ESTIMATING THE COST OF PHARMACEUTICALS
MANAGING COST AND EXPECTATIONS

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Recently the headlines have been addressing the high cost of pharmaceuticals. In many cases the consumer has a legitimate concern about the price. Contrary to what it may seem, greed does not drive most of the cost, it is the unknown. Science itself provides a big piece of this, but the regulatory pathway to licensure is almost as big a factor, and in some cases bigger. Estimating new products requires a solid methodology and forward-thinking approaches to adequately bound the cost, as well as expectations.

There are two segments to the pharmaceutical market place, commercial and federal. Each have a unique approach to getting a product to market, but both markets have the same life cycle phases. It is how each market segment attacks these phases that things really start to diverge. Each have the familiar Research Development Test & Evaluation (RDT&E), to include a Science and Technology (S&T) phase, a Production or Procurement phase, and then the Sustainment phase.

Motives are key to how each approach the solutions. The commercial segment wants to be first in the market place to provide a solution to a health-related issue and to provide a solid return on their investment that satisfies investors or stock holders. The federal segment wants to solve a health-related issue that is a concern for either a public health emergency (e.g., flu) or a military medical treatment or counter measure (vaccines for protection).

Life Cycle

The life cycle phases are the same for pharmaceuticals as for any other product. They go through discovery to fielding and sustainment. Therefore, estimating costs and benefits follow the same approach. These are discussed a little later. The following paragraphs highlight the differences between the two segments.

RDT&E

Discovery (S&T)

In the commercial segment, the company will typically meet weekly to review potential products in their S&T portfolio. It is at this time they evaluate progress and potential success and will cut potential products that are not moving forward quickly. The federal segment may fund S&T for years to advance one, maybe a few

solutions that can solve the problem. Both segments' budgets can be quite large at this stage. One approach has many solutions at one time, but decision are made early to remove the less promising very quickly. The other will nurture a few solutions that may work as identified in the research plan or get modified as information is learned about the potential solution.

At this early phase science can cause much uncertainty. The S&T phase occurs at the bench level and invitro (cell culture dish) stage before moving into advance development. Late in the S&T phase is where much of the research design will start to show if there is promise in further development. Please note that is "…start to show if there is promise." From the S&T phase the product moves toward advance development

Advance Development

As the candidate product moves further down the licensure pathway, it moves into non-clinical studies for initial safety data and information, as well as for the preparation and filing the Investigational New Drug (IND) application. The IND is necessary for the start of clinical studies. If these non-clinical studies progress without any major problems, and there usually are some problems, then the developer looks as completing the clinical protocol, which is a major part of the development process.

The clinical protocol describes how the clinical (in humans) trial will be performed and identify the desired outcomes. It provides very detailed steps about the trial and is reviewed by the Institutional Review Boards (IRB) of the organizations that will carry out the trial.

Another key step in this phase of the process is completing the engineering runs that demonstrate that the product can be produced at full scale production (equivalent to low rate initial production (LRIP)). Please note that this step is critical in a biologic, because it determines the volume of output, but more on this later.

Operational Development

Clinical trials occur in this phase of the RDT&E and lead to filing license application with the FDA. There is much scrutiny of the trials process and data outcomes. There are three clinical trial phases and prior to proceeding on to the next phase, the outcomes must be vetted by all parties involved and finally approval by the FDA to move forward. The ultimate goal is approval of the license and to move into production and to the market place.

Production

This phase only starts after licensure (or permission to operate under IND status) and is like almost every other production phase. The commercial segment will typically enjoy market exclusivity for about 7 years and then begin planning for a long-term spot in the market for the stated and licensed indication or need.

With regard to the federal segment, there can be a similar scenario especially for a public health need, such as the flu vaccine when a large and steady demand exists. If the need is a more focused federal objective, such as a military medical counter measure against a specific threat, such as anthrax for example, then the production plan would be to satisfy the initial immunization objective (e.g., all active duty members). After this objective is achieved, the plan is typically to sustain a stockpile for attrition and accessions, and potential surge requirements.

Sustainment

This is considered Phase 4 and requires the company in both market places to track the product and document any issues that may arise as its long-term use gets underway. One aspect of sustainment requires that the product be produced or manufactured at least once per year to maintain currency in the process (approved SOPs) and the license of the product. For commercial products this typically is not an issue. The licensed product will be manufactured to meet annual sales goals and therefore in a constant manufacturing mode.

With respect to the Federal market, a unique product will be manufactured to meet the initial objective, and then will have to be produced annually to maintain a stated stockpile, but also to maintain the product license and maybe even to maintain the facility license.

