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The Changing Geography of Biomanufacturing

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Biomanufacturing, specifically of large molecules, is one of the most complex types of manufacturing that exists. The challenge of scaling up living organisms combined with purifying their products to ensure safe administration to human beings creates a high-risk process technically, financially, and from a public health perspective. It is this complexity that rooted the industry in the U.S. two decades ago, spurred continued investment over the past twenty years and today plays to the country's competitive advantages – a technologically advanced, innovative industry that requires highly skilled workers with commensurately high pay.

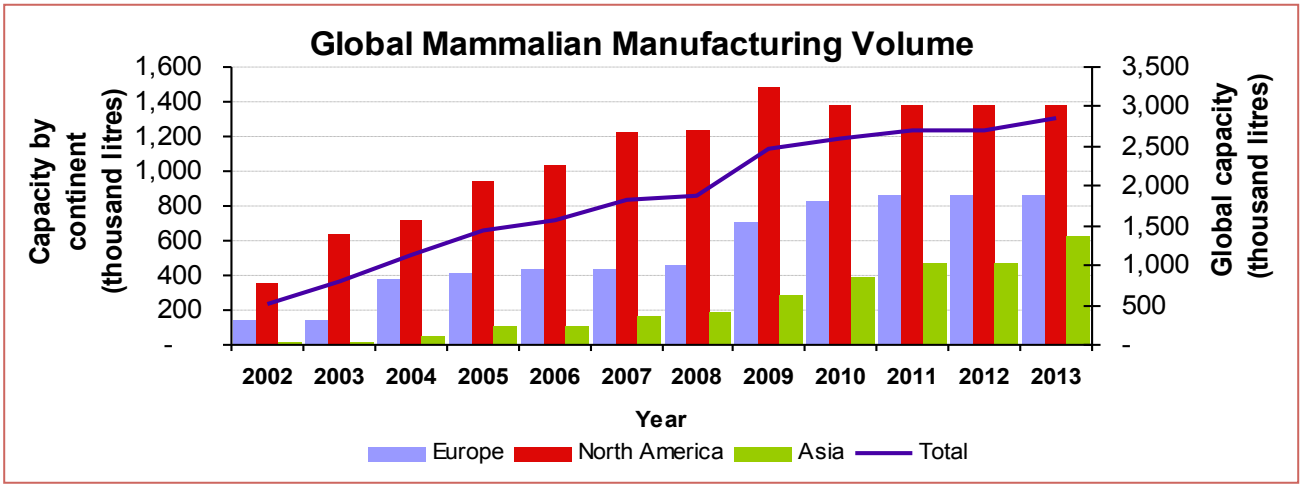
However, as the industry matures, we see a familiar pattern emerging, albeit with some twists. While industry location is still dependent on skilled labor, the globalization of talent and increased standardization of bioprocessing, including increased regulatory harmonization and use of international inspections, has given companies wider latitude in determining where to commercially manufacture their products. In the last decade, many biopharma companies who have been manufacturing in the U.S have opened new commercial biomanufacturing facilities "offshore" seeking both new markets and higher profits, driven primarily by tax incentives. This raises interesting questions regarding the future of the industry in the U.S. and whether this "modularization of production" will lead to the loss of yet another manufacturing industry in the country.

Much has changed since the beginning of the 1990s when there was concern over a worldwide shortage of biomanufacturing capacity and every company with a successful drug was forced to build more capacity. A decade-plus later the concerns have shifted to overcapacity as increased productivity through higher titers and consolidation in the industry have led to the mothballing of existing facilities or the scuttling of plans for building new ones. Given these changes, it is useful to review what has historically driven the location of biomanufacturing investments and what factors might influence these decisions going forward.

Investments in Biomanufacturing Globally

Overall, as Figure 1 shows, North America (the U.S.) leads the world in overall mammalian-based capacity.[i] This is no surprise given the biotech industry – both the underlying science of rDNA as well as the development and scale of process technology - was largely invented in the U.S. and thus the legacy of the first large facilities built remain in the country. Global capacity increased steadily from 2002 to 2009, but in 2009, the issue of potential global overcapacity became better understood and close to half a million liters of capacity was eliminated (or announced that it would be). The steady increases in productivity and the use of disposables (which is not captured in these data) result in flat growth in North America and Europe between 2010 and projected out to 2013. Only in Asia, where contract manufacturers like Lonza and Celltrion continue to build, is there a sign of increasing investment. The demand in Asia for more capacity is driven in part by the growing biosimilars market, but also may reflect some substitution effect, where capacity in North America is being replaced by capacity in Asia. The first signs of this phenomenon can be seen with Genentech's (Roche) decision to close their Vacaville facility in 2009 and buy the Lonza facility that they had rights to in Singapore.

