Globalization of Biopharmaceutical Manufacturing

by

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Abstract

The biomanufacturing industry is changing due to increasing globalization. However, it is changing differently from other high tech industries like software/ semiconductor/ automobiles. In this study we use global biomanufacturing investment data, industry survey data as well as interviews with members of industry and academia to understand the extent of microbial biomanufacturing activity (total volume, number of facilities, type of facilities) and nature of biomanufacturing activity (complexity of products and processes across both mammalian and microbial production) in different regions of the world today.

The study shows that traditional centers of expertise in US and EU still house most of the worlds biomanufacturing capacity. The facilities in US and EU perform a larger number of operations within their facilities and also more technically complex operations than facilities in Asia. US facilities support the most complex products (median unit operations =13) and processes (cell culture, purification) and maximum average products per facility(12.2). Asian facilities support simpler products (median unit operations =7), simpler processes (fermentation, fill/finish) and fewer products per facility on average (3.25).

These results support the idea that managing technical complexity is one of the biggest challenges in biomanufacturing today and it can determine where a biologic can be manufactured. While economic forces push manufacturing of biologics to low cost locations, the need to develop expertise may prevent manufacturing from scattering across the world. Instead, there may be a more guided flow to locations with an expertise in certain types of products and processes.

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Chapter 1

Introduction

The National Research Council defines globalization as *'the expanding international flow of capital goods, knowledge and people'* [22]. Since 1990 trade flows have grown faster than the world's GDP. In the National Intelligence Council's most recent report on future global trends, globalization is referred to as *'a mega-trend ... [and] a force so ubiquitous that it will substantially shape all the other major trends in the world of 2020.'* [30]

In terms of size, speed and direction of flow, the force of globalization is unprecedented in modern history. [22] Lower costs combined with government policies have shifted the locus of most manufacturing and some service industries to other parts of the world [16]. Many products use globally sourced materials and flow through multiple processes that end in products assembled in locations far away from the location of manufacture of its components. [11, 26]

In the recent years, the bio-pharmaceutical industry has been a witness to this globalization. *"There has been a perfect storm - more products, more manufacturers, more countries and more access"* said Commissioner of Food and Drugs Margaret A. Hamburg, M.D. *"Global production of FDA-regulated goods has exploded over the past ten years."* [12]

This is an industry that began in the 1980s with the development of recombinant technology. Biotechnology has been used to make bread and wine for centuries. The advent of recombinant technology has allowed the industry to scale production of

proteins which were earlier derived from animals. Advances in genetic engineering have allowed the production of many more biotherapeutic molecules of different types, shapes and complexity than was possible before. The US has been a pioneer in biotherapeutics and is still a global leader. However, with globalization of the industry, important structural changes taking place in the industry that may challenge this predominance.

Globalization of high-tech industries like software [1], semiconductors [19] and pharmaceuticals [5] has been studied in detail. These industries have undergone a global shift in production activities as well as a modularization of activities termed vertical specialization . Vertical specialization is defined by Macher *et al.* as *'the development of an industry structure populated by firms that specialize in one or a limited set of activities who contract with other firms that specialize in different activities in the region.'* [18, 23]

In the past, most biopharma companies have been highly vertically integrated in all functions from R&D, through process development, manufacturing and marketing. This supports the product cycle model where US firms develop new products for the domestic market. As the product and/or technology matured, it eventually is manufactured offshore in cheaper locations. [31, 25].

The first approved biotech drugs in the mid-1980s stayed onshore for 20 years before production was moved to a low cost location [25]. However, the pace at which the biopharmaceutical industry has been globalizing indicates that firms may not be waiting for products to mature to move the manufacturing offshore. *"In addition to an increase in imported finished products, manufacturers increasingly use imported materials and ingredients in their U.S. production facilities, making the distinction between domestic and imported products obsolete"* said Commissioner of Food and Drugs Margaret A. Hamburg, M.D in a press release in June 2011. [12]

Critics of the product cycle model believe that using global production networks would allow firms to gain maximum efficiencies by allowing firms to specialize within their specific range of skill, knowledge or ability. [18]This vertical specialization is beginning to emerge with the rise of contract manufacturing. Much of the growth

of the industry however, is 'cluster driven' [1] [6, 13], though the number of clusters have been increasing both within the United States and outside it [17]. This may be attributed to the fact that the knowledge production process in biotechnology and related industries have spillover effects in the region [13] as well as over time.

The persistence of 'cluster driven innovation' is unique to the biotechnology industry and differentiates biomanufacturing from other traditional manufacturing sectors like semi-conductors and automobiles and make it an interesting topic of study. Many studies have looked at the factors that affect biotech clusters and innovation within these clusters. Studies claim that new clusters perform low-value and low margin activities while they catch-up with the leading clusters that exist in US today [17].

The idea that complexity of manufacturing determines its globalization has been suggested in many studies. There have been many studies comparing the difference in the extent of innovative activity across biotech clusters (through number of patents, VC investments and number of new startup firms). Other studies have also illustrated how geographic proximity, organization and processes affects the flow of knowledge through a network [3, 8]. Some studies have suggested that biotechnology industries have clustered based on the strength of the science and technology base [29]. There is sparse literature that explores how the complexity (diversity and specialization) of technology itself varies across various geographic locations in science based clusters [9].

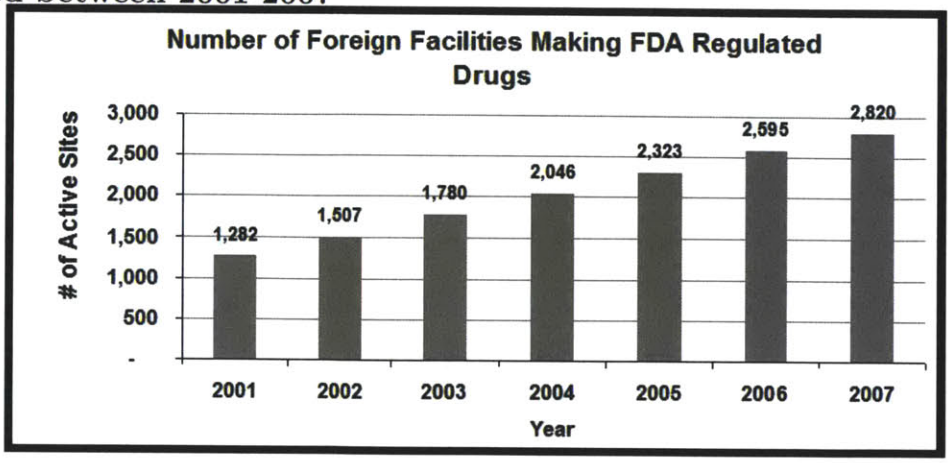
1.1 Globalization and Biomanufacturing

Complexity of technology is central to the operations of a manufacturing facility. Extending the biotechnology argument to biomanufacturing, one can expect the complexity of biomanufacturing operations to vary between US facilities, EU facilities and Asian facilities.

For biomanufacturing, globalization brings forth some unique challenges to the

[1] Porter defines clusters as a geographically proximate group of interconnected companies and associated institutions in a particular field, linked by commonalities and complementarities.

Figure 1-1: **Number of foreign sites manufacturing FDA approved drugs has doubled between 2001-2007**



Source: FDA,2011 [11]

industry as well as the regulators. [Figure 1-1] shows the number of foreign sites manufacturing FDA approved drugs has doubled from 2001-2007. As the biopharmaceutical industry grows in importance, the globalization of biomanufacturing becomes increasingly relevant to different stakeholders today for a variety of reasons:

- *Local Innovation and Regional Competitiveness:* In order to focus on core competencies many firms choose to out-source low value added activities. This may eventually lead to outsourcing of R&D operations. Many fear that sophisticated engineering and manufacturing capabilities that underpin innovation in a wide range of products have been rapidly leaving too, as a result of this trend. Pisano and Reynolds both point to a growing concern that the US *'has lost or is in the process of losing the knowledge, skilled people, and infrastructure needed to manufacture many of the cutting-edge products it invented.'* [24, 25]

- *Quality and Safety of Drugs:* The decision to balance the advancements in cutting-edge technology and the upholding the standards of quality and safety is made more tenuous in a rapidly changing global industrial landscape. Concerns of quality and safety have increased over the past years as more drug recalls and adverse events have been reported. In 2001 in a statement before a Senate committee, Bernard Schwetz listed inspection activities and drug-related

adverse events among the challenges that the FDA faces in the 21st century.

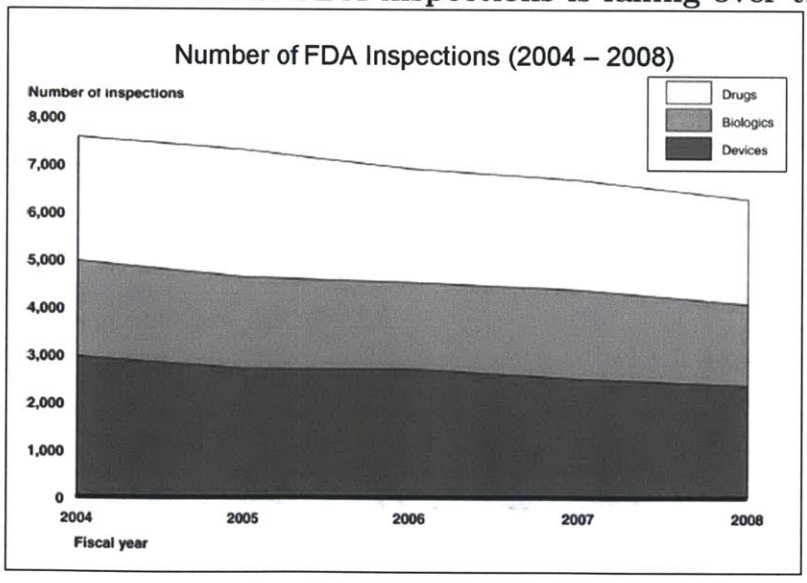
- *Regulatory Challenges:* Over the past decade, the sheer number and unique geographic locations of biopharmaceutical manufacturing facilities requiring inspection has increased substantially. Many new biopharmaceutical manufacturing sites have been established - several in China and India. New sites in China and India represent more than 40% of FDA-registered foreign pharmaceutical locations - making inspection and oversight increasingly costly and cumbersome [34].

Table 1.1: **Cost of Foreign vs. Domestic Inspections** - The average cost of foreign inspections is two times the cost of a domestic inspection.

Average Cost of FDA Inspection (approx)	
Domestic	**Foreign**
$23,000	$52,000

Source: FDA,2011 [11]

Figure 1-2: **Number of FDA inspections is falling over time**



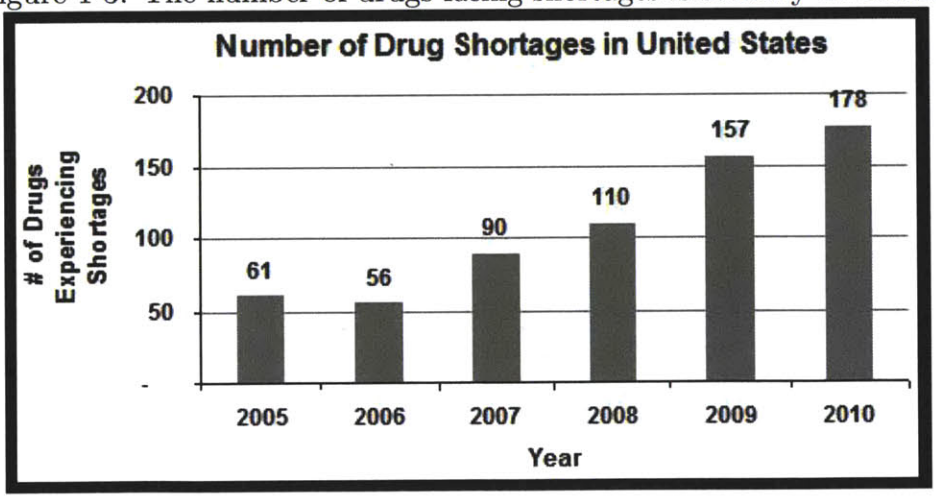
FDA, 2011 [11]

Inspection of an international facilty costs the FDA almost twice the cost of inspecting a local facility [Table 1.1]. Budget cuts have resulted in severe

shortfalls in the FDA budgets [32]. In their special report released in June 2011, the FDA admitted that it does not have the resources to keep pace with the pressures of globalization given the breadth and complexity of the industry that it is regulating. Even with a risk-based approach, at the current rate of inspections, it would take nine years for the FDA to inspect every high priority pharmaceutical facility just once. [11]

- *National Health Security:* Without any manufacturing in the country, governments fear that in times of crisis they will not be able to manufacture drugs locally to meet the demands of its people and will be at the mercy of other nations in time of need. Recent epidemics of swine flu and bird flu have brought to attention the need to be able to manufacture large amounts of drugs and vaccines for the population [20]. In 2010, 178 drug shortages were reported to the FDA, in 2005 this number was only 61. The drugs recalled include cancer drugs, anesthetics used in surgery, a large number of "sterile injectables" – medicines that are given intravenously – and "crash cart" drugs used in emergency treatments [4]. The FDA blamed quality and manufacturing problems that led to recalls of the drugs.

Figure 1-3: The number of drugs facing shortages is steadily increasing



**2010 numbers do not include shortages of vaccines and products made from blood, tissue and other biological sources. FDA said the number would be even higher if shortages for those products were also added in.* [4]

One of the main challenges in studying the biomanufacturing industry is the availability of data. Much of the data is proprietary and there is no single source of data or unambiguous approach to study the globalization of the industry. This study aims to provide some insight into the nature of biomanufacturing activity in different locations (US, EU, Asia).

1.2 Thesis Objectives and Approach

The study is divided into two parts.

The first part of this thesis builds upon an earlier study by Reynolds on the trends in globalization of mammalian biomanufacturing in the world today [25]. This study was conducted through the Industrial Performance Center(IPC) and aims to provide a high level picture of the rapidly evolving global microbial manufacturing landscape. This section is not intended to be comprehensive, but to illustrate the extent to which advanced technologies are being developed and disseminated worldwide. For example :

- *Where are the main microbial manufacturing facilities in the world ?*
- *Where are the newer facilities being added?*
- *Where is the newer capacity being added and by whom?*
- *What are the major trends microbial manufacturing that are of interest to industry leaders?*

Microbial manufacturing is a mature technology so one may expect to find much of the manufacturing activity to have moved to low cost locations. We do find a trend in vertical specialization with emergence of contract manufacturing especially in Asia. However, we find that Europe and US still play a major role in terms of both capacity and number of firms. This contradicts the 'product life cycle' theory and suggests that factors other than the maturity of technology and market are at play that may need companies to keep manufacturing located primarily in Europe

and US. Complexity of the process, the need for highly skilled workers, and large costs in setting up facilities, among many others, are likely to play a large role in the manufacturing activity of different locations.

The second part of the study tries to better understand how complexity of the technology affects manufacturing activity in different locations. Biomanufacturing activity varies widely across regions and facilities. Even within facilities, a range of operations and processes can be supported that vary in number and complexity. In this study, we look both the number of operations and processes and the complexity of these operations to compare manufacturing activity. Using data and metrics embedded in the manufacturing processes and engineering principles we attempt to answer the following questions:

- *How do facility characteristics and organization vary by location in the industry?*
- *How do biologic products manufactured vary by location?*
- *How does the approach to quality and safety vary by location?*
- *How do quality issues in biomanufacturing vary by location ?*

Unlike other industries, biomanufacturing complexity cannot be defined by a few metrics. I use facility level information (number of products, capacity utilization, age of the facility), process information (organization of employees across different manufacturing activities, processes supported) and product level information (number of unit operation for each of the products manufactured in the facility, quality issues faced during product development and manufacturing) to get a finer understanding of manufacturing activity within facilities. The data indicates that facilities in US and EU support more processes for more products and markets than Asian facilities. Manufacturing facilities in US and EU specialize in upstream, innovative processes. The individual processes in US and EU are also more complex than processes in Asian facilities.

Details on manufacturing activity within facilities is proprietary. I am using preliminary data gathered from a survey conducted by the Center for Biomedical Innova-

tion(CBI) at MIT as a part of a larger study to understand the impact of globalization on regulatory compliance and quality approaches. The survey is still underway at the time of writing of this thesis. My analysis includes data from 14 facilities across USA, Europe and Asia. The number of facilities used in this study may not be sufficient to cover the breadth of manufacturing across the world. However, the data set is rich in its depth of information on manufacturing activities in facilities. The analysis provides interesting insights to biomanufacturing in different locations of the world and highlights patterns that would be interesting to study in detail in the future once more data is collected.

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Chapter 2

Methods and Limitations of Study

Information on local production as well as the number and capacity of drug substance and drug product suppliers is very fragmented and possibly proprietary. In particular, both Active Pharmaceutical Ingredient (API) suppliers and generic manufacturers in the U.S. and Europe require their activities to be confidential and secret, lest their preparations for filing dossiers for generic market approval become known to the branded manufacturers.

In the case of this research, I have used data from available databases and industry wide survey for analysis. I turned to qualitative semi-structured interviews and discussions with focus groups comprising of MIT faculty (academia), industry experts at Center for Biomedical Innovation (CBI), members of the Massachusetts Biomanufacturing Roundtable (industry) and representative of Massachusetts Technology Collaborative(MTC) (policy makers), to interpret and provide context to some of the observations of the data.

2.1 Study of the Microbial Biomanufacturing Landscape

The first part of the study looks at the global microbial biomanufacturing landscape. This research project was funded by the Massachusetts Technology Collab-

orative (MTC) to analyze global microbial production data and determine trends in the industry with respect to location and technological change, and determine to what extent Massachusetts is or could be competitive in microbial production. This project was a continuation of an earlier study of mammalian production conducted by Reynolds [25]. In this study, I have used a data set similar to the mammalian study.

