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## How Do You Solve a Problem Like Manufacturing?

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A frequent pharma headline these days carries the news that a large cap is restructuring its internal manufacturing operations to generate cost savings. Often, such articles quote executives describing the manufacturing function as "non-core," while reaffirming the centrality of R&D and marketing functions. Take AstraZeneca's dramatic announcement last fall that it would outsource all manufacturing within 10 years. Said David Smith AstraZeneca executive vice president of operations, "Manufacturing for AstraZeneca is not a core activity. AstraZeneca is about innovation and brand-building. ... There are lots of people and organizations that can manufacture better than we can."

The fact that the announcement was partly retracted by the public relations staff indicates the level of confusion and anxiety that an outsourcing decision generates. But with a little effort, even a distracted pharma exec can get up to speed on the mystery of manufacturing, and figure out a rationale to use in determining the best course of action.

### The Core of the Issue

It is not common for the head of manufacturing to have a seat on the top-level management committee at large pharmaceutical companies. Manufacturing issues are rarely discussed unless they have to be—most often as a result of such painful events as product stock-outs, large capital expenditures, or regulatory compliance issues. Periodically, strategic reviews identify manufacturing as a potential cost-savings opportunity because of the large asset and employment base. The all-too-easy executive decision is "Just outsource it."

### Wide-Ranging Results

Pharmaceutical products are very challenging to forecast, given the diversity of factors affecting demand. MedPharma Partners has analyzed forecast data from several firms, and developed the composite forecast accuracy vs. product lifecycle chart (below). Looking three years out, which is about the right lead-time for formulation capacity or modest expansions of API facilities, the forecast for pre-launch products ranges from 100 percent too high (which means the product has failed or is delayed in the clinic) to over 150 percent too low. The accuracy improves over the life cycle, but can still vary substantially—even for mature products.

In part, manufacturing is a victim of its own success. Products are generally available where and when they're needed, and there's little recognition of what it took to make that happen. Marketing and R&D are notoriously poor at forecasting product approvals and commercial success, so manufacturing has to be prepared for wide-ranging demand scenarios (See "Wide-Ranging Results"). As a result, substantial capital is invested to support drugs that may not be approved, or that may have underwhelming sales. On the flip side, demand often far exceeds forecasts, leaving manufacturing chiefs scrambling to keep up.

Immunex's Enbrel is a case in point. Launched in 1998, Enbrel (etanercept) sales quickly approached \$800 million annually before manufacturing capacity for the recombinant-DNA arthritis drug became a constraint in 2001. Revenue growth was severely limited as patients

#### Wide-Ranging Results

were added to a waiting list. Not until Amgen's purchase of Immunex and the rushed construction of a Rhode Island factory did supply meet demand.

Also on the list of nasty surprises is the issuance of an FDA Warning Letter, which always seems to appear out of the blue, threatening a company's ability to ship existing products or gain approval for new ones. In the aftermath of a consent decree, companies can spend billions on remediation simply to get back to their prior position, with new product launches suspended until sufficient progress is made in addressing deficiencies.

The overall result is a limited understanding of the value manufacturing brings to the company as a whole. From the executive suite, manufacturing looks like a black hole that absorbs significant resources. Although it generally

produces the required products, it does so at high cost and with periodic dramatic failures. The temptation to simply turn this over to an external organization and focus on the "core" areas of R&D and brand building is absolutely unsurprising.

But before jettisoning manufacturing, companies would be wise to understand its strategic contributions, including the ability to respond to rapid increases in demand, thereby avoiding costly stock-outs; opportunities for close partnerships with product development to ensure smooth, rapid product launches and create barriers to entry for generics firms; and the generation of substantial tax benefits due to operating in tax-advantaged locations. Strategic use of third parties can provide access to advanced technologies, improve flexibility, and reduce cost. While it is an easy decision, outsourcing is no easy answer.