FIGURE 1



The Drivers of Location:

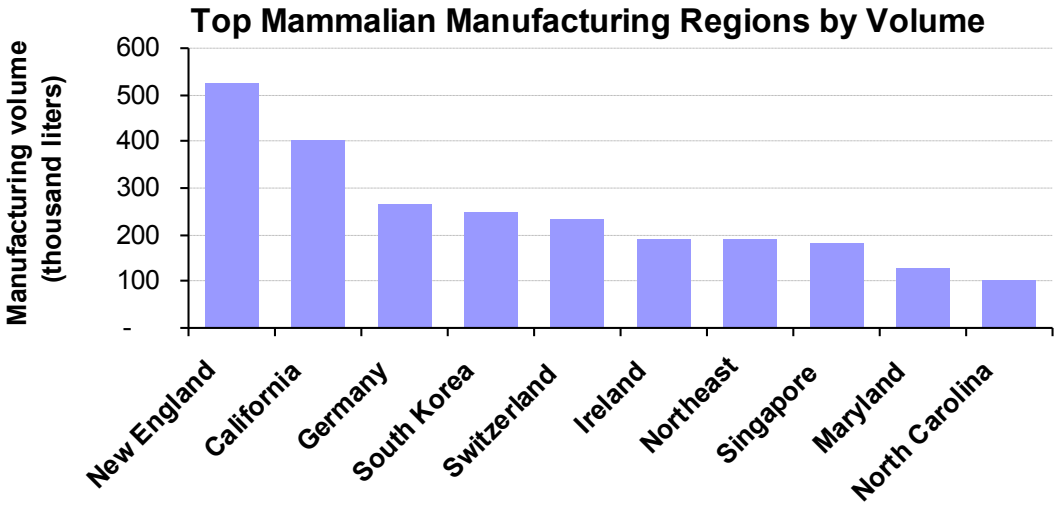
Talent and Proximity to R&D

These slight shifts in global biomanufacturing might underscore a point of view that one hears often in the U.S.: manufacturing has little future in a high-skilled, high-wage region given competition from lower-cost countries, and high-tech regions like Silicon Valley and Boston's Route 128 need to focus on design and innovation, and "let others produce what Americans think up."

However, biomanufacturing flies in the face of this kind of thinking. For reasons related to locating a skilled workforce and being close to biotech research and development to aid process technology transfer, (R&D) biomanufacturing facilities have historically been located relatively close to company R&D centers[ii] and stayed "on shore" for much longer periods of time. Particularly in the early stages of a drug's development, when a compound is being scaled up in the pilot and early clinical stages (Phases I and II), the need for close communication between R&D and manufacturing team keeps the two teams relatively close to each other . Unlike

other industries in which R&D and manufacturing have been vertically disintegrated, the co-location of these two aspects of the biotech value chain speaks to the level of vertical integration that still exists in the industry. In addition, to avoid the risk of regulatory delays, Phase III clinical manufacturing is generally located in a facility where the drug can be manufactured commercially if approved. In order to carefully monitor the scale up of a first product launch, commercial facilities are often kept in close proximity. Biomanunufacturing may be one of the few industries that adds an "M" to R&D, at least for early stage manufacturing. Figure 2 shows the top 10 regions in the world for biomanufacturing, five of which are in the U.S. All of the countries listed but for Singapore (Ireland is combined with the UK) are among the top six countries globally for biotech R&D (as measured by employment).[iii] If one looks at countries that are strong in R&D but not in manufacturing, Canada stands out as the only country without any biomanufacturing presence, presumably because they can piggy back on capacity that is close by in the U.S.

FIGURE 2



Projected Volume through 2013.

A more micro-look at the location of clinical and commercial facilities suggests that product lifecycle and company growth also play key roles in determining where

facilities are located. Approximately 80% of all clinical production facilities are within 100 miles of their company's R&D center (or one of their centers). Clinical facilities are used for relatively short campaigns of small batches, and ideally continually replenished with new drug candidates that are just going into clinical trials, thus proximity is helpful at the early stage of a drug's development.