The data set for microbial production was provided by BioProcess Technology Consultants (BPTC), a biopharmaceutical consulting firm based in Woburn, Massachusetts. BPTC specializes in process and product development; manufacturing; quality and regulatory affairs for biologics. Their clients include all of the major biopharmaceutical firms as well as midsize companies in the US and abroad. The firm maintains both demand side and supply side databases related to biomanufacturing. The information provided in the data set by BPTC was gathered from public sources including trade magazines, corporate documents and newspapers. The company also publishes an annual industry report outlining the state of global supply and demand for biomanufacturing and current trends. These databases are described in detail in the following sections.

2.1.1 Facility database (Supply side)

BPTC maintains a database of all public announcements of new capacity, planned capacity and when facilities go offline. The database was created in 2002 when the firm first began tracking existing facilities and contained information about facilities planned up until 2013. The database contains records for 150 facilities across 24 countries.

The database is fairly robust for facilities in North America (Canada and US - 60 facilities) and Europe (61 facilities) given the companies' experience and expertise in these regions. Also, there are fairly few investments made year to year in new facilities in this region. However, it is somewhat limited when it comes to facilities in Asia where biosimilars are being manufactured for local and some international markets.

The database of facilities contains the following information for each facility:

1. Company Information
2. Location of Facility (City, Country)
3. Facility Type (Mamalian / Microbial)
4. Company Type (whether a product company or a contract manufacturing organization (CMO) or Both)
5. Manufacture Type (whether it is a commercial or clinical facility)
6. Stage (whether the facility is online, in construction, in planning, or in the validation stage)
7. Year the facility went into operation (or year estimated to be online)
8. Number of Reactors
9. Size of reactors (in liters)
10. Total volume in thousands of liters.
11. The type of processing used at the facility (batch-fed, perfusion, roller bottle, disposable)

2.1.2 Market size database (Demand Side)

The demand database maintained by BPTC tracks biological recombinant drugs that have been approved and those that are currently in clinical trials. The database also includes estimated sales for each of these drugs.

The database of drugs contains the following information for each drug:-

1. Phase of Development (Phase 1, Phase 2 , Phase 3 , Pending Approval or in market)
2. Manufacturing Technology (Mammalian, Microbial, Other)

3. Company

4. Product Name US (Brand name if the product was approved in the US)

5. Product Name EU (Brand name if the product was approved in the EU)

6. Generic Name

7. Product Type (Hormone/ Antibody/ Antibody fragment (fAb)/ Cytokine etc.)

8. US Approval Date

9. EU Approval Date

10. 2008 Sales ($M)

The high level of risk and uncertainty in the drug development process makes the predictions on the demand side more unreliable as we go beyond 2008.

2.1.3 Analysis

The analysis performed on this database was similar to that used by Reynolds on the mammalian database. Pivot tables were used to aggregate data by different sets of variables like geography (continent, country, state); by size in terms of facility and volume (clinical, commercial, greater than 5kl, 10kl); by type of company (product companies vs. CMOs); and by number of facilities. All microbial facilities were batch-fed so the volumes of regions could be summed up. When classifying the facilities into geographic region, Japan and Australia were grouped into Asia.

2.1.4 Qualitative Data Collection and Analysis

Quantative analysis was also supported with qualitative semi-structured interviews to provide context to and aid in interpretation of the quantitative data. This included 12 interviews with leaders in biomanufacturing primarily around the Massachusetts

region. Many of the interviewees are leaders of large global firms that cater to international markets and had facilities around the world including research or manufacturing facilities in Massachusetts.

In addition to face-to-face interviews, findings and data analysis were discussed with three focus groups, sponsored jointly by MITs Industrial Performance Center and the Massachusetts Technology Collaborative (MTC). These meetings were held in March, April and June 2010. Each of these meetings was attended by 12 to 25 people from industry, academia and the non-profit world and allowed for industry leaders to vet and respond to my research. These groups served as an informal working group of the larger effort of the Massachusetts Life Sciences Collaborative around biomanufacturing. Findings of my research were also reported to the MTC and the chairs of the Massachusetts Biomanufacturing Roundtable every month. In this study, I will refer to these meetings as 'MTC interviews'.

2.2 Industry Survey of Biomanufacturing: Facility Characteristics and Approach to Safety and Quality

The industry survey is a part of a larger study being conducted by the Center for Biomedical Innovation (CBI) to examine the effect of globalization on biopharmaceutical product manufacturing, regulatory policies, compliance and economics. The study is funded by the Alfred P. Sloan foundation.

There is no comprehensive database available to describe the current state of biomanufacturing processes within facilities across the world. Much of this information is tacit and proprietary. In order to collect this information, we constructed a list of questions that were used in an online survey to be answered by biomanufacturing facility heads across the world.

A survey was chosen because it allowed us to capture data from facilities across the world with the relative ease. No questions in the survey were mandatory. This

was important to ensure that the data collection was not too burdensome for the respondents and their privacy was maintained as their participation was completely voluntary.

The survey was created based on inputs from MIT faculty as well as leaders from the industry. It is comprised of 6 sections

1. *Facility Information* - basic information about the facility.

2. *Facility Organization* - details about age, ownership, capacity, number of products manufactured, local and international markets served and regulatory authorities.

3. *Quality* - number of employees, organization across functions, quality issues and how they are managed.

4. *Inspections* - frequency and nature of inspections for each agency that the facility interacts with, perceptions of the stringency and standing, how inspections are dealt with by different teams, etc.

5. *Product Specific Questions* - respondents were allowed to fill in data for up to 5 products. Questions included information about product characteristics, complexity, manufacturing process, quality issues faced etc.

6. *Role of academia in biomanufacturing* - to what extent academia can play a role in biomanufacturing quality and safety.

A list of over 90 contacts for microbial and mammalian facilities across the world was provided by Bioprocess Technology Consultants. This list was supplemented by contacts in the MIT Biomanufacturing Program. All contacts were emailed with the survey link. In addition, the study and survey were advertised in Pharma Magazine. All the responses were voluntary, and no question in the survey was mandatory. All responders were assured that the responses would be made anonymous for analysis. Each responder is to receive a survey report showing them where the facility stands against other anonymized respondents. The report aims to incentivize facilities to

respond to the survey by offering them information that they would otherwise not be able to get from other sources.

2.2.1 Unique Challenges of Surveying Biomanufacturing

The survey of biomanufacturing facilities was based on a similar study of pharmaceutical manufacturing focused on manufacturing performance of pharmaceutical manufacturing facilities by Macher *et al.* called the Pharmaceutical Manufacturing Research Project (PMRP). The PMRP survey was used as a reference point to begin designing questions for biologics. The survey evolved on its own into a different format based on feedback from various members of the CBI study who served as consultants and advisors to the group.

A large variety of operations can be categorized under the umbrella of biomanufacturing. A biologic is usually a very large organic molecule that exists in various configurations making it difficult to characterize. Inducing a biological system to produce a molecule that it doesnt normally produce in nature is a tricky business. The complexity increases with molecule size, with host cell (microbial to mammalian) and also with the scale of manufacture. Most processes in a manufacturing facility, like technology transfer, manufacturing, quality assurance and packaging, are developed based on the needs of the product and host cell. In addition to the cell culture and purification of the biologic product, there are a wide variety of operations that are performed and a range of skill sets that are housed within a facility. For example regulatory affairs, quality activities, deviations and quality issues when they arise, training, inspections etc. These functions are also unique to the product that is being manufactured in a facility, making each biomanufacturing operation unique in its complexity and the challenges it faces.

As a result, biomanufacturing facilities are a metaphor for the biologics they manufacture. They are not easy to characterize or compare. Each facility has a unique history based on its products, ownership and organization and set up. Unlike nameless factories in other industries, biomanufacturing facility are often addressed as *'The [insert firm name] [insert city name] facility'* indicating that they have a unique char-

acter or personality.

This made surveying manufacturing facilities a huge challenge. A wide variety of metrics were required to get a basic understanding of the operations in the facility. Much of the knowledge of manufacturing resides with the people performing specific operations. This is especially relevant for compliance related information. As a result, the survey design required inputs from people with expertise in a variety of operations.

The team designing the survey involved members from academia, industry as well as specials employees from FDA and EMA that were associated with the Center for Biomedical Innovation. The process of designing the survey took around 6 months. The design process involved 4 main stages:

1. Identifying the variables that would address the research questions listed in the Sloan proposal

2. Identifying the questions that would help extract that variable from the survey

3. Framing the question and the options based on cGMP guidelines and industry accepted terminology

4. Setting up an online survey that would be convenient for responders to use and beta testing

At each stage, I gathered feedback and insights into questions from the design team. The survey that resulted was long and could also not be answered completely by one person alone. The project team decided to address the survey to the facility manager but allow the survey manager to forward the link of the survey to employees who can answer specific sections of the survey.

A lot of effort was put into ensuring that the gathering of data was efficient and convenient for the responders. A survey vendor was chosen on the basis of the feature that allowed responders to jump from and/or skip to any section of the survey. This would allow multiple people to respond to different parts of the survey.

Tom Ransohoff from BPTC and Steve Kennedy beta-tested the survey in February and filled a questionnaire created for feedback. The feedback was used to trim the

survey down to 115 questions. The final survey was released April. A survey link was emailed to a list of contacts prepared based on the contacts of BPTC and MIT - CBI. In addition, the survey link was also provided to Pharma Magazine to email its subscribers. [See Appendix C]

2.2.2 Survey Limitations

It is likely that if the survey has been answered by only members or contacts from the CBI, there would be a strong bias in the sample data. Firms that associate with MIT and CBI are likely to be firms that are academically oriented and thus highly innovative in their functions. They are also more likely to be prominent firms in the industry with a high level of sophistication and expertise by virtue of their association with MIT. Emailing the survey from a large database that included facilities that were not familiar with MIT and the CBI Sloan study ensured some amount of randomness to the responses.

However, since there were no honoraria provided to the respondent, there is a possibility of self-selection bias in facilities that respond to this survey based on:

Interest in globalization - Facilities interested in serving new markets and regulators would be more interested in this survey than those that focus only on local markets. Facilities serving local markets are less likely to care about the mission of the research or to know their standing against biotech firms in other countries that are not their competitors. This is particularly true of small and medium sized firms and firms in emerging markets. Emerging markets serve huge populations and contain many biologics firms that serve only the local population. Differences in local regulatory policy, IP laws and customers in emerging markets are more likely to be reflected in the organization of these facilities. In contrast, facilities that serve both local and global markets would need to adhere to FDA or EMA standards and inspections. Thus, the survey may be biased toward global or more forward looking firms, especially in emerging markets.

Concerns of safety and quality - Facilities and manufacturers exist that are concerned about economic gains above risk for human health and safety. Many cases of counterfeiting, fraud and intentional use of substandard materials and processes have been reported by the FDA in their inspections [11]. Such facilities are unlikely to be interested in the study on global approaches to safety and quality. The issues of quality are likely to be underreported in a study which relies on voluntary participation.

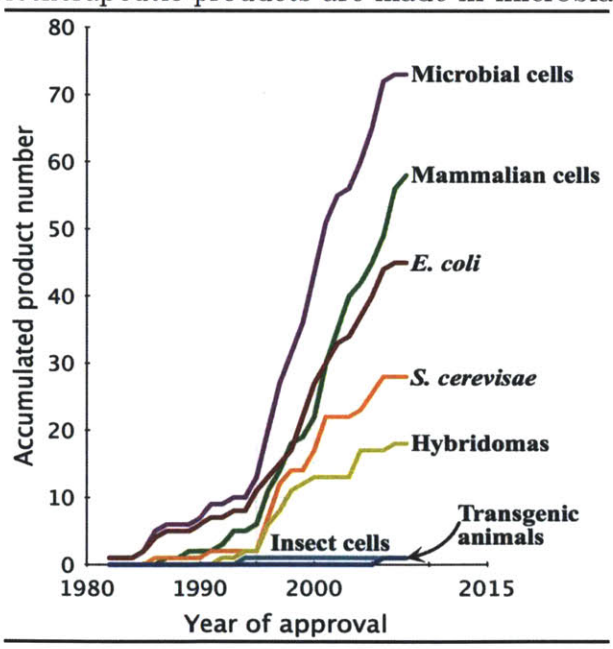
The survey was launched in April 2011. By 14th June 2011, 14 facilities across the world had responded completely to the survey and responded to product-specific questions for 31 products. Many more facilities had accessed the survey and were in various stages of completion. The respondents in the analysis include some of the largest and well known biopharma firms in the world and many smaller, lesser-known facilities. At the time of writing of this thesis, the survey was still online.

In the present analysis, I use data from 14 facilities across North America, Europe and Asia. This number of facilities represents small fraction of the total number of facilities in the world. The data also does not represent facilities in South America which is also an increasingly large producer of biotherapeutic products. Due to the small sample size it may not be representative of the global population. As more data is collected, it would be useful to revisit these analyses and test for statistical significance.The analysis can be used to obtain empirical evidence, directional insights, recognize patterns, and highlight key issues for further investigation.

Chapter 3

Microbial Manufacturing Landscape

Figure 3-1: **Growth of recombinant therapeutic products by host-cell type** - The number of microbial therapeutic products has increased exponentially. The highest number of biotherapeutic products are made in microbial systems.



Source:- Ferrer, 2009 [10]

Microbial biotherapeutics were the first recombinant products made commercially. These products are still on the market today. Microbial manufacturing has grown

tremendously since then. [Figure 3-1] shows the exponential growth of recombinant microbial therapeutic products since the early 80's. Microbial systems are one of the most popular biomanufacturing hosts. The robust cellular structure of bacteria and yeast make them amenable to culturing. Microbial cell lines tend to be stable and the manufacturing processes are less complex than mammalian systems.

In this chapter, I attempt to paint in broad strokes, a picture of microbial biomanufacturing today to understand:

- *Where are the main microbial manufacturing facilities in the world ?*
- *Where are the newer facilities being added?*
- *Where is the newer capacity being added and by whom?*
- *What are the major trends microbial manufacturing that are of interest to industry leaders?*

I will begin by studying global trends in biomanufacturing volume by continent. The analysis will then proceed to increase in granularity by looking at individual continents. Volume of manufacturing informs only one aspect of biomanufacturing. In order to get a better understanding of the industry we will look at the trends in contract manufacturing as well as clinical manufacturing by region. Compared to product companies, contract manufacturing firms need to focus on low cost manufacturing for profitability. Their presence indicates a vertical specialization that is emerging in some parts of the industry. Clinical manufacturing involves smaller volumes of product but is critical step in product and process development in biomanufacturing. Clinical manufacturing is a good indicator of the innovative capacity of a region and also a critical building block in the development of a robust foundation for future commercial manufacturing capability for a firm. Following the region wise analysis we will look at the top 10 countries in this industry - both by volume as well as by number of facility.

In order to provide context to the data, I followed up the quantitative analysis with qualitative interviews with leaders in microbial manufacturing in US, UK and

India. In [Section 3.3], I will discuss trends that emerged from the discussions with industry experts.

3.1 Trends in overall global manufacturing capacity by region

[Figure 3-2 and 3-5] track biomanufacturing investments from 2002 projected to 2013. A number of observations can be made from these graphs.

3.1.1 Trends in global and regional volume

While growth in manufacturing volumes has been more or less stable for microbial products for most of this decade, it is projected to level off in North America and Europe by 2010. [Figure 3-2] These trends are primarily due to productivity gains in the industry.

From [Figure 3-2] and [Figure 3-5] we see that Europe commands almost 50% of the world capacity by volume (commercial + clinical). This is in contrast to the mammalian study of biomanufacturing investments where US was a global leader in mammalian biomanufacturing capacity. [25]

3.1.2 Emergence of Asia

Another interesting trend that can be observed from these charts is is the steady growth of capacity in Asia over the past seven years. The database is particularly weak in its estimation of Asian facilities so it is likely the the actual capacity in Asia is higher than that depicted in the graph. In order to gain a better understanding of Asian manufacturing I conducted interviews with contract manufacturing firms that owned facilities in Asia, large pharmaceutical companies that collaborate with teams in Asia and indigenous product companies in Asia.

