downstream, QC/QA, and inventory) affect biologics supply and access? For example, standardizing approval throughout the African continent.
  - Which innovations can help better understand the landscape of drug shortages and stock-outs in LMICs, as well as overcome inefficacies in procurement, inventory management, and supply chain logistics?
- Organizational structures and business models
  - What will the effects of centralized vs. distributed manufacturing be on cost and supply of biologic products? What is the influence of centralized vs. distributed supply chains?
  - What is the influence of collaborative manufacturing campaigns, contract manufacturing organizations (CMOs), and outsourcing?

Expanded access to such treatments can potentially be met by innovations in pharmaceutical manufacturing, supply chain delivery, regulation, organization structures, and policy. However, gaining foresight into the potential consequences of different investments can be valuable in an increasingly complex and resource constrained system. Appropriate and timely decisions are key to effectively prevent, manage, and treat NCDs. Decision making processes, while involving actors from multiple sectors with similar end-goals, will also need to overcome misalignments in order to not only be responsive to current health demands but also to future, evolving, and emerging circumstances.

5.3 Conclusion

The shift in disease burden from infectious to chronic diseases, with a disproportionate impact on LMICs, puts pressure on the need for adaptation within the biopharmaceutical industry to better supply biologics to patients who need them. This research focuses on the biomanufacturing component of the biologics value-chain, specifically monoclonal antibody production, as one area

where disruptive change has the potential to lower costs in efforts to increase global supply of biologics. The manufacture and supply of biologics to patients over an unequal landscape is a challenge. As the WHO General Assembly prepares to assess global and national progress on the GAP in September 2018, accelerated efforts are needed to increase access to affordable, quality medicines to meet the 80% global target. While many studies have looked broadly at access to essential medicines, as well as barriers faced by patients in seeking care, few have focused on the challenges with the manufacture of biologics and their implications on larger health systems. Given the projected rise in NCDs, especially in LMICs, there is particular concern with closing gaps in access to biologic medicines, given their molecular, regulatory, manufacturing, and supply chain complexities. However, with a concerted effort from many different stakeholders, effective data-driven solutions can be found, allowing the entire world, no matter their income level or location, to move forward into a healthier future.

Approaching such a complex problem will require iterative analysis informed by insights from different perspectives, ranging from producers to patients, in order to address barriers to global access across the system. Another consideration, which goes beyond the scope of this research, 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 supplying pharmaceutical dispensaries, 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 research into practical, real-world impact.

Appendix

Appendix A: Interview Questionnaire and Experts

Questions

Costs in the centralized manufacturing system
1. What are currently the most common manufacturing models in terms of geographic location?
2. What are the most important cost centers?
3. What are the costs associated with each cost center?
4. How generalizable vs. specific to disease/process are costs?
5. How does scale impact these costs?

"Distributed Model"
1. How would you define and describe a distributed model in the biotech context?
2. How would the identified cost centers be impacted under a distributed model?
3. Where would costs increase or decrease?
4. Beyond cost, what other advantages/disadvantages/challenges do you see with the distributed model?

Research approach for comparing costs
1. Advice on methodology for a more quantitative comparison of the costs associated in a distributed vs. centralized model?
2. Case study of a specific biologic? Which one?
3. Sources of data on manufacturing costs?
4. Use of real-world distributed models or proxies (e.g., local manufacturing)?
5. Impact of biologics?

Experts Interviewed

Jeffrey Baker, Office of Biological Products, US FDA
Michelangelo Canzoneri, Sanofi
Klaus Graumann, Novartis
John Erikson, GlaxoSmithKline
Parrish Galliher, GE Healthcare
Stephen Hadley, Bill & Melinda Gates Foundation
René Labatut, Sanofi
Harold Nusser, Sandoz/Novartis
Tom Ransohoff, Bioprocess Technology Consultants
Jim Thomas, Just Therapeutics
Jorg Thommes, Biogen

Appendix B: Sample Codes

```
# This script simulates the COGs for the production of monoclonal antibodies, given user-defined parameters

## Process and Operations
# Defining variables

bio_num <- 1                    #number of bioreators
run_days <- 15                  #run duration
ttime <- 3                      #turn around time
itime <- 30                     #idle time
success <- 0.9                  #rate of success (% of batches)
total_runs <- floor((365-itime)/(run_days + ttime)) #total runs in year
bio_vol <- 10000                #Bioreactor volume
titer <- 5                      #titer (g/L)
ds_yield <- 0.8                 #DS yield
dp_yield <- 1                   #DS to DP yield

#calaculting product volume per run
product_run = bio_vol*titer*ds_yield*dp_yield
product_year = product_run*floor(total_runs*success)

## Labor Cost
# Defining variables

shifts <- 2
FTE_admin <- 5                  #administration
FTE_eng <- 5*shifts*bio_num        #engineering
FTE_mat <- 5*shifts*bio_num        #materials
FTE_ops <- 8*shifts*bio_num        #operations
FTE_qc <- 10*shifts*bio_num        #quality systems
FTE_other <- 10*shifts
FTE_total= FTE_admin+FTE_eng+FTE_mat+FTE_ops+FTE_qc+FTE_other
FTE_mean <- 200000

#calaculting labor cost
labor_cost = FTE_total*FTE_mean

## Materials Costs
# Defining variables

mats_raw <- 8*bio_vol           #$/L
mats_cons <- 13.5*product_run       #$/g
mats_other <- 4*product_run         #$/g

#calaculting materials cost
materials_cost = (mats_raw+mats_cons+mats_other)*total_runs

## Utilities Costs
```

```
# Defining variables

util_base <- 5*10^6            #$
util_run <- 10000             #$

#calaculting materials cost
utilities_cost = util_base+(util_run*total_runs)    #$

## Capital Costs
# Defining variables

capital_base <- 25*10^6            #$
capital_scale <- capital_base*(((bio_vol*bio_num)/1000)^(6/10))        #$

#calaculting capital cost (depreciated 10 years, plus 10% of capital for maintenance)
capital_cost = (capital_scale/10)*2                #$

## Fill and finish Costs
# Defining variables

vial_vol <- 1                #g
vial_num <- product_year/vial_vol        #
vial_cost <- 1
vial_process <- 9

#calaculting fill and finish cost
fillfinish_cost = (vial_cost+vial_process)*vial_num

## Taxes and insurance
# Defining variables

tax <- 0.02*capital_cost        #g
insurance <- 0.01*capital_cost        #

#calaculting fill and finish cost
tax_insur_cost = tax+insurance

cost_vector <- round(c(labor_cost,
        materials_cost,
        utilities_cost,
        capital_cost,
        fillfinish_cost,
        tax_insur_cost)/10^6,0)

#total_cost
total_cost = sum(cost_vector)
#cost_components
cost_components = (cost_vector/total_cost)*100
#Cost of Goods ($/g)
COGS = (total_cost*10^6)/product_year
```

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