In the case of commercial facilities, where scale, continuity and repetitive non-stop production is key, there are different considerations at play. Just over half of all commercial sites (almost all first commercial facilities) are located within 100 miles of company R&D. As companies figure out scale up issues during Phase III clinical trial production, they keep manufacturing in close proximity, after which, if all goes well, they begin commercial production in the same facility to increase their efficiency in getting the product to market. For companies launching their first commercial product, the emphasis is on product consistency and getting their product to market, less so on costs. But as a company grows, requires additional commercial capacity, and develops more confidence with its biotechnology and product inventories, it will look further afield to seek out new markets or higher margins, or both. As technology transfer capabilities have improved and production platforms have become more routinized, companies are less concerned about locating production on another continent, as long as they can find or import the talent.

Drug Sales and Tax Advantaged Locations

For companies with one approved product with relatively modest sales, manufacturing usually stays nearby or is outsourced to a CMO, particularly for small, emerging companies. If a product is highly successful and achieves significant sales - "blockbuster" status, for example - then profit maximization becomes more of a consideration when determining where to manufacture. One of the most noticeable trends in the location of biomanufacturing facilities in the past decade is the emergence of tax-advantage locations for biologics production. Since 2004, seven out of the 14 companies with mammalian-based blockbuster drugs have built

facilities in tax-advantaged locations (TALs), as has one CMO (Lonza) (See Figure 3). Countries such as Ireland, Puerto Rico, Singapore, or regions such as particular cantons in Switzerland offer significant tax incentives for biomanufacturing, sometimes as low as 0% for 20 years[iv]. Compared to a corporate tax rate of 35% in the US (though effective tax rates will be lower), moving production to one of these locations is a "no-brainer," according to some, assuming the talent is available or importable.

FIGURE 3: New Commercial Facilities Built or Licensed in TALS Since 2004

Year	Company	TAL Country	Number Facility
2004	Baxter	Switzerland	2
2006	Abbott	Puerto Rico	2
2006	Pfizer	Ireland	2
2008	Amgen	Puerto Rico	4
2008	Centocor (J&J)	Ireland	4
2009	Lonza (CMO)	Singapore	3
2009	Genentech	Singapore	4
2010	Lilly	Ireland	1

While this is a clear trend, and follows the progression of small molecule pharmaceutical manufacturing, it does not tell the whole story. There are a number of companies with blockbusters who, for a variety of reasons, have not yet built biomanufacturing facilities (defined as the primary manufacturing of drug substance as opposed to secondary manufacturing such as fill/finish) in TALs – Bayer, Biogen, Genzyme, Medimmune (Astra- Zeneca), and Novo Nordisk.

Acquisitions, the economies of scale derived from building upon an existing facility, new strategies for meeting production capacity needs given excess capacity, the use of CMOs and disposables, all help explain this. No doubt tax rates are an increasingly important factor in the manufacturing of biologics, particularly as big pharma companies see downward pressures on their margins and biotech companies become more sensitive to cost. TALs are likely to be part of a company's overall manufacturing strategy as it grows, (all but one of the 10 facilities built in TALs was a second or later facility), providing capacity for established, large volume products that are straight-forward to make (most likely monoclonal antibodies). However, recent challenges in some production facilities (Genzyme for example) are reminders that there is no such thing as risk-free production and proximity is still important for monitoring and evaluating process performance.

Biomanufacturing has followed the classic product life cycle model in which the process of innovation to codification of knowledge leads to a manufacturing process that initially stays "onshore" to ensure successful scale up and reduce uncertainties, but later moves to cheaper locations as the production process is standardized and the product matures. In this situation, however, tax rates more so than lower production costs in the form of labor or infrastructure, are driving location decisions. While tax policy has played a role in company location decisions for decades, it has become a more aggressive tool used today in international competition.[v] Many find the product life cycle model antiquated given the ubiquitousness of innovation today, the speeding up of the product life cycle, and the growth of new markets in emerging economies. The rapid diffusion of new technologies around the world, as well as the ability to move manufacturing to low-cost locations even before the production process has been standardized clearly changes the classic model of successive expansions into new markets. However, in biotech, this model still has currency because of the high barriers to entry that exist, (in part due to drug patents) that delay the introduction of competition. While biopharma companies are becoming increasingly comfortable moving biologics production off shore (particularly for well established processes), the complexity

combined with a strict regulatory regime make this an industry with few comparables.