The increase in biomanufacturing capacity in Asia can be explained by several factors. First, a number of Asian countries are targeting the biomanufacturing industry

Figure 3-2: Global trends in microbial manufacturing capacity (commercial volume)

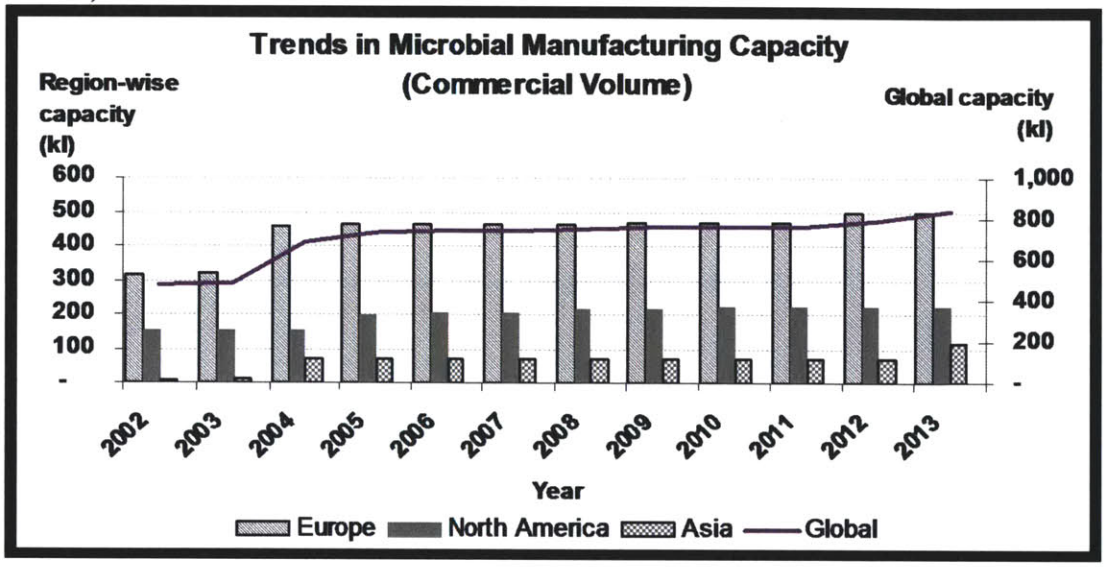
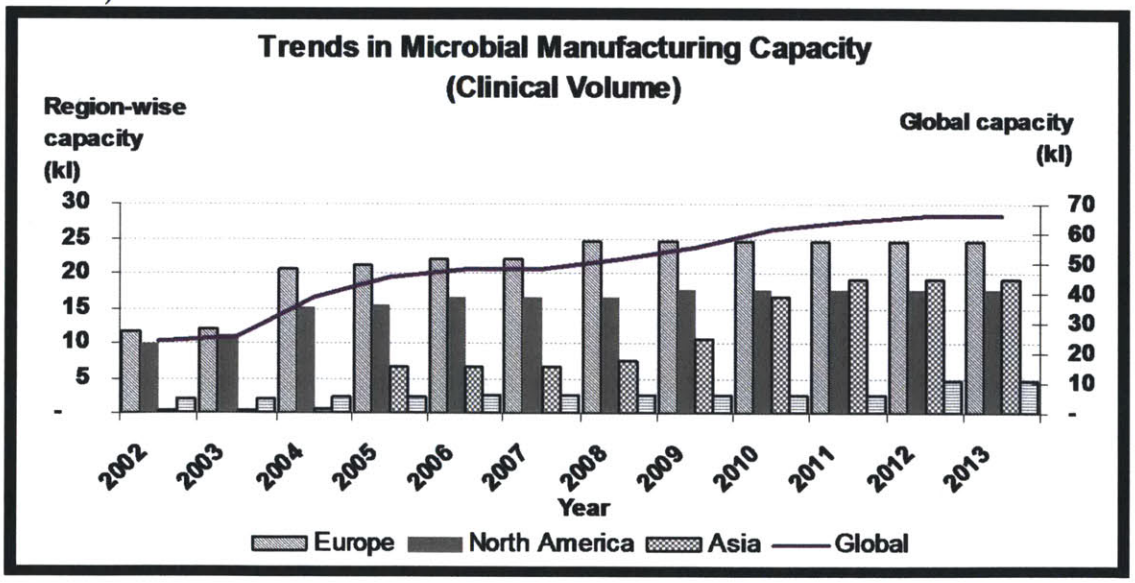


Figure 3-3: Global trends in microbial manufacturing capacity (clinical volume)



as a growth industry and thus have made a concerted effort this decade to grow and develop capacity. Malaysia, India and China are prime examples of this. Many firms in these locations previously served local markets. They are looking to expand to newer markets across the world using a wide variety of strategies. Some governments offer tax benefits to firms that set up operations (Malaysia) or use other means to attract foreign investment (China and India). Firms in Asia are developing contract manufacturing capacity to offer the option of low-cost manufacturing to those that do not want to set up their own operations (India).

Secondly, the possibility of low-cost manufacture has also driven collaborations between large, well established pharmaceutical firms to acquire and develop capacity in Asia as a strategy to enter these markets. Asia is particularly attractive for the production of microbial biotech products. Microbial biotech products have smaller margins than mammalian products. There is more pressure on margins thus pushing manufacturers to seek low cost manufacturing locations. Many of these acquisitions have been driven by generics and small molecules in the past. However, new collaborations over biosimilars are emerging that are likely to drive further growth in this area. Amongst the prominent collaborations include the Biocon/Pfizer partnership for human insulin and analogs. Daiichi Sankyo's acquisition of Ranbaxy in November 2008 was also driven in part by Ranbaxy's biosimilar capabilities. Biosimilar versions of 2 microbial biologic drugs (recombinant human growth hormone and filgrastim) already exist in the European market.

The growth in Asia is being driven by CMOs. Only 3 of the 19 facilities in Asia are product companies. Of the rest of the 16 firms, 5 are exclusively contract manufacturing organizations. A majority of the firms in Asia (11 of 19) do both product manufacture as well as contract manufacture (mostly clinical). These firms are using contract manufacturing as a foothold to gain entry into international markets themselves. Contract manufacturing in general is playing a large role globally as we will see in the coming sections.

3.1.3 Analysis by number of facilities

Total volume of capacity is one way to measure the presence and concentration of the industry by continent. However, manufacturing volumes in microbial facilities vary widely. Of the 86 clinical facilities, only 2 facilities had capacities larger than 5000l. Clinical capacity, which denotes important innovative capacity of a region, accounts for only 10% of the total global volume. [Table 3.1.3] shows most microbial facilities have capacity than 5000l (clinical + commercial). Less than 15% of all reactors command 80% of the total global volume.

Table 3.1: Number of microbial facilities by size

		# of Facilities		
Region	**Total**	**≥10kl**	**5kl-10kl**	**≤ 5kl**
Europe	61	13	6	42
North America	59	6	2	51
Asia	22	2	2	18

In addition, due to the huge market for the product, insulin manufacturing facilities have a capacity of 60,000l or more. Insulin manufacture thus dwarfs any other microbial product when analyzed by volume. Looking at the number of facilities will help provide some more context to microbial biomanufacturing.

Anlayzing data by volume [Figure 3-2 and 3-5] show Europe to be leading in global manufacturing capacity. More than a third of this volume is contributed by 3 large insulin facilities in Germany, Denmark and Sweden. The number of large facilities in Europe are much more than in USA. These large facilities are significant investments in both continents that will not easily be moved or made obsolete. Most of these facilities were set up before 2002 where the database begins. These 'sticky' assets that were established more than a decade ago play a large role in the prominence of microbial manufacturing in Europe. With recent advances in titres, not too many new facilities are of the same size. Only 2 new facilities larger than 10kl have been planned in the future. Both these planned facilities will be for contract manufacture. See Appendix A for a list of all facilities more than 10kl.

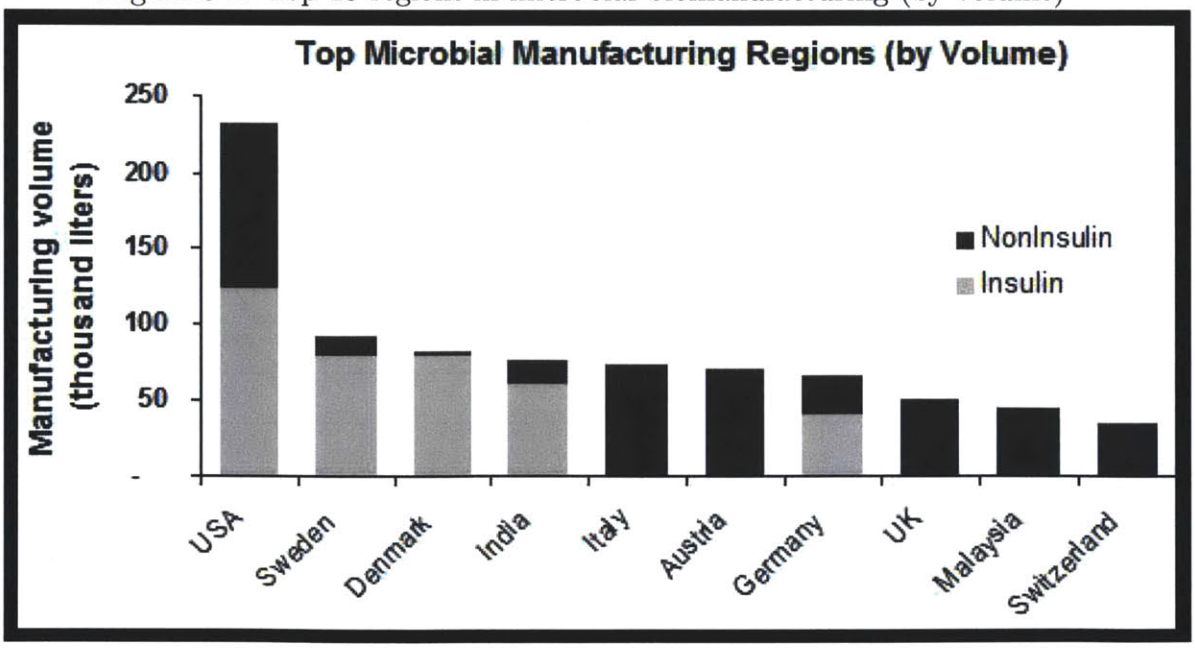
If we look at the number of facilities, US and Europe are comparable with 61 and 59 facilities respectively [Table 3.2]. US has a larger share of clinical facilities than Europe indicating innovative activity. Asia has less than half the number of clinical facilities compared to the US but they form a larger share of the total facilities in Asia. Many of these facilities are contract manufacturing facilities.

Table 3.2: **Share of clinical facilities by region**

		# of Facilities		
Region	**Total**	**Clinical**	**Commercial**	**% Clinical**
Europe	61	33	28	54%
North America	59	38	21	64%
Asia	22	15	7	68%

3.2 Top 10 Regions in Microbial Manufacturing

Figure 3-4: Top 10 regions in microbial biomanufacturing (by volume)



[Table 3-4] increases the granularity of the analysis to look at the top 10 nations in microbial biomanufacturing by volume and by number of facilities. US leads all

other nations in terms of both manufacturing volume and number of facilities. This highlights the role the US has always played as a pioneer and leader in the industry since its inception. The large volume of insulin facilities plays a significant role in this ranking as we see in [Figure 3-4]. Following the US (2 insulin facilities) in microbial manufacturing volume are Sweden, Denmark, India and Germany. Apart from Denmark, all the other locations also have a large presence of other facilities [See Table 3.3].

The US also leads the pack in number of facilities by a large margin. It is followed by a trail of countries with less than one fourth the number and less than half the volume of US facilities. A large number of the facilities in each of these regions are clinical facilities which form the foundation of innovation and process development in the biomanufacturing industry.

Table 3.3: **Top 10 Biomanufacturing Locations by Volume** - US leads the list by a large margin. India is the only Asian location. All others are European.

Country	Volume	Total # of Facilities	Clinical	% CMO*	% Clinical
USA	233,365	53	33	64%	62%
Sweden	92,470	6	2	33%	33%
Denmark	83,000	2	1	50%	50%
India	76,245	13	11	100%	85%
Italy	73,300	3	2	67%	67%
Austria	71,500	7	3	100%	43%
Germany	66,870	11	6	82%	55%
UK	50,775	12	9	92%	75%
Switzerland	34,250	4	2	75%	50%
Netherlands	23,950	5	1	100%	0%

**Includes all facilities that do contract manufacturing (dedicated CMOs and product companies with CMO operations)*
A 45,000l contract manufacturing facility has been planned in Malaysia. Since this volume has not been realized yet, Malaysia was not included in this list.

Looking at the manufacturing type gives us some insight into the nature of manufacturing activity in these regions. In [Table 3.3], we see that a large majority of

the top 10 facilities are involved in some form of contract manufacture (include dedicated contract manufacturers and firms that manufacture their own products and also contract out a part of their capacity). Contract manufacture is seen to dominate amongst facilities in the top 10 nations due to emergence of new CMO organizations and also due to consolidation of the industry and excess capacity in firms that were using a facility to manufacture their own product. [See discussion in Section 3.3.2]

3.2.1 Insulin

It is interesting to observe that the global market for insulin is served by 5 locations in the world alone. Only one of these 5 locations is in Asia, even though Asia is projected to have the highest growth rate of diabetes patients in the world. In the US, insulin is manufactured in the Midwest and Puerto Rico. As emerging markets grow, it would be useful to observe how manufacturers in these higher cost locations compete with manufacturers in location like India and China which are already serving the local market at a fraction of the cost. Partnerships between Pfizer and Biocon over insulin have already emerged indicating that many large pharma, perhaps, intend to shift their manufacture to low cost locations to compete with low cost manufacturers.

To add to this, in the coming years more clarity in biosimilar regulation is likely. If this happens, as is the case with the human growth hormone, biosimilar manufacturers are likely flood European and Asian markets with low cost products. Thus manufacturers in US and EU will lose the advantage that they claim to have. In the words of Friedman *"the playing field will be leveled'* and facilities no longer have a home advantage and will not be competing for their respective regional / developed markets / emerging markets. Instead, the battle will be for global markets and facilities will be forced to be competitive across the world. Insulin is a much simpler product than other microbial and mammalian products existing in the world today. The market for insulin has also been differentiated by newer delivery methods (pens / vials and in the future perhaps oral insulin) that aim at patient comfort. In addition to product differentiation, factors like regulatory stringency and technological complexity, market differentiation and size of manufacture may impact the speed with

which low-cost products enter the market.

3.3 Discussion of the main trends

Following the quantitative analysis of the data, I conducted qualitative interviews with leaders in the industry as well as focus groups. A number of trends emerged from the quantitative analysis and subsequent qualitative interviews that are interesting to observe :

3.3.1 Overall manufacturing capacity is reaching a steady state

The overall capacity that serves US and EU markets seems to have been stable over the past few years. Due to simpler processes, developments in technology have been able to improve yields of microbial products to a greater extent than any other biotech manufacture type. As a result, capacity utilization of microbial facilities has been dropping. Based on industry reports, capacity utilization has dropped by 13% for microbial fermentation over 2004 -2008 [2]

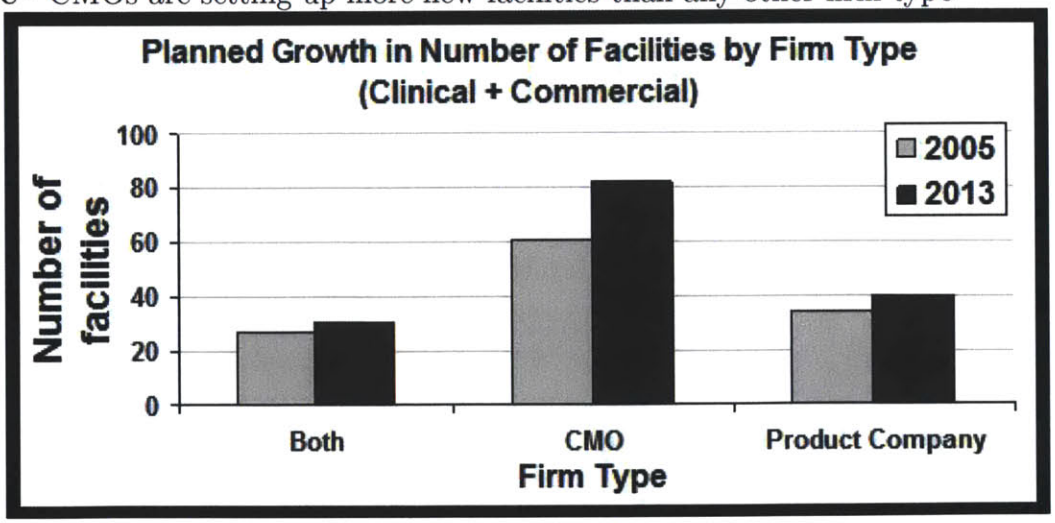
Upstream production efficiencies continue to generate higher product yields. So far, improvements in upstream yields have been enough to meet any increase in demand for microbial capacity. The need for the additional capacity is decreasing as many large biopharmaceutical companies are using the extra capacity they have acquired for contract manufacturing e.g. BI (12,000 litre capacity reactors), Novartis/Sandoz (40,000l and 6,000l), and Merck/Diosynth (14,000 and 7,500l).

However, there are certain segments of the industry, including larger biopharmaceutical developers that continue to experience capacity constraints. These are mainly contract manufacturing organizations (CMOs). Over the past decade, CMOs have been the main class of manufacturers to set up new facilities [Table 3.4]. All other segments of manufacturers (product manufacturers and manufacturers that contracted out some of their own capacity) did not face any capacity constraints. This trend

Table 3.4: **Increase in number of facilities by firm type** - CMOs have set up the largest number of new facilities.

	# of Facilities			
	Clinical		Commercial	
	2005	2013	2005	2013
Both	17	21	10	10
CMO	45	60	16	22
Product Company	10	11	24	29

Figure 3-5: **Increase in number of facilities(clinical+commercial) by firm type** - CMOs are setting up more new facilities than any other firm type



for contract manufacturers is likely to increase in the coming years and will impact the biomanufacturing landscape. Most contract manufacturers rely on their expertise and ability manufacture at extremely low costs in order to be profitable. Many CMOs choose to locate themselves in locations that are either low cost or provide tax rebates to maintain margins. As the industry depends more on contract manufacturing we can expect the contract manufacturing industry to play a role in pushing the industry away from its R&D centers and clusters. Whether or not they will succeed will depend on the state of technology and complexity and regulatory policies at the time. [see Section 3.3.2]

3.3.2 Growth of contract manufacturing

In spite of dropping capacity utilization in the industry, there is expected to be a a rise in contract manufacturing organizations. Contract manufacturing organizations are the only segment in the industry that is facing capacity constraints. This may be attributed to the increasing risk associated with biomanufacturing. The FDA in particular has been increasing the requirements for drug approval. At same time, the approval times have become longer. The business of biotechnology is now risky and uncertain due to complexity of technology as well as well as regulatory uncertainty. According to Di Masi, probability of Phase 3 approval is now as low at 26% for biotech firms on average. For a small biotech firm, this means that if they set up manufacturing for a new biotech drug, there is a 74% probability that the facility will not be used at all. As the costs of drug developments increase, more and more small biotech firms will find it difficult to set up their own manufacturing operations. Most small biotech firms are now choosing to either license to large pharmaceutical firms or contract out to CMOs.

In addition to the sunk cost of setting up a facility, the firms also have to bear the risk of manufacturing and FDA approval that they have little or no experience with. This is where CMOs offer a unique value proposition. Most CMOs offer to manufacture small quantities of a product in early stages of development and bear the risk of approval. In return, small biotech firms pay manufacturers for manufacture of

the drug before approval and also promise to assign the contract for commercial scale manufacture to the CMO. This provides a win-win situation for both small biotech as well as CMOs. CMOs develop expertise in manufacturing and regulatory approval while small biotech firms can focus their attention and efforts on drug development.

3.3.3 Downstream processing costs

With improvements in upstream titres, there is additional pressure on building more efficient and cost effective downstream purification systems. Downstream purification is not easily scalable and is currently the main critical bottleneck. All interviewees across both mammalian and microbial manufacture identified improving downstream performance is an area of keen interest. Microbial manufacturing in its upstream processes involves low cost media and high yields. As product yields become higher, purification downstream becomes more costly. As a result, downstream purification for microbial products contributes to almost 60% of the cost while upstream accounts for 40%.