Estimating

The estimating process for a pharmaceutical is relatively straightforward and the same for both commercial and federal. The R&D phase has a process that can be scoped for the desired outcome. However, science can throw things off course at any time inth R&D phase, especially in the S&T segment. Even in the S&T it is straightforward to design and plan your research. Working with some researchers and scientists, it has been said that you can't plan science, which implies that you cannot estimate it. This is not true, you can't plan the outcomes of science; however, you can plan the steps of scientific research and this is how the estimate is completed. It is the success of these steps that will impact the final cost, and therefore it is important for the estimator to work with the researcher to adequately bound the risk and uncertainty. These steps in the R&D process can be estimated with a solid estimating approach.

There are required activities that the would-be manufacturer needs to complete to have the data for the IND application and clinical trials. There are certain tasks that must be done to achieve the desired outcomes to start the clinical trials. The clinical trials themselves have well defined activities and tasks that must be followed. Depending on the product and condition to be treated, there are variations, but basically have the same steps and requirements. This phase in the life cycle process can best be estimated by a grass roots buildup of the activities. The process is will defined, the number of animal studies, toxicology tests, and required number of subjects for the clinical trials. All of these can be priced from catalogs, vendors, and experience with other pre-clinical and clinical trials.

Production is relatively easy to estimate because the manufacturing process used to support the clinical trials and the license application is what will be used in production. The process cannot be changed without a redoing a lot of the RDT&E work that was completed to support the license application. Making changes after licensure is extremely expensive and time consuming. More on this in the discussion on managing expectations.

Manufacturing a biologic pharmaceutical product is a true art and science. The art is trying to hypothesize the approach that will lead to the desired outcome. The science is in two parts, the R&D that is investigated and leads to a solution, and then process that produces the solution or end item. The manufacturer must have a good idea of what the production volume will need to be as the process is essentially licensed as well. The production process coming out of R&D produces all of the information for potency, purity, and effectiveness that is submitted as part of the license application. The end product will have the license but the process, in effect is also licensed, as well as the facility. The process needs to be planned and licensed at the lot size and not total volume. The lot production process must be repeatable with the same outcomes every time. This is critical in projecting surge or increased production volumes.

Risk vs Uncertainty

As most are aware, risk and uncertainty, are two very different factors especially when estimating a system or product. This is very true with pharmaceuticals, more so with biologics. With drugs, once a solution is developed, it is essentially a chemical process. You mix the various components, put them through a tablet press and you have your product. Of course, this is an oversimplification of manufacturing a drug, but for the most part this is what most consumers are familiar with. A biologic, on the other hand, can be made with fermenter or cell culture equipment/processes, as well as eggs, i.e., your flu shot. Making it more complex.

When using a biologic process, and for example using a fermenter (and all you home brewers will be able to relate), there are a lot of variables that come into play. The volume, the heat generated in the manufacturing process, and the cleaning of apparatus must be understood to be successful.

Risk

In the S&T phase the major risk is finding a solution that has the potential to work. This can take a long time. In the federal space there is patience as the market is much smaller and the medical condition or threat is narrow. For example, finding a medical counter measure, or vaccine, for ricin is very specific. In the commercial segment the market is larger with many targets to solve, and typically can benefit a large number of individuals. This is where the payoff can be very big. Therefore, the commercial segment is not willing to nurture solutions for extended periods of time as you typically might find in the federal space. The commercial segment will frequently conduct reviews to cull or push products to get a solution into the market. They are trying to minimize the risk that a solution will not be effective or take more R&D funds than needed to get to market. They want an effective solution that gets to market quickly and provides a faster payback.

Even products that are pushed further along the R&D phase still have various risks to address. These include:

- Safety
- Effectiveness
- Producibility – can they be scaled to full rate production from bench top

Once enough data is gathered and information is learned, the product moves forward into clinical trials, a major portion of the R&D phase. Here the product is really observed for its safety in humans. In addition, its effectiveness as a treatment can be observed and measured against desired outcomes. A key aspect of its effectiveness is, are enough people helped (unless it is an orphan drug – 2,000 or less patients) and are any side effects minimal for the treatment to be worthwhile or better than any current treatment solutions in the market place. The FDA can be reluctant to license a product for market if there are really no improvement to current treatments.

These are risks that are known and can be anticipated to some extent. Some can be addressed, but as most are aware, addressing the risk typically comes with added costs. Costs can be minimized by taking the time to develop a strategy that tries to mitigate the risk, for example adding a few more preclinical studies and properly sizing the clinical trial with enough individuals to collect the data and information needed to gain licensure.

Regarding production, as mentioned earlier, the biologic process must be scaled to the anticipated market demand. The risk here can be building a manufacturing facility that is too small for demand, or too large and create excess capacity. When the Joint Vaccine Acquisition Program (JVAP) was being initiated, senior leaders assumed that large Pharma (major manufactures) would be able to provide much of the vaccines to counter the biologic agent threats facing our armed forces. After visiting most of the large manufactures, it was revealing to learn that for the most part there was no excess capacity to provide these countermeasures. Big Pharma "right sized" their production facilities to meet market demand.