Innovation in Biomanufacturing and Geographic Implications

For the 30 years since its inception, the biomanufacturing industry has been highly innovative, particularly in process innovation. However, the industry has had to walk a fine line between adopting new technologies, and creating quality concerns by altering their processes and final product, potentially slowing down regulatory approval of their product. Due in large part to the complexity and sensitivity of the products, the biomanufacturing culture has historically been driven more by concerns for unexpected product changes than by the opportunities created by developing new technologies (though this began to change with the FDA's Critical Path Initiative in 2004). It is fair to say that innovation in the industry takes place at a relatively slow rate and has been characterized more by *sustaining technologies* than *disruptive technologies.*[vi] Sustaining technologies improve upon established products and processes. Most new technologies in an industry are sustaining in nature, improving and developing an existing industry with well-established products. Disruptive technologies, on the other hand, radically change the value-proposition of a particular product on the market. Innovations in biomanufacturing are incremental in nature since process changes must be validated to manufacture products equivalent to those used in clinical trials. However, given the enormous time scales and dollars invested in biomanufacturing, incremental changes that can improve efficiency can result in significant cost savings over time.

Just as some new technologies can be disruptive and lead to the decline of one industry while replacing it with a new one, new technologies can also create a new geographic map for an industry, making some locations more accessible and amenable to an industry while diminishing the advantages of the industry's existing locations. Improvements in communication technology, for example, have made offshoring of many services easier. For example, locating call centers in emerging

countries such as the Philippines, India, or Eastern Europe has become standard practice for companies today.

The next section reviews four of the most important technology-related trends that have emerged in recent years in biomanufacturing and hypothesizes how these either currently or in the future may affect location of the industry over time. These innovations are dramatically reducing costs and timelines in the biomanufacturing process.

Increased Productivity: Higher titers have had a profound effect on the industry. The suggestion that there might be a two-fold increase in industry-wide productivity, reducing overall biomanufacturing capacity requirements by 25% by 2013[vii], will impact investments and production strategies significantly going forward. Increased productivity, along with possibly smaller volume, niche products (driven by personalized medicine) means less large-scale bioreactors and fewer plants built. The desire for a smaller footprint will also diminish the difference in size between pilot and commercial facilities, possibly leading to continuous production in one place, rather than separating pilot and commercial production.

Single-Use Technology: Introduced in the early 2000s, single use technologies or "disposables" are providing companies with enormous flexibility for their early stage manufacturing (up to 2,000 liters). Because of the use of plastic rather than stainless steel, disposables result in more rapid deployment, greater flexibility and lower costs. Such advantages provide more modularity, creating a "plug and play" turn-key operation that companies can easily move. "This is a technology that you can locate in any tax haven, any IP haven, any labor market, " said one executive. Such technology may play in particular to the advantage of smaller companies, who can afford single-use technologies and thus control their early-stage production.

Multi-product Facilities: New facilities are now designed to handle up to six or seven separate products at the same time. Of course no one facility can fit all products or processes, but they are designed to handle any scale of production from milligrams per liter to grams per liter and from preclinical to commercial. A multi-product facility provides greater flexibility for companies and less of a need for multiple plants.

PAT and Quality by Design: PAT, or Process Analytical Technologies, has been a major initiative of the FDA and embraced by the industry. PAT helps take some of the uncertainty and thus the risk out of the biomanufacturing process by introducing ways to measure what is going on at each stage of development and creating expectations that then help explain what's gone wrong when those expectations are not met. Quality by Design (QbD) provides another driver for implementing PAT since it will benefit significantly from in-process data, allowing manufacturers to understand process limits, not just test the final product. This allows a company's biomanufacturing experts located in different parts of the world to confer about in-process data and collectively problem-solve.

How do all of these innovations affect the future location of biomanufacturing investments? Lower costs, shorter timelines, new facility footprints and importantly, greater ease and flexibility in the separation of manufacturing activities, ie, the ability to move the different stages – pilot, clinical and commercial – away from R&D and each other, all suggest that technology is greatly facilitating the geographic expansion of the industry. At the same time, this technology is also reducing the cost of biomanufacturing, making it more accessible to growing companies that may want to control their manufacturing processes. Other factors also affect the industry's global growth – the globalization of talent, a greater sensitivity to cost and new, growing markets, are all forces that propel the industry beyond its traditional location.

But despite the view that some day biomanufacturing will act more like a commodity, there is still substantial risk in this industry (as the Genzyme experience underscored), which is why there is a future for the industry in the U.S. These trends underscore the "sweet spot" for the country – early stage manufacturing (including first commercial launches) for more innovative, complex types of production and as well as smaller, niche volumes. If process development is "where the real innovation takes place," process development teams are firmly rooted near R&D teams and not following commercial manufacturing facilities farther a field. In addition, for smaller companies and smaller volumes, where the economics of manufacturing off shore don't add up and the complications that come with working with a CMO are daunting, locating manufacturing facilities closer to R&D might provide the best return on risk-reward analysis.