In contrast, in mammalian manufacture, upstream processes involve more expensive and complex media, lower titres and longer times. Downstream processes for mammalian products are more complex than their microbial counterparts, but less expensive than upstream mammalian manufacture. Overall they account for almost 40% of of the total costs while upstream manufacture forms the remaining 60%. [1]

3.3.4 Upstream innovation focus varies by firm

All firms interviewed were aware of different challenges in upstream innovation in microbial and mammalian systems. However, within the firm the focus of innovation varied. Some firms with established expertise in a mammalian system did very little innovation upstream on microbial platforms. Other large firms had dedicated groups that explored possibilities of using diverse platforms (mammalian/microbial/others) for the same product. Manufacturing concerns were factored in early on in the devel-

[1] Source: from MTC interviews

opment of the product and some firms had established team structures and processes that would allow incorporation of learning from manufacturing teams in upstream innovation e.g. reagents, processes, cell lines. Scale up of microbial systems and manufacturing processes did not come up as a major issue.

Many firms were looking at better disposable reactors that that can be used for both mammalian and microbial manufacture. Some CMOs also mentioned how using the same facility for mammalian and microbial based products provides significant cost savings in time, space and infrastructure. Co-location of manufacturing units also allows shared use of personnel and expertise. This promotes increasing interest and R&D in the use of disposable reactors, especially in contract manufacturing.

3.3.5 Offshoring and outsourcing

Most firms that were interviewed suggested that there was constantly a push to decrease costs. This is even more applicable in microbial manufacturing given the narrow margins of microbial biopharma. There is increasing pressure on biopharmaceutical firms to reduce the cost of health care which is further encouraging firms to relocate manufacturing to offshore low cost locations. Tax benefit locations like Ireland , Malaysia and India provide attractive options to microbial biopharmaceutical manufacturers. However, not too many firms have taken this option as we saw in [Section 3.2]. India is the only Asian location to feature in the top 10 regions for biomanufacturing. Many firms prefer to the test waters through contract manufacturing and collaborations. Thus in new locations that are away from traditional centers of knowledge in the US and EU are likely to either be involved in a different kind of manufacturing activity or perform the same kind of manufacture differently. In order to further investigate this, we must drill deeper into the organization and function of the facilities themselves in order to uncover the difference in the nature of manufacturing activity. We proceed to this through a global facility level survey that will be discussed in the next chapter.

Chapter 4

Nature of Manufacturing Activity by Region

In the previous section we saw a high level snapshot of the global microbial biomanufacturing industry today. In this section we delve deeper to understand the finer aspects of biomanufacturing using a global survey of the industry conducted by the Center for Biomedical Innovation. Despite imperfections in the data, the current dataset demonstrates several key patterns in the globalizing industry. In this section we study differences in the nature of manufacturing activity among various regions. Manufacturing facilities are difficult to compare given the wide variations in the type and complexity of products that they manufacture. In this chapter we try to compare manufacturing activity across regions by:

The scope of operations ('how much') - Number of products, markets and regulators served by facilities.

The type of operations ('what kind') - Efficiency of manufacture, complexity of products and processes, focus on research vs commercial manufacture etc.

4.1 Scope of operations

4.1.1 Products, markets and regulators

Understanding the products, markets and regulators served by a facility gives us a good understanding of the scope of its operations. A facility that serves more markets and regulators is likely to be 'world class' in the sense that it has been approved by multiple regulators and its product serves patients around the world. Though all manufacturing regulations are based on cGMPs (current good manufacturing practices), regulatory authorities around the world have different requirements and procedures for approval. Serving many markets and regulators also indicates that facilities fulfill a superset of requirements and have the expertise needed to maintain a level of quality and safety that is acceptable to most regulatory authorities.

Table 4.1 summarizes the average number of markets and regulators served per facility in each region. The markets included US, EU, Canada, Japan, South America, Asia, Middle East and others. Regulating authorities include FDA - CDER, FDA - CBER, EMA and relevant authorities in Canada, Brazil, Japan, China, India, Australia, Gulf Council and South Korea. Only 1 of the 4 Asian facilities that responded served an international market; the other 3 served only domestic markets. In two cases, facilities that were serving markets outside US and EU only interacted with regulators from FDA and EMA respectively. This is because the developing nations that they serve recognize standards by the FDA and the EMA and allow facilities approved by these organizations to serve their markets.

If we look at the average number of biologics per facility, we see that US has the highest average number of products per facility (12.2) while Asian facilities have an average of just more than 3 products [Table 4.1].

The difference between the number of products manufactured by Asian and US/ EU facilities may be due to many reasons - clinical operations, less complex operations, different type of firms or larger facilities. We discuss each of these below.

More clinical operations

Some of the American and EU facilities also support clinical processes while Asian fa-

Table 4.1: **Products, markets and regulators served by facilities by region** - US leads in all three parameters, followed by Europe.

Facility Region	Avg # of Markets served by each facility	Avg # of Regulators interacted with per facility	Avg # of Biologics manufactured per facility
Asia	2	2	3.25
EU	4.2	2.6	6.75
USA	4.6	4.8	12.2

The markets included US, EU, Canada, Japan, South America, Asia, Middle East and Others.
**Regulating authorities include US - FDA - CDER, US - FDA - CBER, EMA and relevant authorities in the following regions: Canada, Brazil, Japan, China, India, Australia, Gulf Council, South Korea*

cilities support only commercial scale manufacture. As clinical development requires lower volumes, it is possible for facilities to support many products. Clinical operations indicate greater innovative activity in a facility. However, this is beyond the scope of the survey as it did not capture whether the manufacture was at a commercial or clinical scale for each of the products.

Type of firm - Contract Manufacturing Organization or Product Company

Firms that perform contract manufacturing, because of their business model, usually support more products within the same facility. In this dataset, the number of products manufactured by CMOs[1] varied between 4 - 25 products. Even when comparing across CMOs in this limited dataset, the ones in the US supported more products than those in EU or Asia.

Larger facilities with more employees

Another reason that explains how some facilities manufacture more products is the number of employees employed in the facility. However, we see no correlation between the two variables, which may indicate that the US facilities are more productive. [See Appendix B-2 for correlation] We discuss this in detail in the next section.

Simpler operations for more products

The total number of products supported by a facility is also likely to depend on the kind of process it supports. For example, upstream cell culture processes with large

[1]defined as facilities $\leq$50% capacity used for manufacturing

volumes of cultures require weeks for a batch to run through. In contrast, fill/finish and product packaging operations can be completed for a batch within a few days. Even within cell culture, differences in complexity of the culture or the fermentation operation may limit the number of the products that can be manufactured (typically, microbial cell fermentation processes take less time than mammalian operations). Facilities that perform simpler processes have more time to support multiple products within the same facility; this may be responsible for the difference in number of products manufactured by the facility. We will see in [Section 4.4] why this is not true, and how US/EU facilities support more complex processes compared to Asian facilities.

Manufacturing a large number of products in a facility is a challenge. A large number of products in the same facility increases chances of contamination and requires better control over processes to maintain quality and safety. The risk and cost of decontaminating a facility is very high. Contamination or quality issues may result in loss of revenue or market and sometimes even death of patients. However, most facilities in the survey manufactured more than one product in the facility and, based on interviews, it is most likely to increase because of the reasons discussed below.

4.2 Productivity of facilities by region

When trying to characterize the manufacturing activity in a facility, efficiency and productivity of the employees can help us understand whether the facility is doing more with fewer or similar resources.

In this section, we will try to compare facilities that are making more products or serving more markets with 2 of the resources that they have - manufacturing capacity and the number of employees.

4.2.1 Utilization of capacity by region

Manufacturing more products in a facility may be driven by the need to utilize excess capacity. With improvements in upstream yields, it is possible to manufacture more

product per volume. The desired demand is then met by running fewer batches which leads to spare manufacturing capacity once the product run is complete.

Manufacturing sites which produce a larger number of biologics were associated with the highest capacity utilization. [Table 4.2]

Table 4.2: **Capacity utilization and number of biologics manufactured** - The table has been divided into 3 sections - High, Medium and Low Performers. 3 of 4 facilities in the bottom segment were in Asia.

Facility	Perfusion Utilization	Batch Utilization	Number of Biologics	CMO*	Large Pharma
Facility1	***	61% to 70%	25	Yes	
Facility2	***	81% to 90%	25		Yes
Facility3	26% to 50%	71% to 80%	12	Yes	
Facility4	26% to 50%	26% to 50%	8	Yes	
Facility5	***	51% to 60%	5	Yes	
Facility6	$\leq$ 25%	26% to 50%	5	Yes	
Facility7	$\leq$ 25%	51% to 60%	4		
Facility8	$\leq$ 25%	71% to 80%	4		Yes
Facility9	71% to 80%	$\leq$ 25%	4		
Facility10	91% to 100%	91% to 100%	3		
Facility11	***	$\leq$ 25%	3		
Facility12	***	$\leq$ 25%	2		
Facility13	***	***	1		
Facility14	***	$\leq$ 25%	1		

**Facilities where more than 50% of capacity is used for contract manufacture*

In [Table 4.2] we see that the facilities can be divided segmented into 3 types based on the number of products and their capacity utilization :-

1. High Performers (large number of product *and* a high capacity utilization) - There are 3 facilities in this category that manufacture more than 12 products and have a capacity utilization higher than 60%.

2. Medium (3 or more products *or* a very high capacity utilization) - Most facilities fall into this category. Their capacity utilization varies between 26% to 100% and number of products ranges between 3 - 8 products. In this group, facilities with a large number of products had a lower capacity utilization (26-60%) while the facilities with low number of products had a relatively higher capacity utilization (51-100%).

3. Low Performers (few products *and* low capacity utilization) - These facilities are the least efficient in terms of utilizing capacity. The facilities are less than a quarter of their capacity and manufacture only 1- 3 products.

Maintaining excess capacity in US and EU facilities is a greater burden due to the fixed cost in setting up a facility as well as the high cost of maintaining a facility and its GMP status. Facilities in EU and US have more reason to manufacture more products within the same facility. 2 of the 3 facilities in the top segment are US facilities.

In contrast, the cost of setting up a new facility or acquiring an existing facility is relatively lower in locations like Asia [28] which forms a majority of the last segment. 3 of the 4 facilities in the last segment were in Asia. Even though these facilities have excess capacity, they are not using it to manufacture more products. This hints to either an inefficient process or the lack of incentive to utilize full capacity or a combination of both. [Appendix B] shows a weak correlation between the number of biologics manufactured in the facility and capacity utilization.

4.2.2 Productivity of workforce

There was no correlation between the number of employees and the number of products manufactured in a facility. This implies that facilities that manufactured more products were doing so without adding more employees. Employees in US/EU facilites perform more operations for more products than their Asian counterparts with fewer products and markets. [See Appendix B-2 for details.]

US/EU facilities can possibly be considered more productive than Asian facilities. However, this may just be due to the lack of expertise in Asian facilities to mamange more products. Studies show that there are gaps in expertise in workforce in some parts of the Asian biopharmaceutical industry [27, 33]; expertise usually plays a large role in the efficiency and productivity and growth of the industry. [25, 18, 15, 14]

4.3 Accumulation of expertise

In [Section 4.1], we saw how a maintaining a large scope of operations in a facility is a challenge that not all facilities or regions are able to support. In this section I discuss how the ability to perfrom more operations may be linked to its expertise acquired over time.

Older facilities have more employees, make more products, serve more markets on average than younger facilities

In [Table 4.3] we see that facilities older than 15 years on average, serve more than twice the number of markets and interact with thrice the number of regulators than younger facilities.

Older facilities also employed more people [Figure 4-1] and manufactured more products [Table 4.3][See Appendix B-4 for details]. One could argue that facilities in Asia, due to cheap labor, could possibly employ more workers. However, even in the small sample used here, we see large facilities in Asia,the US and the EU with more than 500 employees. Each of these facilities is more than 20 years old. This indicates that facilities progressively grow with success of a product and serve more products with time.

Number of products and number of employees had some correlation with the age of the facility they were not correlated to each other. [Appendix B-2]. Thus facilities appear to grow in size not only because they are making more products but something else that is added over time - investment in R&D and expertise. There may also be knowledge that is acquired over time that allow facilities to build on their efficiencies and allow them to successfully manufacture more products with time.

Table 4.3: **Number of markets and regulators served by older facilities** - Facilities older than 15 years serve more markets and manufacture more products than younger facilities. With time younger facilities may be expected to develop expertise in their processes and increase the services they offer - in terms of markets served or products manufactured.

Facility	**Age (in yrs)**	**# of Emps**	**# of Mkts Served**	**# of Regulators** [2]	**Avg # of Mkts** [3]	**Avg Regulators** [4]
Facility1*	55	≥ 500	5	4		
Facility2	29	101 to 500	7	11		
Facility3	28	≥ 500	5	3	5.7	5.2
Facility4	21	≥ 500	7	8		
Facility5	17	51 to 100	4	4		
Facility6	16	Less than 50	6	1		
Facility7	13	51 to 100	1	1		
Facility8	12	Less than 50	1	2		
Facility9	11	Less than 50	1	2	2.3	1.9
Facility10	10	51 to 100	7	4		
Facility11	9	101 to 500	4	1		
Facility12	6	101 to 500	1	2		
Facility13	2	Less than 50	1	0		
Facility14	2	Less than 50	2	3		

*This facility is an outlier due to its age. It is likely to have been manufacturing non-recombinant proteins from animals before the 1980s when recombinant technology was introduced. It has been upgraded over time. Excluding this facility does not change the overall result.

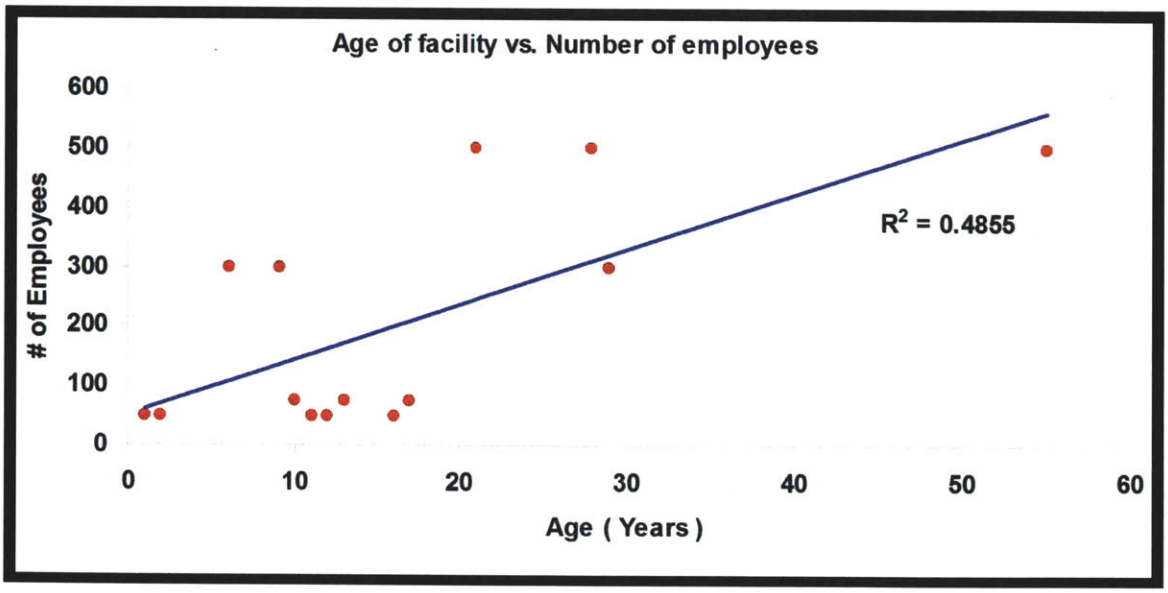


Figure 4-1: **Number of employees vs Age of facility**- Correlation between age of a facility and number of employees indicates clustering of expertise in a facility with time. Older facilities serve more markets and products. See [Table 4.3]
]

Studies show that newer entrants (new clusters) into the biotech arena need to 'catch up' to clusters and firms that have existed in this industry for more time. [17]

From [Table 4.3] we may be able to deduce that younger facilities are not *choosing* to manufacture fewer products for fewer markets. Instead, they *need* to first develop expertise with a few products. Over time, they can use the revenue generated to perform more R&D and build their expertise allowing the facility to grow in size and scope.

Learning acquired over time may not be the only reason younger facilities are doing less. Another factor that can play into scope of operations that a new facility can support is the time required for approval. Approvals by regulatory authorities are slow processes and firms typically attempt to get approval from one agency first. This allows them to begin earning revenue sooner rather than waiting for approval from all authorities for many markets and then beginning production. It would be useful to study the trends in growth of large facilities to be able to compare the rate at which these facilities acquire expertise and build on their learning. This is however, beyond the scope of this study.

4.3.1 Clustering of facilities in US and EU

Another possible reason for older facilities having more products is due to clustering. In the MTC interviews, different firms provided different reasons for the clustering around established centers like Boston. Interviews with facilities around Massachusetts revealed that for some manufacturers, one of the factors determining the location of the facility was its proximity to pre-existing well established facilities owned by the same organization[5]. The proximity would allow them to share resources- both technical and administrative across these facilities. This was a common theme across well established biopharma firms and contract manufacturers. Around Massachusetts, most of the large and small biotech firms focused heavily on upstream research and process improvement. Most firms have clinical capacity and are not manufacturing on a commercial scale which might have some influence on their views on the importance of cluster for manufacturing.

Some facilities are also trying to share resources across both mammalian and microbial products. Since both these processes vary widely, traditionally a facility is defined by its manufacture type. However, facilities are increasingly looking to create 'hybrid facilities that support both these processes. If that were to happen, we would see an even higher number of biologics in a facility. Some CMOs also mentioned how using the same facility for mammalian and microbial products provides significant cost savings in time, space and infrastructure. Co-location of manufacturing units also allows shared use of personnel and expertise. This also explains the increasing interest and R&D in the use of disposable reactors.