### Responding to Demand Spikes

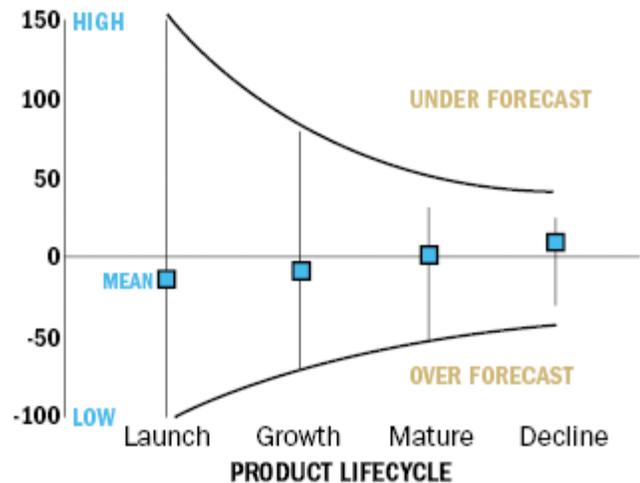
Predicting approval and commercial demand for a new product is particularly difficult. Unlike in other industries, pharma R&D efforts can look extremely promising for years only to uncover late-stage side effects or be hit with an FDA "approvable letter" requiring additional years-long studies. Vanlev (omapatrilat) is an unfortunate example of how negative safety signals can ruin the best laid plans. Bristol-Myers Squibb spent \$500 million on a chemical plant in Ireland before FDA's concerns about the cardio drug led to the program's cancellation in 2002.

### Forecast Accuracy for Drugs

Numbers are typically low for pharmaceuticals

FORECAST SALES 3 YEARS AHEAD VERSUS ACTUAL SALES

FORECAST 200  
VARIANCE (%)



Forecast Accuracy for Drugs

On the other hand, a product can become an unexpected success. Lipitor (atorvastatin) is the ultimate example of a drug selling beyond anyone's wildest expectations. Launched in 1997 as a "me too" drug, the fifth entrant into the statin category, first year sales of Lipitor were expected to be less than \$100 million. So Warner-Lambert's manufacturing executives were taken completely off-guard when what they thought would be a three-month supply vanished within days. They rushed to purchase a plant in Ireland to keep up with demand as sales zoomed to nearly \$1 billion in the first year and over \$2 billion in 1998. Sales reached a high of nearly \$13 billion in 2006—30 percent more than analysts had predicted two years after launch.

Compounding the problem of inaccurate forecasting is the significant lead time required to add new capacity. It can take anywhere from two years (for a formulation facility) to five years (for a biologics manufacturing shop) to come online. Starting production of a drug in an existing facility also takes time—a year or more to make saleable product, including the time for qualification and stability batches. Maintaining excess capacity is one way to ensure against escalating demand.

Naturally, third party outsourcers are loath to maintain spare capacity without significant up-front payments. Even for specialized capacity, it is often more economical to have a third party custom-build capacity rather than building internally.

### Partnering With R&D

One advantage of internal manufacturing is the ability to work closely with R&D on product and technology development. There is an opportunity to develop common technology platforms so that new products can fit seamlessly into existing capabilities. In that way, one product failure does not render a manufacturing asset unusable.

GlaxoSmithKline has adopted this approach at its Cork, Ireland, shop with an R&D pilot facility and a manufacturing facility on the same site. Similar technologies are used at both facilities, supporting rapid scale-up and launch. Technical staffs are rotated frequently between R&D and manufacturing, enabling rapid transfer of know-how. Another example is Merck's construction of a development-and-launch platform for product formulation at its Ballydine, Ireland, facility. During the development stage, formulation scientists use a standard technology, such as roller compaction, which allows smooth transfer to manufacturing.

Achieving these benefits with third party manufacturers is difficult. Contract manufacturers work with many customers, making it difficult to synchronize technology with any one. In addition, they may not be at or even near the cutting-edge of technology. For example, few contract manufacturers have invested in Process Analytical Technology (PAT), which can cause delays and additional costs in product transfer.