A growing market for biotech drugs combined with increased manufacturing capacity abroad is a positive development for the industry. There is an opportunity for the U.S. to continue to be a leading force for innovation while also maintaining and growing the 300,000 or so higher-skilled, high wage jobs (average salaries of over $90,000) that are generated by the industry. The following points will help the country achieve this:

1) While competing on tax rates is a slippery slope, there is room for the U.S. to become more competitive in this arena. Reducing corporate tax rates will make the U.S. less of an outlier compared to other developed countries and more competitive for mobile investments. At the same time, to encourage more investment in the country's biomanufacturing "sweet spot", tax incentives should focus on increasing innovation-related investments in such areas as capital equipment, education and training and R&D.
2) Product and process innovation are key components to keeping the country's competitive edge in the industry. More federal R&D funding, particularly in process innovation, would clearly help with some of the bottlenecks that continue to be a challenge (downstream processing for example). But an equally important area deserving of greater attention and innovation is the

interface with regulatory authorities. Given the culture of risk aversion and caution that is deeply rooted in the industry, the establishment of accepted, standardized common steps within the biomanufacturing process (the use of disposables, viral validation) that are recognized as valid if performed according to protocal, will significantly cut costs and speed up the licensing of products, and particularly help smaller companies in their race against time. Industry should work collaboratively with the FDA (and EMA) to improve efficiencies where possible along the regulatory pathway.

3) The creation of a pool of skilled talent through education and training are clearly critical for retaining and growing biomanufacturing in the country. A strong link between school curricula and industry at every stage of the education ladder – from community colleges, to B.A.s to graduate levels programs - is an essential component of a good feeder system.
4) Smaller countries have an easier time coordinating their activities so they can speak and act in one voice. While this is not an appropriate model for the U.S., there are ways in which the expertise and capacity around the country could be better understood and promoted. Like Ireland and Singapore, the U.S. biomanufacturing community should communicate to each other and the outside world the significant amount of expertise and research that exists in the country in this field.

These are just a few ideas that would help support this important niche industry in the country going forward. Biomanufacturing represents the kind of advanced manufacturing the country should excel in, particulalry as the market grows and expands globally.

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[i] This data was generously provided by BioProcess Technology Consultants. It covers only mammalian-based GMP clinical and commercial facilities. I also only include batch-fed and perfusion processes when referencing volume of capacity since it is difficult to accurately know the volume for other processes such as disposables or roller bottles. The data set uses 2002 as a base year, thus that year's totals represent all biomanufacturing investments up to that date. Data represents

biomanufacturing capacity based on when it is projected to go online. Thus, for example, investment projects announced in 2005 do not appear in the data until 2009, when the facility is expected to go online. Projects that are in the planning, construction or validation phase are also included. For announcements that a facility is going to be closed, the data accounts for that closing in the year of the announcement. The data account for all announcements made up to December, 2010.

[ii] This data does not speak to where specific drugs are manufactured, only that there is a facility in proximity to a company's R&D centers. As we know many

[iii] Hermans, et al. 2008

[iv] While other locations may have significant tax incentives for biomanufacturing, I have only included these four locations because they were the ones most cited in my research. I have not included new facilities in TALs for companies headquartered in a TAL or for companies that have expanded upon an existing facility built before 2000. While taxes may be a consideration in the latter case, economies of scale are another critical factor.

[v] The issue of international corporate tax rates as a new form of competition has become a hot topic. See Martin Feldstein, "Want to Boost the Economy? Lower Corporate Tax Rates," *Wall Street Journal*, February, 15, 2011; Andrew Liveris, *Make it in America: The Case for Re-Inventing the Economy*, Wiley and Sons, 2011; Rob Atkinson, *Effective Corporate Tax Reform in the Global Innovation Economy*, the Information and Technology Foundation, July 2009; and Chris Edwards and Daniel Mitchell, *Global Tax Revolution: The Rise of Tax Competition and the Battle to Defend It,* Cato Institute, 2008;

[vi] Clayton Christensen, *The Innovator's Dilemma: When New Technologies Cause Great Firms to Fail,* Harvard Business School Press, 1997.

[vii] Howard Levine, BioProcess Technology Consultants, presentation, May 19, 2010.