When it came to choosing locations, different factors are favored by small and large firms. In the interviews conducted around Cambridge and Massachusetts, most small biopharma were spun off from a collaboration with MIT and other academic centers. As a result, they mainly set up or expanded existing R&D centers due to proximity to centers of innovation and collaboration. Many of these firms found it easier to get experienced hires for locations in Massachusetts due to the vibrant cluster. Most of these companies believe that locating elsewhere can significantly increase project

[5]Reactor sizes and facilities at the manufacturing site were primary factors driving the decisions.

management, general management, rejection rates, logistics, and distribution costs. As a result, when they move out of their pilot phase, they usually choose to keep their manufacturing locations close to the R&D locations. Increasingly, due to the risk and cost of setting up manufacture, many facilities are choosing to contract out their operations.

Large biopharmaceutical firms have the infrastructure for outsourcing and have well established organizational processes that would help teams collaborate over long distances. Some of the interviewees in large firms did not feel that the cluster effect was crucial to their success in manufacturing but was a nice 'bonus'. Their primary reason to be located in Massachusetts was the access to expertise and academic research proximity.

Thus the simpler and more stable product, the likely it is to be moved to a new location. [6] For example, a large pharmaceutical firm with a mature microbial based product and very stable processes was moved from its old facility in Europe to a facility in Massachusetts in a consolidation effort since it was deemed easier and lower risk than to move a complex product to any low cost location. The number of biologics manufactured, the global markets served by the facilities, the regulators and numbers of employees in a facility indicate increased clustering of manufacturing facilities and consolidation of expertise in EU and USA. Thus firms prefer to manufacture certain products in EU and USA instead of moving that manufacture to a low cost location.

In summary, these graphs, tables as well as quaitative interviews suggest that older facilities may have an edge over newer facilities when it comes to availability of experienced employees and other resources which allows them to manufacture more products for more markets and also be more efficient.

[6]MTC Interviews and anecdotal evidence

4.4 Organization and processes in manufacturing facilities by region

In the previous section we looked at the number of operations in order to understand the manufacturing activity in a facility. However, the number of operations tell us only half the story. It is possible that a facility performs a large number of simpler operations while others try to perform a smaller number of very complex operations. In order to better understand the difference in manufacturing activities in different regions, we look in further detail at the operations of the facility in different locations. The next section analyzes how different facilities approach their processes, organization and the parameters of safety and quality differently.

4.4.1 Uniform organization across functions

Table 4.4: **Percentage of total employees in key roles by region** [8] The distribution of employees is more or less uniform. US and EU facilities have more employees (over 30%) in QA+QC functions compared to Asia where more employees are involved in manufacturing operations.

	Function				
Region	**Quality Assurance**	**Quality Control**	**Engg. Support Services**	**Manufacturing**	**Technical**
USA	15%	16%	9%	41%	19%
EU	9%	23%	7%	44%	17%
Asia	11%	16%	8%	48%	17%
All Regions	**12%**	**17%**	**8%**	**45%**	**17%**

Table 4.4 shows the distribution of employees across 5 major functions. Organization of the facilities is more or less uniform across all locations with some minor variations. Based on the preliminary data, Asia has marginally more people involved in the manufacturing operations. US and EU had a slightly greater share of employees (over 30%) involved in QA and QC while Asian facilities employed only 27% of their employees in QA and QC operations. There is too little data to test if the

variations across regions are statistically significant. Fewer employees in QA and QC could indicate either a lax approach to quality or that the manufacturing operations in Asian facilities are simpler, well understood and easily controlled as compared to those in US and EU facilities.

4.4.2 Comparison of type of processes by region

Looking at the types of manufacturing processes help us further understand the functions of the facility. The types of processes in a manufacturing facility vary widely in complexity and value. [Figure 4-2] shows that 89% of European products and 80% of US products involve cell culture while only 29% of the Asian products manufactured in facilities are supported by the same processes.

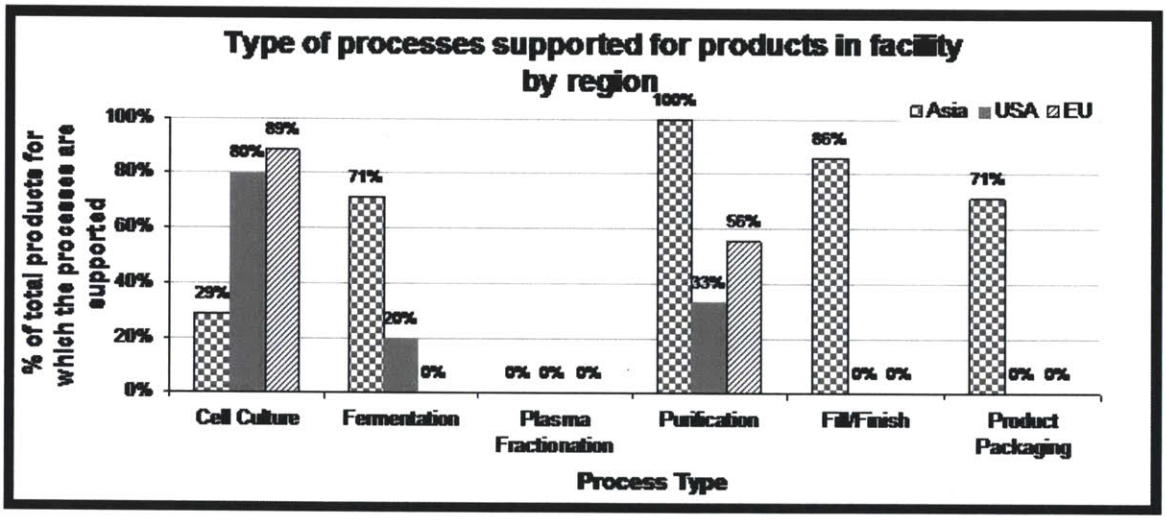


Figure 4-2: **Type of processes supported for products in a facility by region** - US/EU facilities specialize in a few processes (cell culture/purification) compared to a broad spectrum of facilities in Asian facilities. Asian facilities perform simpler processes (fermentation over cell culture) and low value downstream operations like fill/finish and product packaging.

Type of processes supported vary in type and complexity

As we analyze the types of operations, we see that none of the US or European facilities performed any sort of product packaging (fill/finish), which is a relatively low value process compared to cell culture. It also requires less expertise as the product has already been manufactured and purified. All of the Asian facilities that have

responded to the survey support product packaging processes. This may be because Asian facilities are able to replicate simpler processes at a lower cost.

Asian facilities support a broad spectrum of processes like fermentation, purification as well as packaging for a fewer number of products in the facility. This indicates a more integrated manufacturing with all processes performed in the same location. In contrast, US/EU facilities specialized in a cell culture and purification for a large number of products. [See Section 4.1]

There were some US/EU products where cell culture was performed in one facility but it was not purified at the same location. This explains the disparity in the cell culture and down stream purification(DSP) for US and EU facilities. This may have been due to infrastructural limitations when the company was building or expanding their existing manufacturing facility. For example, if the land in one spot on campus is only enough to house the fermentation unit, the DSP would have to be housed in a separate nearby location. This happens to established companies more than new start-ups. Tanker trucks are used to transfer the harvested broth to another location on the same campus for DSP. Separation of cell culture from DSP is not a common practice, but it exists. [9] It is also possible that when responding to the survey, respondents assumed cell culture to include purification. (All cell culture is followed by purification).

4.4.3 Comparison of cell culture by region

When comparing cell culture processes alone, more Asian products were manufactured from (microbial) fermentation processes, an older, widely understood technology, instead of (mammalian) cell culture which is relatively newer.

There are exceptions to this. Some well established cell cultures are not more complicated in operations than microbial systems. A better metric to compare the complexity of a cell culture / fermentation process or even the overall manufacturing process of a product is the number of unit operations. We discuss this in the next section.

[9]Discussion and consensus with CBI focus groups and anecdotal evidence

4.5 Complexity of processes by region

4.5.1 Unit Operations - A brief introduction

A unit operation in chemical engineering refers to a step or function in the manufacturing process. A process with a large number of unit operations is one that involves several steps / operations on or with materials to form the final product. Amongst industry leaders, it was generally agreed that a large number of unit operations is an indicator of product complexity.

In the survey, the respondents were asked to specify the number of unit operations in each of the following processes: cell culture, purification and fill/finish. The numbers of operations in each process were summed up to find the total number of unit operations for the product in the facility. The total number of unit operations involved in the manufacture of a product is a good proxy for the complexity of the overall manufacturing operation. In this section we analyse the overall complexity of the product/process across regions. We also try to control for the kind of processes a facility supports (upstream vs. downstream) by comparing complexity across only cell culture and purification across regions. (All regions supported cell culture (mammalian or microbial) and purification in their facilities. Finally, we try to control for product type and compare compare the number of unit operations of mammalian products and microbial products across regions. A total of 27 products across 9 facilities were studied for this analysis.

4.5.2 Total unit operations (cell culture + purification + fill/ finish)

When looking at a distribution of products across the number of unit operations by region we see that the most complex process in Asia has only 11 unit operations compared to 13 unit operations in Europe. US products had the highest unit operations at 19. The median of the distribution of unit operations in Table 4.5 indicate a higher overall complexity in US and Europe as compared to Asia.

Table 4.5: **Median, Max and Min unit operations supported by facilities by region** - US facilities are supporting more more unit operations followed by EU and finally Asian facilities.

Unit operations (Cell culture + purification + fill-finish)				
Region	**n**	**Median**	**Max**	**Min**
Asia	6	7.5	11	7
EU	9	9	13	7
USA	12	13.5	19	4*

** Does not include fill finish. The minimum unit operations for a facility that did enter number of fill finish operations was 10.*

Differences between the US and Asia facilities are significant at 94% confidence. The number of data points here is too small to be able to generalize this result on the general population. [See Appendix A.2]. Nevertheless the pattern displayed here is significant and highlights an important difference in the nature of manufacturing activity between regions.

4.5.3 Complexity of upstream processes only (cell culture+ purification)

Table 4.6: **Median, Max and Min unit operations supported across cell culture + purification by region** - When controlling for the processes supported, we see the pattern remain unchanged. US facilities still support products with the highest numbr of unit operations. The most complex product in Asian facilities is simpler than those in EU and US.

Unit operations (Cell culture + purification)				
Region	**n**	**Median**	**Max**	**Min**
Asia	6	6.5	9	5
EU	9	9	12	6
USA	12	10	15	4

In [Section 4.4.2], we saw that processes supported by a facility are different. We try to control for this by comparing the number of unit operations in the cell culture

and purification processes alone. (Only Asian facilities did fill/finish.) Table 4.6 compares the number of unit operations in the cell culture and purification processes alone. We see that US products still have the most unit operations. The average number of operations for US products is the highest of the 3 regions. The maximum number of operations for a product in the US was higher than the corresponding product in EU followed by Asia.

4.5.4 Complexity by host cell type (mammalian and microbial) by region

Complexity of processes also vary by manufacture type. In [Table 4.8] we compare only mammalian products across the regions. We still see similar results with US having the highest average number of unit operations followed by Europe and Asia.

Looking at microbial products alone, we see the pattern remains unchanged with US facilities having the highest average number of unit operations followed by Asia [Table 4.7]. No EU facility that responded manufactured microbial products.

Table 4.7: Average unit operations for microbial products by region

Region	Culture type	n	Average
US	Microbial	2	16.5
Asia	Microbial	4	9
Europe	Microbial	0	NA

Table 4.8: Average unit operations for mammalian products by region

Region	Culture type	n	Average
US	Mammalian	10	11.8
Asia	Mammalian	2	7
Europe	Mammalian	9	9.8

It is interesting to note that the average number of unit operations for microbial products is more than that of mammalian products. This is contrary to the general perception that microbial processes are simpler than mammalian processes. Discussion with CBI focus groups reveal that this may not always be the case anymore.

With time the number of unit operations between microbial and mammalian processes may be comparable. Two reasons can be hypothesized:

1. Process turn around times: At times, since the microbial processes are shorter in duration, more time is spent in turning the process around than cell culture, and actually requiring more labor allocation per year.

2. The establishment of standards in mammalian production: A standard process platforms and configurations of methods like Protein A columns (and other ionic exchange columns) has streamlined mAb production. Most companies (in US/EU) now have a high level of knowledge and experience allowing operations to become simpler. On a per weight basis, mAb is very low on a cost of goods sold (COGS) curve compared to other growth factors made by microbial process. In comparison, some processes making a special protein with E. Coli most likely are customized for that protein and more complicated; as a result, these processes are not practiced by other companies in the industry. It is a misconception that making cell culture product is more complicated and more expensive. [10]

This is supported by data in [Table 4.7] and [Table 4.8] where we see microbial products in US facilities with higher unit operations indicating highly innovative 'special proteins' that were described above.

4.5.5 Unit operations as a metric

Analysis of unit operations further strengthens the hypothesis that products in Asian facilities are indeed less complex than those in EU and US facilities. Even with increasing financial pressures, the products that firms are comfortable manufacturing in Asia are simpler and on average face fewer quality issues than products that are manufactured in the US and EU facilities.

Unit operations can be a useful metric to compare length and complexity of manufacturing operations in bio-manufacturing. Unit operations are understood across the industry by all persons. They are rooted in engineering principles and do not

[10] CBI focus group and anecdotal evidence

vary by regulatory guidelines.

Lack of standards across facilities on how to define a unit operation may create some confusion in analysis. For example, a purification step may involve filtration through several columns. Between different filtration steps, the columns have to be de-salted. Some facilities may include desalting as a separate operation while others may include it in the filtration process making the number of unit operations reported by one facility double even though both facilities are performing the same operations. However, if defined consistently, they can provide deep insight into manufacturing activity and complexity.

4.5.6 Unit operations and quality issues

There are several implications of supporting a high number of unit operations, the most important being that an increasingly complex process gets progressively more difficult to control, leading to quality issues. In the survey, facilities were asked questions relating to quality issues. This included questions on the percentage of lots that are rejected, number of of critical deviation and number of unresolved deviations. As deviations in a biopharmaceutical production facility can have legal implications, there is considerable reason for facilities to choose to not reveal that information or under-report it and understandably, many facilities chose not to respond to those questions.

The percentage of total lots rejected have fewer regulatory implications for the facility. Lots of product may be rejected because of any inconsistency between batches that was identified by the quality teams at any time during the operation. In some cases batches are rejected in case there is any reason for QA to believe that the final product may not be of consistent quality. In such cases, it would be cheaper to re-do an entire batch rather than waste time and resources on completing a batch of product that you woild have to test and discard later. Being able to reproduce consistent quality product, batch to batch, is a indicator of a well controlled process. The percentage of total lots of product that are rejected can therefore be used as a

proxy for extent of quality issues faced by the facility. [Figure B-3] shows a correlation between the number of unit operations and % of Lots Rejected. Fewer % rejected lots indicate better control over processes to ensure consistency between batches of manufactured product and thus less likelihood of safety or quality issues. In some cases, fewer percentage of lots rejected may indicate that QA personnel are not doing their job correctly and substandard products are entering the market.

4.6 Manufacturing quality issues by region

The number and kind of quality issues faced by a facility are an indicator of the kind of innovative activity in a facility. The stage at which a quality issue is discovered defines the robustness of its R&D and process research as well as the efficiency of its operations. Facilities that catch more issues earlier on in the development process avoid issues in commercial scale when they are more expensive and time consuming to correct and also detrimental to the firms image.

In this section we look at the kind of quality issues and the stage at which they are discovered by region.

4.6.1 Stage at which quality issues are discovered

Of the facilities that responded in [Figure 4-3], most US facilities discover quality issues for their products in early stages like process research and pilot development. Fewer US products have quality issues discovered in later stages of the manufacturing process. In case of Asian and European facilities, we see the opposite trend with fewer facilities being discovered in earlier stages and a larger number of issues being seen in full scale production. Discovering quality issues during full scale production is extremely expensive and sometime detrimental to the facilities standing with regulators and the general public.

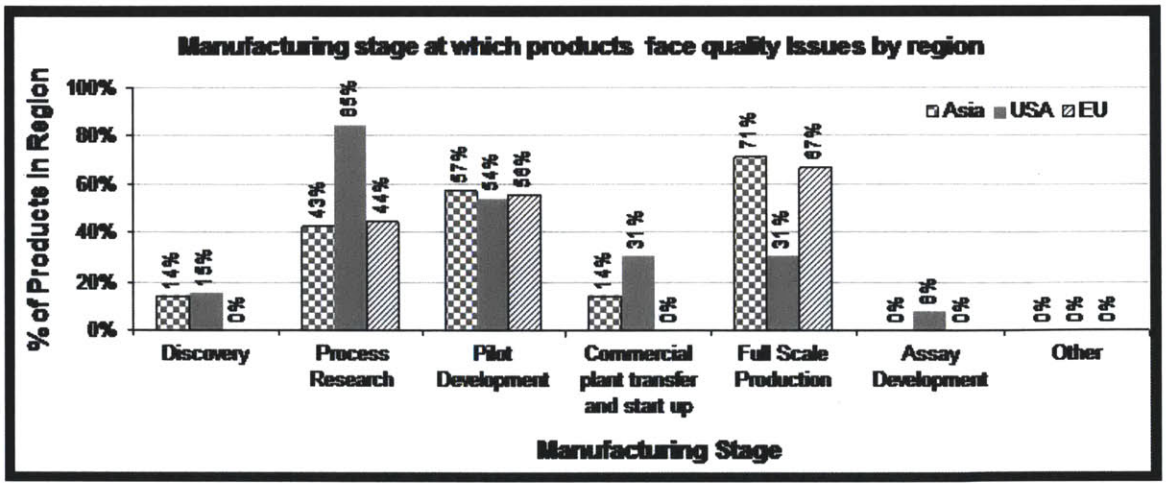


Figure 4-3: **Stage at which quality issues are discovered-** US facilities discover most quality issue in early stages of process research and fewer issue in subsequent stages. Most EU and Asian facilities find few issues early on and more issues in late stage manufacturing or pilot development.