### Forestalling the Tax Man

## The Tax Man Cometh

Subpart F of the US Tax Code (§§951–964) requires that US-based companies pay income tax on all income produced by overseas subsidiaries, known as controlled foreign corporations, whether or not the income is actually given to the parent company. However, companies are not required to pay US tax on the income earned by manufacturing activities under Subpart F until the earnings are repatriated. In practice, companies almost never repatriate earnings, making the tax savings quasi-permanent. Manufacturers in tax-advantaged locations can realize tax rates of 2 percent to 12 percent vs. the US rate of 38 percent (average state and federal combined). Ten-year tax holidays are also available in some locations to support new facility construction. Occasionally, temporary repatriation windows are opened, the most recent being the 2004 American Jobs Creation Act, which allowed companies a one-year window to repatriate overseas earnings at a 5.25 percent tax rate, locking in tax savings accrued over many years.

For US-based pharmaceutical companies, one of the largest factors keeping manufacturing in-house is the ability to realize significant tax savings by locating production in tax-advantaged locations. Firms aren't building plants in Puerto Rico, Ireland, Switzerland, or Singapore because of the weather. The main motivation to choose these comparatively high-cost locations is reduction in taxes—from the US federal statutory 35 percent rate to 2 to 10 percent in other countries. Companies like Pfizer have sliced their tax bill in half thanks to Puerto Rican and Irish operations. (See "The Tax Man Cometh").

Some firms are looking to reap similar benefits by setting up contractual arrangements with third party manufacturers instead of owning bricks and mortar. In general, however, these deals are more complex and less time-tested than direct ownership. Smaller, virtual pharmas may be better positioned to leverage these structures given that the full benefits available from ownership are less possible.

### Benefiting From Third Parties

#### The Tax Man Cometh

internal manufacturing operations, strategic use of third party manufacturers and packagers also can be beneficial. One key benefit is access to technologies that a company does not currently possess, such as hard-gel liquid capsules, or challenging product requirements such as highly potent drugs needing high-containment operations. Instead of building the internal capability to handle such products, pharmas can rely on a contract manufacturer. Then, should the product fail, a company will have avoided the significant expense of building and validating a specialized capability only to have it sit idle.

Although there are many benefits of having

Flexibility to meet changing volume requirements is another reason companies outsource. Contract manufacturers make investments for more than one client, which spreads risk. These arrangements help companies handle surges in capacity requirements without tying up assets during slower periods. In some instances, a pharmaceutical company will turn a plant over completely to a supplier, eliminating the need to absorb the overhead of idle facilities and staff. Should the plant close, the supplier, rather than the pharma, carries the onus of layoffs or a shutdown. This is especially useful in European countries that have tied pricing and approvals to in-country employment.

# The Whole Cost

Preference for internal manufacturing often relates to the perceived economics of insourcing vs. outsourcing. A company that has already invested significant funds in internal capacities, such as bottling lines or granulation suites, will be strongly motivated to leverage these investments before turning to outside suppliers. (A significant issue is whether a complete business case was prepared before significant capital funds were invested.)

Once capacity is in place, the economic comparison often used is the incremental cost of running the equipment (direct labor and incremental operating cost) vs. a vendor quotation, which must cover the full economic cost of the

vendor's capital and operating outlay. This comparison often shows that continuing with in-house manufacturing is less expensive. The key to reaching the best long term decision is for companies to ensure that a complete economic analysis is performed prior to capital investments.

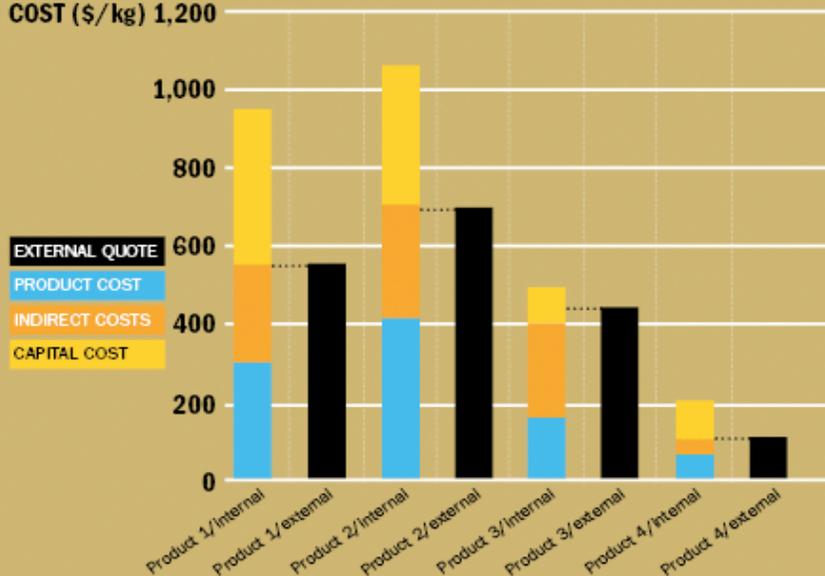
As shown in the chart, although a full-cost approach will often favor the use of outsourcing, the incremental approach often favors insourcing. An important factor is how the cost of capital is considered.