4.6.2 A difference in approach to manufacturing quality

[Figure 4-3] speaks to the importance of process research in manufacturing. If we look at quality issues faced by US facilities, we see a large number of products facing issues in process research. However, in each subsequent stage, the issues drop dramatically in contrast to EU and Asian facilities. This also highlights a fundamentally different approach to manufacturing in US facilities that put a lot of focus on robust process research. The overwhelming share of process research related issues faced by products in the US indicate that either most of the innovative process research happens first in the US, following which, the products are manufactured in other parts of the world. In contrast EU and Asian facilities to little or no process research and as a result, a greater share of the issues they face are in later stage development and manufacture. This is consistent with the kind of issues faced by EU and Asian facilities that we see in the next section.

4.6.3 The kind of quality issues observed

In the survey, respondents were given 4 options for quality issues that were observed :

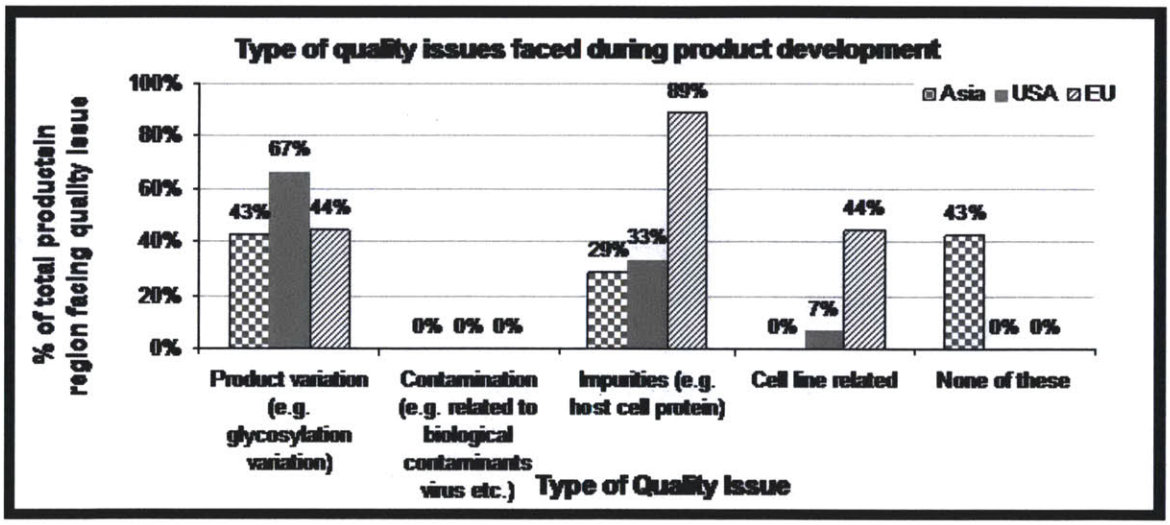


Figure 4-4: **Types of quality issues faced during product development by region** - US products saw more issues related to product variation while EU facilities saw more issues related to impurities. Asian facilities saw no issues or issues not related to the 4 categories provided.

1. Product Variation

2. Cell Line Related

3. Contamination

4. Impurities

5. None of these

Option 1 and 2 are issues linked to product complexity. We see that all facilities manufacturing a mammalian product faced issues of glycosylation variation. Thirteen of twenty-one mammalian products faced issues of product variations, which was also the most common type of quality issues faced by across manufacturers followed by product impurities. This also highlights that the complexity of the product plays a large role in quality issues faced by the facility.

Option 3 and 4 relate to process complexity. Impurities were the second major challenge faced by more than half of the US and EU facilities and some Asian facilities. Contaminations issues, which in the recent past have received a lot of press were

not the major challenge that manufacturers face. These are also likely to be under reported.

Most US and European manufactured products face issues related to product variation, impurities and contamination which are all linked to product and process complexity. Product glycosylation-one of the main challenges of mammalian manufacture was the most common issue seen in US facilities. This also confirms that the main challenge in biomanufacturing is still linked to product and process complexity. Much of these challenges are being faced by US facilities, where, as we saw in the previous section, a large part of process research is still located.

EU manufactured products faced issues that were related to commercial manufacture which is possibly where a a greater focus of their operations lie. The difference betwen EU and US facilities may possibly be due to differing regulatory focus between the FDA and EMA. However, most facilities in US and EU served both regulators so this is unlikely to be a differentiating factor. This could also mean EU facilities do a better job of managing glycosylation issues than US facilities.

More than 40% of the products in Asian facilities face quality issues that lie outside of the 4 main issues listed in the survey. This may imply that they faced no issues at all or the issues were not categorized under the options provided. Given the simpler processes that they support, it is possible that Asian facilities face no issues in manufacture. In case it is the latter, it would be interesting to follow with the respective firms with qualitative interviews to understand what kind of issues Asian facilities face and how they are resolved.

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Chapter 5

Conclusions

This study aims to paint in broad brush strokes a picture of the global microbial biomanufacturing industry today and then dive deeper to provide finer details about the complexity of the manufacturing activity in different regions. The idea that complexity of the technology is a factor that determines location of biomanufacturing has been around for some time [23, 9, 25, 17]. This study contributed to the existing literature by using metrics embedded in the biomanufacturing process to support that hypothesis. In this study, the complexity of biomanufacturing has been defined in terms of the number of operations as well as the type of operations.

Below, I collate results across both studies to draw conclusions and suggest areas for further study.

5.1 Microbial manufacturing is primarily located in EU and US

A large chunk of microbial manufacturing catering to developed markets is still located around Europe and US. Europe leads in manufacturing capacity with over 50% of global volume. Most of these facilities are large facilities set up before 2002. These huge investments are unlikely to move ('sticky') and play a large role in Europes predominance in manufacturing capacity. US on the other hand has only 6 large

manufacturing facilities. US and Europe are comparable in number of facilities. The strength of US still lies in small innovative facilities performing more clinical manufacture. We see Asia growing but is still a minor player in comparison to US and Europe. A large part of their growth is due to contract manufacturing organizations that are doing clinical manufacture.

5.2 The number of operations performed by facilities is higher in US and EU than in Asia

Studies have shown that there are knowledge spillover effects in biomanufacturing. [13] However, unlike other industries, biomanufacturing is not easily scalable. [21] To make more products, serve more markets and interact with more regulators is a challenge. We see in 4.1 that US and EU facilities have learnt to do more without adding more employees. Employees develop considerable expertise across more products and operations in high performing facilities. In addition, capacity utilization numbers also indicate that US (and EU facilities to a lesser extent) have developed within their operations a greater flexibility to manage multiple products with the same capacity. This is something that Asian facilities have not yet replicated.

The facilities that perform well on both fronts (more products and more capacity utilization) are leaders in the field of biomanufacturing, indicating that competitiveness in this industry is to a great extent, knowledge-based. Only one Asian facility features in the top 10 microbial manufacturing locations. All the leading facilities in terms of capacity utilization and managing many products and markets were US facilities (followed by EU).

5.3 More complex operations are performed by facilities in US and EU

[Section 4.4 of this study suggest that facilities in US/EU perform specialize in upstream processes that are more complex than downstream processing. Even the upstream processes for US products involve more operations. US facilities manufacture mammalian and microbial products with the highest number of unit operations indicating that they are at the cutting edge of technology with newest, most complex products and the knowledge and expertise to manufacture them. US facilities also focus more on process research and are working on more challenging problems (glycosylation variation) compared to EU facilities that encounter issues during commercial scale manufacture. It was particularly interesting to note that robust process research in the US can be linked to fewer quality issues. This justifies the claim of many experts that bio-manufacturing is still an industry that needs support of robust R&D to succeed.

5.4 There is evidence of clustering and specialization of facilities across the industry

Data from both the microbial study as well as the survey data indicate that firms prefer to add products to existing facilities rather than build newer facilities. This has been suggested in other studies too. [25]

Survey data shows US and EU facilities focus on upstream processes like cell culture and purification while fill/finish processes have moved to low cost locations like Asia. There was evidence of specialization in specific kind of processes in facilities in certain regions. Asian facilities supported simpler processes with fewer unit operations. However, they supported both upstream and downstream processes like product packaging. US and EU facilities supported upstream processes like cell culture and purification which are high value processes and also more complex.

In addition, emergence of CMOs and their rapid growth indicates that biomanufacturing may soon become more specialized allowing small biotech to become smaller and focus on pre-clinical development. Small biotech firms in US and EU focusing on drug development do not want to bear the risk and cost of setting up manufacturing facilities. Instead, they hire CMOs or product companies with extra capacity.

The excess capacity and consolidation of the pharmaceutical industry is likely to assist this process as pharmaceutical firms look to small biotech company to fill up their pipelines. *"Small biotech is about to get smaller, the era of big payouts is over"*, said one executive, referring to the lower payout that small biotech companies receive in licensing deals and acquisitions by large pharma. As firms get more and more specialized, we can expect large pharma and contract manufacturing firms to do a lions share of the manufacturing. This is already happening as is evident from the share of contract manufacturing firms in the top 10 microbial manufacturing regions. The entry of new players like Samsung and Fujifilm in the contract manufacturing arena is an interesting development. [7] It would be interesting to see how firms leverage the expertise from the electronic industry into the biomanufacturing industry.

There appears to be a link between age, expertise of employees and rigorous process research and productivity, efficiency and product quality and safety of the facility. These factors are likely to be responsible for clustering of biomanufacturing around some areas of expertise. Economic and regulatory factors pull manufacturing in the direction of low cost manufacturing. The combined effect of these factors may result in the movement of biomanufacturing to newer locations however, it is unlikely that biomanufacturing, will scatter across various numerous specializations and geographies. Instead, there may be a more guided flow to certain areas of clusters of expertise in low cost locations.

5.5 Future work

At the time of writing this thesis the CBI survey was still online. It would be useful to revisit the analyses in this study once more data on unit operations, capacity utiliza-

tion and quality issues and process types has been collected. Performing statistical analyses would add weight to these observations made above and also introduce new metrics and standards for future study. The contract manufacturing industry is set to play a large role in the innovation and globalization of biomanufacturing. There are few studies on this topic and much of the evidence that is discussed is anecdotal. It would be interesting to study from the industry survey as well as other studies, how contract manufacturing will modify the landscape of biomanufacturing.

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Appendix A

Tables

Table A.1: List of facilities greater than 10kl

Date	Company	Location	Country	Firm Type	Capacity	Comments
2002	Lilly	Indianapolis, IN	USA	Product Company	80,000	Insulin
2002	Novo	Bagsvaerd	Denmark	Product Company	80,000	Insulin
2004	Novo	Kalundborg	Sweden	Product Company	80,000	Insulin
2004	Biocon	Bangalore	India	Both	60,000	Insulin
2005	Lilly	Carolina, PR	USA	Product Company	45,000	Insulin
2002	Sanofi-Aventis	Frankfurt	Germany	Product Company	40,000	Insulin
2002	DSM Biologics	Capua	Italy	Product Company	70,000	
2002	Novartis/Sandoz	Kundl	Austria	CMO	40,000	
2002	Amgen	Boulder, CO	USA	Product Company	20,000	
2002	Merck/Schering Plough	Brinney,	Ireland	Product Company	20,000	
2002	Novartis	Vacaville & Emeryville, CA	USA	Product Company	20,000	
2002	Roche	Penzberg	Germany	Product Company	20,000	
2002	Novartis/Sandoz	Kundl	Austria	CMO	13,000	
2002	Pfizer	Stockholm	Sweden	Product Company	10,000	
2002	Roche/Genentech	South San Francisco, CA	USA	Product Company	10,000	
2004	Lonza	Visp	Switzerland	CMO	30,000	
2004	Merck/Diosynth Biotechnology	Oss	Netherlands	CMO	14,000	
2004	Avecia	Billingham	UK	CMO	10,000	
2008	Amgen	Juncos, PR	USA	Product Company	10,000	
2012	*Avecia*	*Billingham*	*UK*	*CMO*	*30,000*	***Planned***
2013	*Trusgen Biologics*	*Nusajaya, Johor*	*Malaysia*	*CMO*	*45,000*	***Planned***

Table A.2: **Statistical significance of the difference in unit operations between region**

Statistical significance of the difference in unit operations between region		
Region	**P Value**	**Confidence**
Asia - EU	0.20	80%
Asia - US	0.06	94%
EU - US	0.13	87%

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Appendix B

Figures

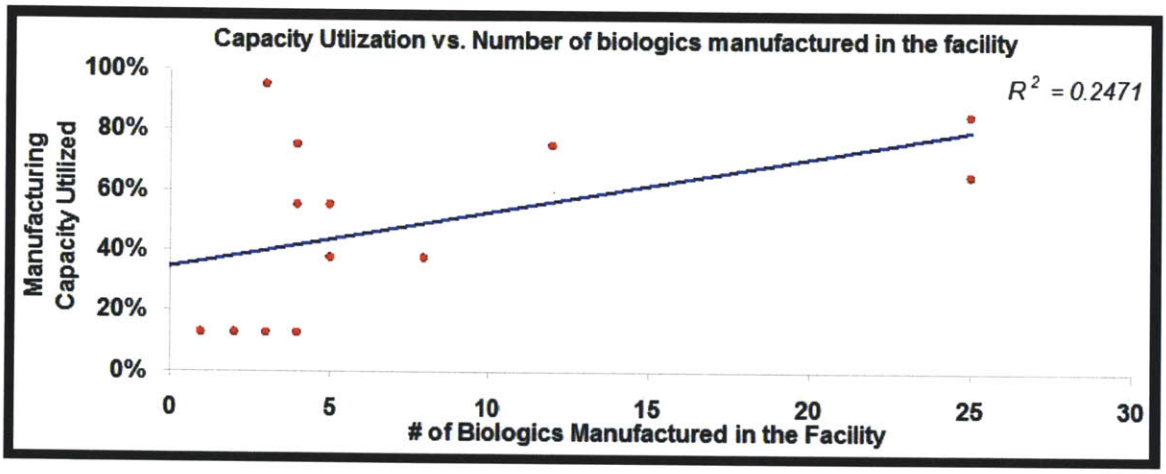

Figure B-1: **Capacity Utilization vs Num of biologics manufactured** - Manufacturing more products in a facility may be linked to a need to effectively utilize excess capacity. As seen in the figure, facilities that manufacture the highest number of products in a facility also have a high capacity utilization. Mid points of ranges were used to plot the capacity utilization on the Y axis.

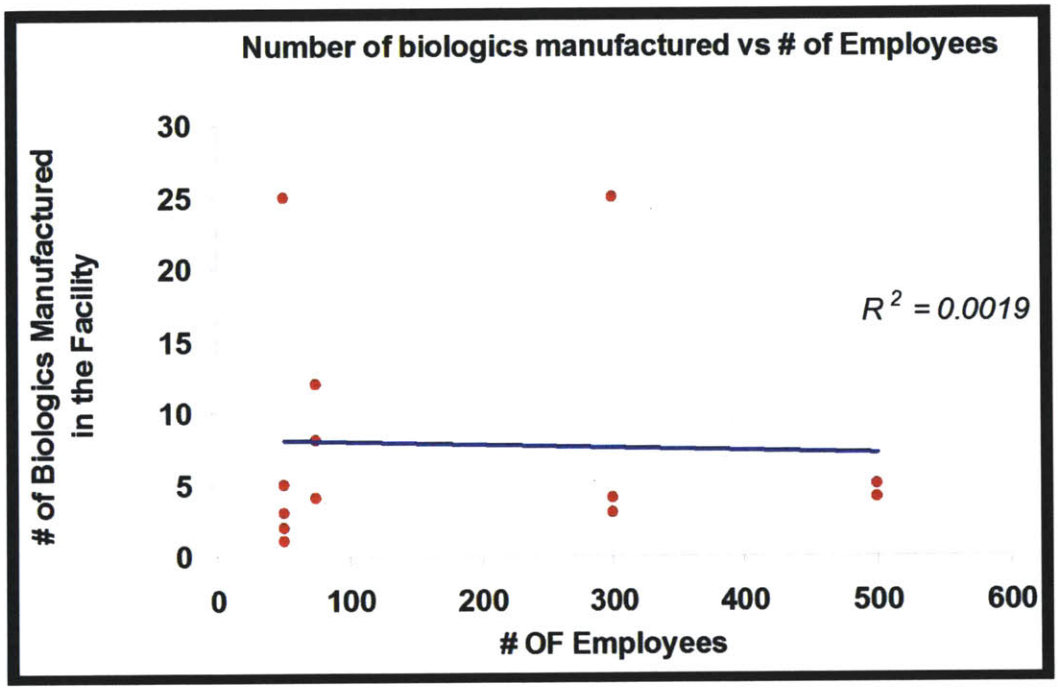

Figure B-2: **Number of biologics manufactured vs Number of employees in a facility-** Little or no correlation between number of employees and number of biologics manufactured. Facilities that are manufacturing more products are not doing it with the help of more employees. These facilities build expertise levels that allow them to be more productive and efficient across more processes and products with the same number of employees.

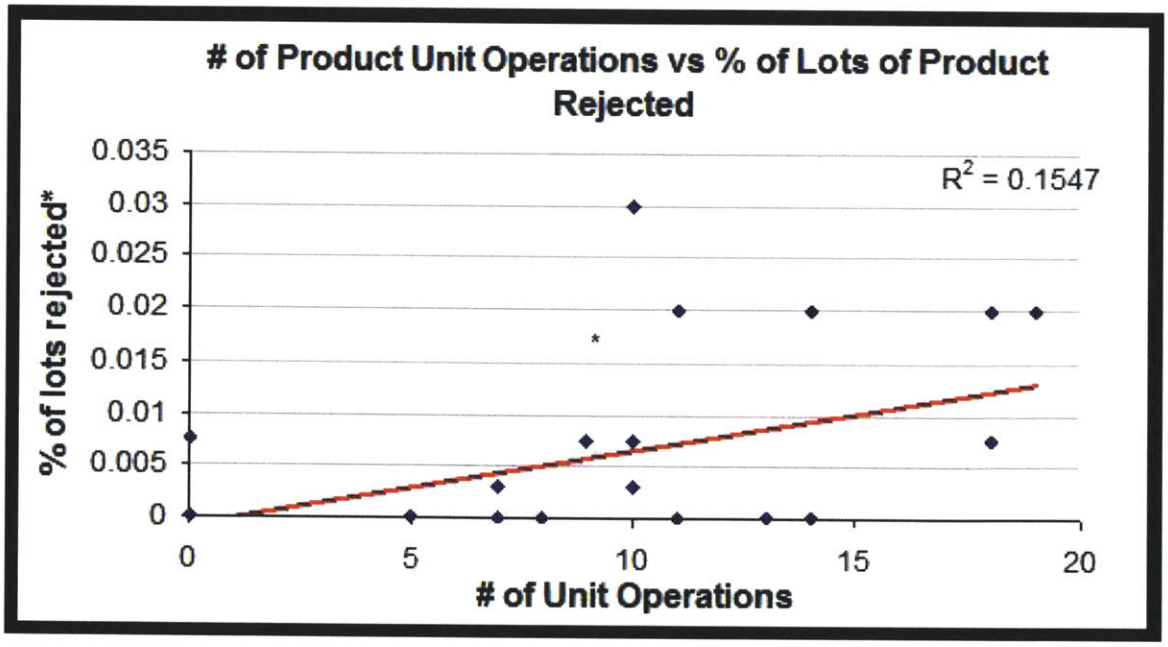

Figure B-3: **Number of unit operations vs Percentage of total lots rejected** Products with more unit operations tend to face more quality issues or batch to batch inconsistency.
0 unit operations correspond to 'Not Answered' or NA

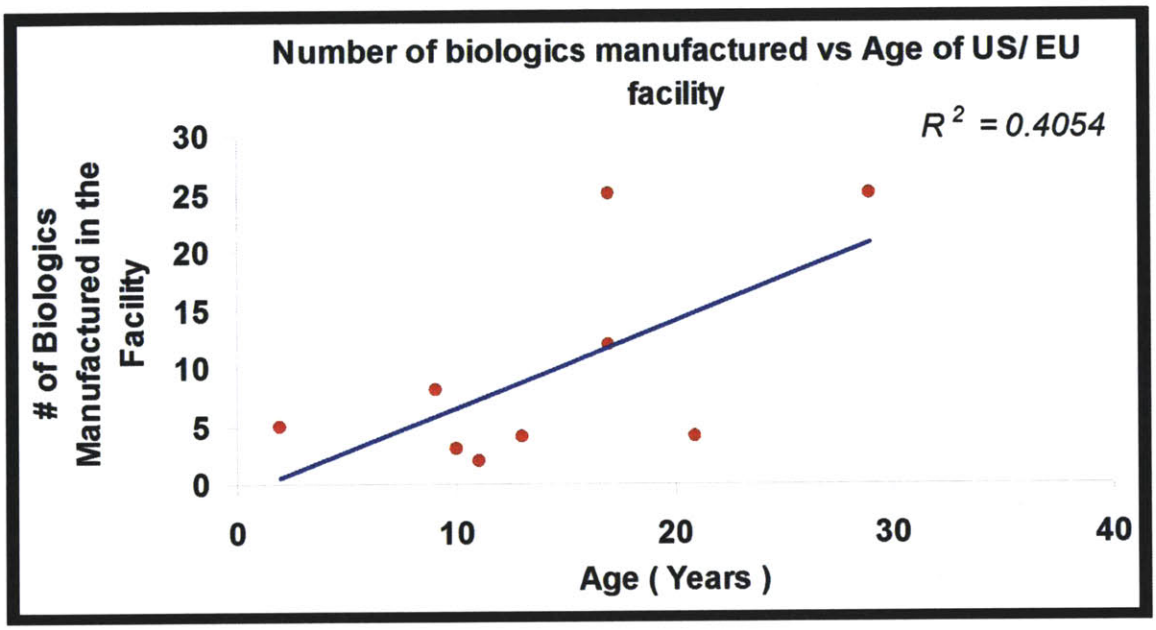

Figure B-4: [**Number of Biologics vs Age of facility (US and EU only)** - The correlation between age of facility and number of products manufactures was strong in US and EU facilities compared to Asia. Setting up new facilities in US and EU is more expensive than in Asia , there is thus more incentive to cluster manufacturing and expertise in an existing facility.

Appendix C

Survey

As a part of the CBI Survey outreach, this text was circulated by Pharma Manufacturing magazine to its subscribers informing them of the CBI Survey.

MIT BioMAN Research Program to Examine Quality Approaches in Biomanufacturing

The Massachusetts Institute of Technologys Biomanufacturing Research Program (BioMAN) is conducting research to examine the regulatory economics of global biopharmaceutical manufacturing.

When the project is complete, BioMAN will report on the manufacturing characteristics and quality approaches that most impact biopharmaceutical regulatory compliance. This information will allow biopharmaceutical manufacturing facilities to benchmark their quality activities and performance against anonymous others.

The MIT CBI is actively looking for interested companies and facilities to participate in this research by completing a confidential, secure, and online survey. If you are interested in participating in the survey, please do so by accessing the following link: `https://survey.vovici.com/se.ashx?s=664A932C022AC38B`

If you have any questions, please contact Dr. Paul Barone at pbarone@mit.edu.

Learn more about the MIT CBI at `http://web.mit.edu/cbi/`

The survey questionnaire used in the online survey can be seen in the pages that follow. The 'End of page' refers to the online page in the survey.

Regulatory Economics of Global Biopharmaceutical Manufacturing

Disclaimer

You have been asked to participate in a research study conducted by the Center for Biomedical Innovation at the Massachusetts Institute of Technology (M.I.T.).

The purpose of the study is to examine the effect of globalization on biopharmaceutical product manufacturing regulatory compliance and economics. Our research has been designed to examine biopharmaceutical manufacturing quality approaches and activities to understand how manufacturing facility characteristics (e.g. location, experience), FDA inspection policy (e.g. frequency, extent), and the increasing role of globalization impact regulatory outcomes. How do company- and firm-level factors impact regulatory outcomes? Does facility location or experience affect performance? Which manufacturing quality activities are seen in facilities with the highest regulatory compliance? When the project is completed we will be in a position to report on the manufacturing characteristics that most impact biopharmaceutical regulatory performance.

You were selected as a possible participant in this study as a member of a biomanufacturing industry with an interest in the questions above.

You should read the information below, and ask questions about anything you do not understand, before deciding whether or not to participate.

This survey is voluntary.

You have the right not to answer any question, and to stop the interview at any time or for any reason.

We expect that the survey will take 30 - 60 minutes to complete.

You will not be compensated for this survey.

In any and all publications that may result from this research, the information you tell us will be confidential.

For participation in the survey, the results of our research will be shared with you in the form of pre-publication reports.

This project will be completed by December 2011. All survey results will be stored in a secure work space until 3 years after that date. The records will then be destroyed.

Please contact Paul Barone, pbarone@mit.edu, or Rachna Pande, rachna_p@mit.edu, with any questions or concerns.

If you feel you have been treated unfairly, or you have questions regarding your rights as a research subject, you may contact the Chairman of the Committee on the Use of Humans as Experimental Subjects, M.I.T., Room E25-143b, 77 Massachusetts Ave,

Cambridge, MA 02139, phone 1-617-253-6787.

CONSENT TO PARTICIPATE IN SURVEY
I understand the procedures described above. My questions have been answered to my satisfaction, and I agree to participate in this study.

❍ Yes
❍ No

CONSENT TO PARTICIPATE IN SURVEY I understand the procedures described above. My questions have been answered to my satisfaction, and I agree to participate in this study. = No; >>>> Skip to End Page: Survey Submitted

(End of Page 1)

Instructions

- This survey has six sections.

- Sections 1 - 4 should take 15 - 30 minutes to complete.

- Section 5 asks questions about the specific products produced at this facility. To aid you in completing this section we have created a data sheet for you to fill out first (Download Datasheet). With completed data sheets sections 5 and 6 should take 15 - 30 minutes depending on the number of products manufactured in your facility.

- The data sheets can be used to collect data for Q5.6,Q5.7,Q5.8, Q5.15-21, Q5.23 and Q5.24. You can submit the data sheet instead of entering the data online by emailing the data sheet to the email address below.

- You will find a progress bar at the bottom of each page to help you gauge how many questions remain.

- In case you cannot complete the survey in one sitting or you wish to revisit the survey for any reason, you can save your responses to resume later using the 'Save' button.
NOTE :- You will only be able to access the saved survey through the generated link.

- Use the 'Back' and 'Next' buttons in the panel at the bottom of the page to navigate the survey

- Use the 'Menu' button to move to any desired page of the survey.
NOTE :- Some of the questions in the latter half depend on your responses to earlier questions. We strongly recommend you complete the survey in order as far as possible.

- The definition of some specific terms have been included in the survey. These terms will be underlined with a dotted line. Please hover over the underlined word with your mouse to view the definition.

- You can submit your responses by clicking on the 'Submit' button on the last page of the survey.

- Please send an email to Paul Barone (pbarone@mit.edu) or Rachna Pande (rachna_p@mit.edu) if you have any questions or concerns.

(End of Page 2)

Section One: Manufacturing Facility Information

Q1.1. Manufacturing Facility Information

Company Name _____

Facility Name _____

Facility Address (1) _____

Facility Address (2) _____

City _____

State / Province _____

Postal Code _____

Country _____

END OF SECTION ONE

(End of Page 3)

Section Two: Site Details

Q2.1. When did the facility first start production? Please enter approximate date if not known. (mm/dd/yyyy)

Date of first production _____

Q2.2. Please enter the year when the facility was most recently expanded, significantly renovated or modified? (yyyy)

Year of most recent expansion/ rennovation/ modification _____

Q2.3. Please enter the number of years that the facility has been owned by the current corporation.

Number of years of present ownership _____

Q2.4. Is this a multi-product site?

❍ Yes

❍ No

Q2.5. Please indicate what % of the manufacturing capacity of the facility has been utilized for contract manufacture?

❍ 0%

❍ 1% - 20%

❍ 21% - 40%

❍ 41% - 60%

❍ 61% - 80%

❍ 81% - 99%

❍ 100%

Advanced Branch: Q2.4 Is this a multi-product site? = No; >>>> Skip to Page 7:
Please enter the following for your facility:

(End of Page 4)

Section Two: Site Details

Q2.6. How are the different products segregated?

❍ Product campaigns are segregated by time in the same manufacturing suite / equipment

❍ Product campaigns are running on separate equipment / suites

❍ Both

Advanced Branch: Q2.6 How are the different products segregated? = Product campaigns are running on separate equipment / suites; >>>> Skip to Page 7: **Was this site designed and built for one or more of the products currently being manufactured in the facility?**

(End of Page 5)

Section Two: Site Details

Q2.7. In your previous response, you stated that product campaigns are segregated by time in the same manufacturing suites/equipment. What is the number of product changeovers in a typical year?

Number of product changeovers _____

(End of Page 6)

Section Two: Site Details

Q2.8. Please enter the following for your facility:

Number of unique biologics currently processed at this site _____

Number of small molecules currently processed at this site _____

Q2.9. Please list the unique biologics manufactured in your facility. We will ask for specific information regarding each biologic in a later section.

Product 1 _____

Product 2 _____

Product 3 _____

Product 4 _____

Product 5 _____

Q2.10. Was this site designed and built for one or more of the products currently being manufactured in the facility?

❍ Yes

❍ No

(End of Page 7)

Section Two: Site Details

Q2.11. Please indicate the <u>current batch manufacturing capacity</u> of the facility (total volume of all reactors in liters).

❍ None

❍ Less than 1,000

❍ Between 1,000 and 5,000

❍ Between 5,000 and 25,000

❍ Between 25,000 and 50,000

❍ Between 50,000 and 100,000

❍ 100,000 or more

Q2.12. Please indicate the current perfusion manufacturing capacity of the facility (total volume of all reactors in liters).

❍ None

❍ Less than 100

❍ Between 100 and 1,000

❍ Between 1,000 and 10,000

❍ Between 10,000 and 20,000

❍ More than 20,000

(End of Page 8)

Section Two: Site Details

Q2.13. What percentage of the current batch manufacturing capacity mentioned above is currently being utilized on average? Please use the most recent year for which data is available to provide an estimate. If you answered "None" on Q2.11, do not answer.

❍ < =25%

❍ 26% to 50%

❍ 51% to 60%

❍ 61% to 70%

❍ 71% to 80%

❍ 81% to 90%

❍ 91% to 100%

Q2.14. What percentage of the current perfusion manufacturing capacity mentioned above is currently being utilized on average? Please use the most recent year for which data is available to provide an estimate. If you answered "None" on Q2.12, do not answer.

- ❍ < =25%
- ❍ 26% to 50%
- ❍ 51% to 60%
- ❍ 61% to 70%
- ❍ 71% to 80%
- ❍ 81% to 90%
- ❍ 91% to 100%

(End of Page 9)

Section Two: Site Details

Q2.15. Approximately how many employees currently work at the site?

- ❍ Less than 50
- ❍ 51 to 100
- ❍ 101 to 500
- ❍ >=500

(End of Page 10)

Section Two: Site Details

Q2.16. Which geographic markets are served by the products manufactured from this facility? Please select all that apply.

- ❑ USA
- ❑ Europe
- ❑ Canada
- ❑ Japan
- ❑ South America
- ❑ Asia
- ❑ Middle East
- ❑ Other (please specify) _____

Q2.17. Please specify the regulatory bodies that you interact with or have interacted with in the past. Select all that apply.

- ❑ US - FDA - CDER
- ❑ US - FDA - CBER
- ❑ EMA (EU or member countries)
- ❑ Canada
- ❑ Brazil
- ❑ Japan
- ❑ Singapore
- ❑ China
- ❑ India
- ❑ Australia
- ❑ Other (please specify) _____

END OF SECTION 2

(End of Page 11)

Section Three: Organization & Function

Q3.1. Do you have a unified company level quality mission statement?

- ❍ Yes
- ❍ No
- ❍ Don't Know

Q3.2. We would like to understand the organizational structure of the facility. Please indicate the approximate number of people in each of the following departments in the facility.

Quality Assurance _____

Quality Control _____

Engineering Support Services _____

Manufacturing Dept _____

Technical Support/ Process Development _____

(End of Page 12)

Section Three: Organization & Function

Q3.3. We would like to understand how various GMP functional responsibilities are distributed throughout the organization. Please indicate which of the following departments are major contributors (> 20% of FTEs) to the functions listed below by checking the relevant boxes below each department.

	Quality Assurance
Change Control	❑
CA/PA	❑
Audits(internal)	❑
Root Cause Investigations	❑
Technology Transfer	❑
Raw Material and Intermediate Release	❑
Product Release	❑

	Quality Control
Change Control	❑
CA/PA	❑
Audits(internal)	❑
Root Cause Investigations	❑
Technology Transfer	❑
Raw Material and Intermediate Release	❑
Product Release	❑

	Engineering Support Services
Change Control	❑
CA/PA	❑
Audits(internal)	❑
Root Cause Investigations	❑
Technology Transfer	❑
Raw Material and Intermediate Release	❑
Product Release	❑

	Manufacturing Dept
Change Control	❑
CA/PA	❑
Audits(internal)	❑
Root Cause Investigations	❑
Technology Transfer	❑
Raw Material and Intermediate Release	❑
Product Release	❑

	Technical Support/ Process Development
Change Control	❑
CA/PA	❑
Audits(internal)	❑
Root Cause Investigations	❑
Technology Transfer	❑
Raw Material and Intermediate Release	❑
Product Release	❑

(End of Page 13)

Section Three: Quality Activities

Q3.4. *At your site*, who has *final accountability* for Quality decisions related to deviations, corrections and preventive measures?

- ❍ QA member assigned to deviation
- ❍ QA manager
- ❍ Head of QA at the plant
- ❍ Plant manager
- ❍ Corporate QA or corporate office (not at plant)
- ❍ Departmental deviation owner
- ❍ Other (please specify) _____

Q3.5. ***In your firm*****, please identify who is** ***most accountable*** **for Quality decisions related to deviations, corrections and preventive measures?**

- ❍ QA member assigned to deviation
- ❍ QA manager
- ❍ Head of QA at the plant
- ❍ Plant manager
- ❍ Corporate QA or corporate office (not at plant)
- ❍ Product manager
- ❍ Other (please specify) _____

Q3.6. On a scale of 1 - 5, 1 being "No experience" and 5 being "Extensive experience", how much experience does this facility have with root cause investigations?

	1 - No experience	2	3	4	5 - Extensive experience
Site experience with root cause investigations	❍	❍	❍	❍	❍

(End of Page 14)

Section Three: Quality Activities

Q3.7. Based on your experience and understanding, what have been the main drivers for quality activities or resource allocation in the past? Which drivers do you expect to play a role going forward?

Key driver in the past

	Yes	No
Problems in raw material	❍	❍
Problems in equipment	❍	❍
Regulatory noncompliance	❍	❍
Problems in production process	❍	❍
Process change due to scale up	❍	❍
Process change due to new technology	❍	❍
Process change due to new markets	❍	❍
Process change due to management objective	❍	❍
Process change due to cost reduction	❍	❍
Process change due to other reasons	❍	❍
Changes to maintain cGMP status when anticipating regulatory changes	❍	❍

Future role expected

	Yes	No
Problems in raw material	❍	❍
Problems in equipment	❍	❍
Regulatory noncompliance	❍	❍
Problems in production process	❍	❍
Process change due to scale up	❍	❍
Process change due to new technology	❍	❍
Process change due to new markets	❍	❍
Process change due to management objective	❍	❍
Process change due to cost reduction	❍	❍
Process change due to other reasons	❍	❍
Changes to maintain cGMP status when anticipating regulatory changes	❍	❍

(End of Page 15)

Section Three: Quality Activities

Q3.8. On a scale of 1 to 5, 1 being "No multidisciplinary teams exist" and 5 being "Extensive multidisciplinary teams", please indicate how you approach internal quality activities such as Change Control, CA/PA, Audits, Root Cause Investigations, Validation, Technology Transfer, Raw Material and intermediate release and Product Release?