There are two major approaches to developing an analysis of outsourcing versus insourcing: incremental cost vs. full cost. The incremental cost approach will typically consider the additional direct labor and materials, indirect labor, and capital cost needed to support a given volume.

## FULL ECONOMICS OF OUTSOURCING

Client economics often ignore cost of capital or other nondirect costs

COMPARISON OF INTERNAL AND EXTERNAL COSTS—DISGUISED BULK DRUG EXAMPLE  
COST (\$/kg) 1,200



All economic costs of running the plant and existing capital are not factored into the analysis. Full cost, on the other hand, aims to determine the full economic cost of making a given volume of product. Each product must support its share of the plant's overhead costs and capital employed.

Incremental indirect costs tend to be underestimated. A typical assumption is that the addition of new products or increased product volumes will have a minimal impact on a plant's indirect staffing. Perhaps the cost of a few QA/QC people or a maintenance technician will be added to the analysis. Following the addition of the equipment and ramped-up volume, a plant or functional group may then request additional head count at the next budget cycle to support the higher workload. This separation of the budgeting discussion from the investment discussion results in a less than optimal decision being made.

Cost reductions are another reason to consider outsourcing. The recent drought of new drugs means that firms must look closely at cost and asset utilization. As in other industries, the value of vertical integration is increasingly in question, as best-of-breed companies show they can outmaneuver their larger, more fully integrated competitors. Therefore, the cost of maintaining all of one's own production and packaging facilities compared to outsourcing some operations to focused companies may not be supportable to the investment community. The challenge is for companies to compare the true cost of making their own products on an apples-to-apples basis with third party alternatives, and strike the right balance between internal and third party manufacturing. (See "The Whole Cost")

## The Question of Balance

A framework for performing this analysis includes the dimensions of product life cycle, product technologies, tax situation, availability of third party capabilities, and the existing internal manufacturing footprint. Applying this framework will enable a firm to identify the best approach, whether fully insourced, fully outsourced, or somewhere in between.

**Across the Lifecycle** Demand requirements are least certain early in the product lifecycle. The choice is whether to build internal capacity to handle optimistic forecast levels, or to utilize a combination of internal and external capacity. This is where utilizing platform technologies pays off. The law of large numbers will result in more predictable levels of demand across a wide range of products. In addition, contract manufacturers can provide a backup option for products that utilize readily available technologies.

**Product Technology** Products that utilize unique technologies pose difficult choices. External capacity is unlikely to be available, or may require up-front capital. In these situations, manufacturing leadership needs to engage even more extensively to ensure that marketing forecasts are realistic in light of competitive offerings. Nothing illustrates that better than Pfizer's recent experience with Exubera. The company wrote off \$2.8 billion after withdrawing the inhalable insulin, which achieved peak sales of only \$12 million. A portion of this write-off was for the unique injection-molding capacity Pfizer had built for Exubera at third party injection molders. A real-options analysis can model the potential outcomes more broadly and identify ways to address optimistic peak forecasts while hedging against the possibility of a bad outcome.

**Taxing Decisions** Each company should develop a tax strategy in concert with its supply chain strategy. Some Big Pharmas focus on realizing tax savings at the API (active pharmaceutical ingredient) stage, and construct bulk drug plants in a tax-advantaged location. Others choose to realize tax savings in their formulation facilities. The increasing percentage of in-licensed products is prompting companies to rethink their strategies because in-licensed products may not provide Big Pharma with API manufacturing rights, rather requiring them to purchase API from the compound innovator.