	1- No multidisciplinary teams	2	3	4	5 - Extensive multidisciplinary teams
Teams for internal quality activities	❍	❍	❍	❍	❍

Q3.9. Which of the following are typically involved in the quality teams specified above?

- ❑ Central R&D
- ❑ Managers/ Supervisors
- ❑ Operators
- ❑ Administrators
- ❑ Technicians
- ❑ Craft workers
- ❑ Engineers

(End of Page 16)

Section Three: Product Transfer and Continuous Improvement

Q3.10. On average, how many scientists or engineers at the facility are involved in a typical incoming product transfer process? Product transfer for this purpose is defined as beginning with the commitment of product to a particular site and ending with the final process validation run.

- ❍ 1 to 5
- ❍ 5 to 15
- ❍ > 15

Q3.11. How many months, on average, is each scientist or engineer involved in a typical product transfer process? Product transfer for this purpose is defined as beginning with the commitment of product to a particular site and ending with the final process validation run.

- ❍ < 1 month
- ❍ 1 - 6 months
- ❍ 6 months - 1 year
- ❍ 1 year - 2 years
- ❍ > 2 years

Q3.12. What has been the role of manufacturing innovation in your site?

- ❍ No Role
- ❍ Some role
- ❍ Major role

(End of Page 17)

Section Three: Deviations and Root Cause Investigations

Q3.13. How many months, on average, are required for corrective/preventive action to be put in place following a typical critical deviation at your manufacturing facility/site?

- ❍ Less than 1 month
- ❍ Between 1 and 6 months
- ❍ Between 6 and 12 months
- ❍ More than 12 months

Q3.14. What percentage of the total operating budget for the site, over the past 5 years, has been expended on QA/QC/regulatory affairs?

- ❍ Less than 25%
- ❍ Between 25% and 40%
- ❍ Between 40% and 55%
- ❍ More than 55 %

Q3.15. What percentage of the total FTE time, over the past 5 years, has been expended on training?

- ❍ Less than 2%
- ❍ Between 2% and 5%
- ❍ Between 5% and 10%
- ❍ Between 10% and 15%
- ❍ More than 15 %

END OF SECTION 3

(End of Page 18)

Section Four: Interaction with Regulatory Bodies

Q4.1. What is the frequency of inspections (in months), on average, for the following regulatory bodies? (e.g. 6 would indicate every 6 months, if you have never been inspected by the authority, please enter zero)

US - FDA - CDER _____

US - FDA - CBER _____

EMA (EU or member countries) _____

Canada _____

Brazil _____

Japan _____

Singapore _____

China _____

India _____

Australia _____

%Q13SPECIFIED_11%

Q4.2. On a scale of 1 to 5, 1 being 'Highly challenging' and 5 being 'Highly collaborative', please summarize your interactions with each regulatory body. Enter your answers at right, fractional answers are accepted (e.g. 4.5).

1- Highly Challenging 2 3 4 Highly Collaborative -5

US - FDA - CDER _____

US - FDA - CBER _____

EMA (EU or member countries) _____

Canada _____

Brazil _____

Japan _____

Singapore _____

China _____

India _____

Australia _____

%Q13SPECIFIED_11%

Q4.3. What is your perception of the site's standing with the FDA?

- ❍ Poor
- ❍ Below Average
- ❍ Average
- ❍ Above Average
- ❍ Good

Q4.4. Assuming there to be a varying degree of stringency across all the regulatory bodies, please rank the top 5 in order of more stringent to less stringent. Drag the items in the list on the left into the box on the right. (The top regulatory body is most stringent)

US - FDA - CDER

US - FDA - CBER

EMA (EU or member countries)

Canada

Brazil

Japan

Singapore

China

India

Australia

%Q13SPECIFIED_11%

(End of Page 19)

Section Four: Interaction with Regulatory Bodies

Q4.5. To what degree do you agree with the following statement: there is consistency between FDA and EMA inspections.

	1- Strongly Disagree	2 - Disagree	3-Neither agree nor disagree	4 - Agree	5 - Strongly Agree
There is consistency between FDA and EMA inspections.	❍	❍	❍	❍	❍

Q 4.6. On a scale of 1-5, where 1 is "Strongly Disagree" and 5 is "Strongly Agree", please rate the following:

	1 - Strongly Disagree	2 - Disagree	3 - Neither agree nor disagree	4 - Agree	5 - Strongly Agree
There is significant variation across FDA inspectors	❍	❍	❍	❍	❍
There is significant variation across EMA inspectors	❍	❍	❍	❍	❍

Q4.7. Apart from the documentation, does your site prepare for inspections with the FDA and EMA differently?

❍ Yes

❍ No

Advanced Branch: Q4.7 Apart from the documentation, does your site prepare for inspections with the FDA and EMA differently? = No; >>>> Skip to Page 22: **Do you involve the central off-site R&D department with the following inspections? Please check all those applicable.**

(End of Page 20)

Section Four: Interaction with Regulatory Bodies

Q4.8. Please explain briefly how your preparation for inspections with the FDA and EMA differ.

_____

_____

_____

(End of Page 21)

Q4.9. Do you involve the central off-site R&D department with the following inspections? Please check all those applicable.

	Informed	Involved	Neither informed not involved
Routine Surveillance Inspections	❍	❍	❍
Compliance Inspections	❍	❍	❍
Pre-Approval(drugs)/ Pre-license (biologics)	❍	❍	❍
For cause Inspections	❍	❍	❍

(End of Page 22)

Section Four: Regulatory Affairs

Q4.10. How many regulatory affairs FTEs are dedicated to supporting the facility?

Dedicated regulatory affairs FTEs supporting the facility

_____

Q4.11. On a scale of 1 - 5, 1 being 'Not involved' and 5 being 'Extensively involved in all steps', please rate the involvement of the regulatory affairs department in the following inspections.

	1 - Not involved at all	2	3	4	5 – Extensively involved in all steps
Internal Inspections	❍	❍	❍	❍	❍
Third Party Inspections	❍	❍	❍	❍	❍
Routine Surveillance Inspections	❍	❍	❍	❍	❍
Compliance Inspection	❍	❍	❍	❍	❍
Pre-approval (drugs)/ Pre-license (biologics)	❍	❍	❍	❍	❍
For Cause Inspections	❍	❍	❍	❍	❍

Q4.12. On a scale of 1 - 5, 1 being "Not involved' and 5 being "Extensively involved in all steps', please rate the involvement of the regulatory affairs department in process development?

	Not Involved	2	3	4	Extensively involved in all steps
Involvement of regulatory affairs in process development	❍	❍	❍	❍	❍

Q4.13. At what stage is the regulatory affairs department involved in product development?

- ❍ Chemistry, Manufacturing and Controls (CMC)
- ❍ Product development - Clinical
- ❍ Product development - Pre Clinical
- ❍ Commercialization

Q4.14. How does the regulatory affairs department stay updated with FDA developments?

- ❑ Meetings with FDA
- ❑ Regular trainings - prescribed by FDA
- ❑ Memos circulated
- ❑ Other _____

Q4.15. Do you assess the performance of the regulatory affairs department in a well-defined way?

- ❍ Yes
- ❍ No

Q4.16. Please explain in brief the process for assessing the performance of the regulatory affairs department.

_____

_____

_____

(End of Page 23)

Section Four: Internal and External Audits

Q4.17. Is an internal audit team involved in preparation for the following inspections? Please check all that apply.

- ❑ Routine Surveillance Inspections
- ❑ Compliance Inspection
- ❑ Pre-Approval (drugs)/Pre-License (biologics)
- ❑ For-Cause Inspections

Q4.18. Has the site had any inspections from a third party (i.e neither internal nor regulatory)?

- ❍ Yes
- ❍ No

Advanced Branch: Q4.18 Has the site had any inspections from a third party (i.e neither internal nor regulatory)? = No; >>>> Skip to Page 26: **NOTE: Before you proceed please ensure that you have answered question Q2.8 and Q2.9 on Page 7 correctly and completely.**

Q2.8 Number of unique biologics curently processed at this site: %[Q2.8]Q5_1%

Q2.9 List of biologics currently manufactured at this site:
Product1
%[Q2.9]Q18_2%
%[Q2.9]Q18_3%
%[Q2.9]Q18_4%
%[Q2.9]Q18_5%

(End of Page 24)

Section Four: Interaction with Regulatory Bodies

Q4.19. If so, how many third party inspections has the site had over the last five years?

_____

END OF SECTION 4

(End of Page 25)

Section Five: Product Specific Section

All questions in the next section are specific to the biologics manufactured in your site. You will be asked to answer this section for each of the products you specified. (i.e if you entered 2 products, you will be asked to answer this section twice.)

NOTE: Before you proceed please ensure that you have answered question Q2.8 and Q2.9 on Page 7 correctly and completely.

Q2.8 Number of unique biologics curently processed at this site: %[Q2.8]Q5_1%

Q2.9 List of biologics currently manufactured at this site:
Product1
%[Q2.9]Q18_2%
%[Q2.9]Q18_3%
%[Q2.9]Q18_4%
%[Q2.9]Q18_5%

❑ **Please check the box if the above info is answered correctly. If not, please use the menu button to update your response on page 7.**

Advanced Branch: Q2.8 (Number of unique biologics currently processed at this site) = 0; >>>> Skip to Page 57: **How would you describe the awareness of the firm/ facility to academic research and training in biomanufacturing? Please choose one of the following options:**

(End of Page 26)

Section Five Product 1

Note : This section was repeated for 5 products

Q5.1. Please indicate the *Molecule Type* for Product1 in this facility. Select all that apply.

- ❑ Protein
- ❑ DNA/ RNA
- ❑ Antibody
- ❑ Vaccine
- ❑ Small Molecule
- ❑ Drug Substance
- ❑ Drug Product

Q5.2. Please indicate the *Cell Type* that is relevant for manufacturing Product1 in this facility. Select all that apply.

- ❑ Mammalian
- ❑ Microbial
- ❑ Egg Based
- ❑ Viral Vector
- ❑ Other

Q5.3. Please indicate the *Process Type* that is relevant for manufacturing Product1 in this facility. Select all that apply.

- ❑ Cell Culture
- ❑ Fermentation
- ❑ Plasma Fractionation

- ❑ Purification
- ❑ Fill/ Finish
- ❑ Product Packaging

Q5.4. Please indicate the *Product Form* of Product1 when it leaves this facility. Select all that apply.

- ❑ Drug Substance
- ❑ Drug Product
- ❑ Intermediate

(End of Page 27)

Section Five Product Complexity

Q5.5. On a scale of 1 to 5, 1 being "Very simple" and 5 being "Highly complex", how would you rate the complexity of manufacture of Product1 at this site relative to other biopharmaceutical products in general (not necessarily in the same facility)?

	1 - Very simple	2	3	4	5 - High complex
Complexity of manufacture of the product at this site relative to other biopharma-ceutical products	○	○	○	○	○

Q5.6. Please specify the number of unit operations for each of the following steps relevant to Product1 at your site.

Cell culture _____

Purification _____

Fill / Finish _____

Q5.7. Please specify the number of distinct Critical Process Parameters (CPPs) in each of the following steps for Product1.

# of distinct CPPs in Cell Culture _____

# of distinct CPPs in Purification _____

# of distinct CPPs in Fill Finish _____

Q5.8. How many Critical Quality Attributes (CQAs) are there for Product1?

Number of Distinct CQAs _____

(End of Page 28)

Section Five Product 1 Quality

Q5.9. What types of quality issues has Product1 faced during development?

- ❑ Product variation (e.g. glycosylation variation)
- ❑ Contamination (e.g. related to biologocal contaminants virus etc.)
- ❑ Impurities (e.g. host cell protein)
- ❑ Cell line related
- ❑ None of these

Q5.9 - 2. If you selected "None of these" for Q5.9, please briefly describe what other quality issues Product1 has faced during development. If there were no quality issues, please enter "None".

Quality Issue _____

Q5.10. When have these quality issues surfaced?

- ❑ Discovery
- ❑ Process Research
- ❑ Pilot development
- ❑ Commercial plant transfer and start up
- ❑ Full scale production
- ❑ Assay development
- ❑ Other _____

(End of Page 29)

Section Five Product 1 Innovation

Q5.11. What has been the role of the following in the manufacturing of Product1?

Role in the past

	No Role	Some Role	Major Role
Role of continuous improvement of manufacturing for Product1	❍	❍	❍
Role of QbD Submissions for Product1	❍	❍	❍

Expected Role in the Future

	No Role	Some Role	Major Role
Role of continuous improvement of manufacturing for Product1	❍	❍	❍
Role of QbD Submissions for Product1	❍	❍	❍

Q5.12. On a scale of 1 to 5, 1 being "No effect/never used" and 5 being "Highly effective/often used", please indicate the perceived effectiveness of the following processes for Product1:

	1 - No Effect/ Never used	2	3	4	5 - Highly Effective/ Often Used
MIS in manufacturing for your site/firm	❍	❍	❍	❍	❍
Multivariate data analysis in manufacturing	❍	❍	❍	❍	❍
PAT in manufacturing	❍	❍	❍	❍	❍

(End of Page 30)

Section Five Product 1 Manufacture

Q5.13. How would you define the frequency of manufacture for Product1?

❍ Regular Basis

❍ Infrequent Basis

Q5.14. For Product1, in which of the following stages have you used single use reactors? Check all that apply.

❑ Not used at all

❑ Discovery

❑ Process development

❑ Clinical development

❑ Commercial plant transfer and start up

❑ Full Scale Production

❑ Assay Development

❑ Other (Please Specify) _____

Q5.15. In the past year, for Product1, approximately what is the number of lots released?

❍ 1 to 10

❍ 10 - 25

❍ 25 - 50

❍ 50 - 100

❍ 100- 200

❍ > 200

Q5.16. In the past year, for Product1, approximately what percentage of lots have been rejected?

❍ 0%

❍ 0.1% - 0.5%

❍ 0.5% - 1%

❍ 1% - 3%

❍ > 3%

Q5.17. How many total lots of Product1 has the site produced in the past 5 years?

Total # of lots of Product1 _____

Q5.18. For Product1, how many deviations have occurred at the site in the past 5 years?

Total # of deviations over 5 years _____

Q5.19. For Product1, what % of the total deviations in the past 5 years were critical? (involved critical process parameters and/or critical quality attributes)

% of critical deviations _____

Q5.20. For Product1, what % of critical deviations in the past 5 years had no assignable causes found?

% of deviations with no assignable cause _____

Q5.21. For Product1, what % of the critical deviations in the past 5 years were associated with your analytical/measurement systems?

% of critical deviations associated with analytical / measurement systems _____

(End of Page 31)

Section Five Product 1 Manufacture

Q5.22. Over the past 5 years, how would you describe the trend seen in manufacturing volume for Product1?

❍ Steadily increasing

❍ Steadily decreasing

❍ More or less Stable

❍ Fluctuating

Q5.23. What is the annual average production of Product1 at this site (In kilograms)?

Annual average production of Product1 _____

Q5.24. Was Product1 produced at a similar scale at a different site previously?

❍ Yes

❍ No

❍ Don't Know

Advanced Branch: Q2.8 (Number of unique biologics currently processed at this site) ≤ 1; >>>> Skip to Page 57: **How would you describe the awareness of the firm/ facility to academic research and training in biomanufacturing? Please choose one of the following options:**

(End of Page 32)

Section Six: Academic Role in Biomanufacturing

Q6.1. How would you describe the awareness of the firm/ facility to academic research and training in biomanufacturing? Please choose one of the following options:

❍ Not Aware

❍ Aware that such research and training exists but currently not involved

❍ Currently actively involved in the academic research and training

Q6.2. Please identify the locations of academic biomanufacturing research and training facilities/capabilities that you are aware of.

Location 1 _____

Location 2 _____

Location 3 _____

Location 4 _____

Location 5 _____

Q6.3. On a scale of 1 to 5, where 1 is "Not at all important" and 5 is "Extremely important", how important is geographic proximity of an academic site to the manufacturing site for engaging in academic biomanufacturing research and training?

	1 - Not important at all	2	3	4	5 - Extremely important
Importance of proximity of academic site for engaging in academic bio-manufacturing research and training	○	○	○	○	○

Q6.4. On a scale of 1 to 5, where 1 is "No value at all" and 5 is "Extremely high value", what value do you believe academic biomanufacturing research and training has?

	1 - No value at all	2	3	4	5 - Extremely high value
Value of academic bio-manufacturing research and training	○	○	○	○	○

Advanced Branch: Q6.1 How would you describe the awareness of the firm/ facility to academic research and training in biomanufacturing? Please choose one of the following options: ≠ Currently actively involved in the academic research and training; >>>> Skip to Page 58: **What areas of academic biomanufacturing research and training do you believe to be of most value?**

(End of Page 57)

Section Six: Academic Role in Biomanufacturing

Q6.5. Please identify the locations of academic biomanufacturing research and training facilities that your site interacts with.

Location 1 _____

Location 2 _____

Location 3 _____

Location 4 _____

Location 5 _____

Q6.6. On a scale of 1 to 5, where 1 is "Do not use at all" and 5 is "Use on a regular basis", please specify to what extent you use academic biomanufacturing research and training?

	1 - Do not use at all	2	3	4	5 - Use on a regular basis
Extent to which you use academic bio-manufacturing research and training	○	○	○	○	○

Q6.7. What areas of academic biomanufacturing research and training do you believe to be of most value?

_____

_____

_____

_____

Q6.8. In what areas do you think academic biomanufacturing research and training needs are currently not being addressed and would be of most value to industry?

_____

_____

_____

_____

Q6.9. To maximize current and/or potential value from academic biomanufacturing efforts, which of the following is best to focus on

- ❑ Research in relevant management and regulatory topics
- ❑ Training in relevant management and regulatory topics
- ❑ Research in relevant technical and engineering topics
- ❑ Training in relevant technical and engineering topics
- ❑ None of the above

END OF SURVEY

You have completed the survey. Please click on the SUBMIT button below to submit your responses and close the survey.

NOTE: Once you submit your survey you will no longer be able to access/modify your responses. If you wish to revisit your survey or modify responses later please go to any other page of the survey to save the survey using the SAVE button.

(End of Page 58)

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