Emerging firms must pay particular attention to their tax strategy when they launch products. Many such firms have a tax-loss carry-forward from years of minimal revenue and high development costs. A common mistake is to ignore the supply chain tax strategy until a product is already established. At that point the tax-savings opportunity will be diminished.

**Growing Third Party Capabilities** Over the past ten years, the capabilities of third party contract manufacturing and packaging suppliers has grown significantly. Recognizing this, some leading drugmakers have announced their intention to source "non-core" technologies externally when possible.

One issue internal manufacturing groups have cited as a reason not to outsource is the higher quality standards of internal manufacturing operations. The record does not support this bias. Third party facilities are inspected much more frequently than internal facilities, by both customers and regulatory agencies. While an internal facility that receives an FDA 483 Warning Letter, or even a consent decree, tends to be rewarded with new capital and resources to address the issues, one wrong move can put a contract manufacturer out of business.

The one area some contract manufacturers have been struggling with is maintaining healthy profits. The irony is that they are often accused by pharma executives of charging high prices and achieving excessive profits. This perception stems from the misunderstanding of cost—and the hidden subsidies that internal manufacturing receives in terms of capital access and transfer costs.

The emergence of Indian, and more recently Chinese, suppliers is also having a profound effect on the outsourcing market. Major pharmas are sourcing significant portions of their key intermediates and APIs from Asian suppliers. This trend is expected to accelerate, with India now boasting over 75 FDA-approved plants and Indian sources representing over one-third of all new-drug master-file submissions. However, in the near term, Asian suppliers are less likely to focus on formulation and packaging for branded products. As a global head of contract manufacturing for a European pharma put it, "Formulation and packaging represent less than half the cost of a tablet, and with competitive pricing available in Europe, it's not worth the additional savings to deal with the complexity and cost of managing an Indian supplier."

Baxter's recent recall of contaminated heparin, made at a Changzhou plant, is giving large-cap management pause to review how it monitors its supply chain, especially in China.

A final consideration in evaluating contract manufacturers is assessing financial stability. It's no secret that some of the larger contract service providers like Patheon and Catalent (formerly Cardinal) have had their share of financial upsets. The future for Catalent is particularly cloudy, as Blackstone, its new private equity owner, looks to squeeze

profits from a business whose growth has been stuck in the low single digits.

**The Existing Footprint** Pharma companies have plowed billions into constructing their own network of plants. The key is to identify a handful of core competencies—specific physical assets, such as sterile lyophilized filling, or a business process, such as technical transfer from R&D to manufacturing—that benefit from having an internal capability. Genentech, for example, sees one of its core competencies as protein manufacturing, and consistently invests hundreds of millions in its facilities. Meanwhile, the firm is comfortable going outside its four walls for services such as vial filling and packaging, and has developed a core competency in the effective management of its contract management supply base.

One pitfall to avoid is using an internal capability because no "incremental" staff or equipment is needed. This fallacy leads to a creeping investment where an a priori decision informed by full costing would have led to a better long term decision.

As with so many other pharma problems, there's no one-size-fits-all solution to the problem of manufacturing. Each company needs to find the right balance of internal and external functions through a detailed and comprehensive analysis. It also requires manufacturing executives to engage in a more transparent discussion about how keeping manufacturing in-house generates value for shareholders and why that value cannot be better captured externally. In the end, most companies are likely to find that jumping off the manufacturing ship entirely in concert with the trend of day is not the best, or even the cheapest, innovation.

#### **About MedPharma Partners:**

MedPharma Partners was formed in 2003 by senior professionals from leading strategy and operations consulting firms, including BCG, Deloitte, L.E.K. and A.T. Kearney. Our commitment to fielding only highly experienced teams has delivered powerful results to companies of all sizes. We have a passion for Health Care Services and Technology, Pharmaceuticals, Biotechnology, and Medical Devices. Our teams have successfully assisted more than twenty client organizations and completed over eighty engagements. We stand ready to tackle challenging problems ranging from strategy to operations. For more information, please contact Patrick Kager ( [pkager@mppllc.com](mailto:pkager@mppllc.com)) or David Williams ( [dwilliams@mppllc.com](mailto:dwilliams@mppllc.com)).



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