The manufacturing process for vaccines is fine tuned to provide a product that meets demand, and is well characterized with respect to purity, effectiveness, and other elements that define it. The risk here is that if the market is undersized then there is market value that is not being tapped. Then there is the issue of increasing production volume after licensure which can have a huge finical impact that requires another large investment in R&D. This is one aspect where managing expectations is critical, especially in the federal sector. For example, when the Department of Defense was buying anthrax vaccine from the State of Michigan (the manufacture at that time), senior leaders asked about increasing the fermenter size, from 120 liters, to 150 or even 200 liters should there be a battlefield need. They were shocked to find out that one of Michigan's other customers wanted to double output of its biologic product, and to do so they built an identical manufacturing facility to mirror what was already there. Their rationale was to minimize risk, and building another facility did that. They knew what the product characteristics were at the 120 liter volume and other than construction costs, the bridging studies to show the two product lines were identical, would cost less than trying to prove the vaccine in the large tanks were just as safe and effective.

Uncertainty

This is where the unknown impacts can really come into play and significantly impact cost. The following are a few examples that have impacted programs:

- Raw material sources withdrawing from the market
- FDA decisions
    - Changing from a device to a biologic
    - Increasing the size of clinical trials
    - Additional non-clinical trials
    - Proving new sources of raw materials are safe
- Demand – unexpected epidemic, e.g., Ebola outbreak
- Treatment target, e.g., flu strain different than anticipated

These examples can have a significant impact on schedule and cost. One product that was moving through the FDA licensure pathway as a device had its premarket

notification, or 510(k), submitted to FDA for licensure. Although the product was based on the process currently used under a humanitarian and emergency use investigational new drug (IND) status, the FDA decided that the new product for large scale use/manufacture really was a biologic. This meant a whole new approach to navigating the license pathway was required, which added three more years to the R&D schedule, along with associated costs.

The same product used bovine (cow) material to manufacture a mesh that would be later absorbed by the body. Use of bovine material is observed with great scrutiny by the FDA due to concerns about bovine spongiform encephalopathy (BSE), or mad cow disease. The product developer/manufacture had a raw material source from a closed herd that was well documented that no BSE was ever present in this herd. The supplier was also heavily involved in the food supply market, and one day decided to exit the medical supply chain market. This meant that the manufacture had to find a new source not involved with bovine material, as the previous supplier had the only FDA accepted herd.

The product manufacture decided to proceed with shark fin cartilage. This material has been successfully used in other pharmaceutical manufacturing, and therefore expected to be accepted by the FDA as the new matrix source material. However, the FDA requested information on the shark sources, and even husbandry. Not only did the product manufacture have to do the R&D to make sure the shark material would work as well as the bovine, they also had to answer the additional FDA requests. This added at least another 18 months to the R&D schedule including additional non-clinical, animal studies. The increase from these two uncertainties added at least $25M to the R&D budget and four more years.

Another potential uncertainty is planning the clinical trial size. Using previous federal pharmaceutical program experience, JVAP planned clinical trials for Phase III at about 1,500 individuals. The size of the trials is determined through statistical analysis to “right size” the trial and costs to adequately show that product is safe and effective. When the protocol was submitted to the FDA, they came back and said the trail size needed to be 3,000 individuals, doubling the costs.

Managing Expectations

Expectations can be high at the outset of planning for a new pharmaceutical product.

In the commercial segment, there are expectations of good, solid returns on investment in a relatively short period of time with an R&D phase that progress quickly and effectively. Managers work to keep R&D costs minimal while addressing product outcomes and potential risk mitigation strategies.

In the federal market, the attention to product effectiveness is as sharp in the commercial space, and there is just as much desire to keep R&D costs down. One key area to address in this space, is managing expectations with regard to production volume and output. With respect to defense medical counter measures, leaders tend to think they can procure and stockpile what is needed and once this quantity is achieved there will be minimal procurements when stockpiles need to be replenished. However, this is typically not the case. The expectations that need to be managed at this point are:

- A shelf life that may need to be restocked earlier than desired
  - Over time shelf life can be studied to determine a more realistic time span
- The will be a need for annual production runs
  - To maintain the product and facility license there will be a requirement for an annual buy (either procurement or O&S dollars)
- Surge demands may not be possible given the licensed production volume
  - Surge or increased demand may require building an identical facility to achieve the new demand at the lowest cost, as mentioned previously
- Unit pricing maybe much higher than planned
  - Although the initial cost to vaccinate a soldier against anthrax was about $60 for a three dose regiment when the Joint Program Office (JPO) for Biological Defense (BD) was created, there was much push back on the price. The interesting thing about this was that the total price was still less than the typical cost to outfit a soldier with a pair of boots.

Expectations can be managed through the development of a sound cost estimate. The experienced estimator can work with the researchers, scientists, and medical experts to build a strong cost element structure that captures nearly all of the activities that need to be completed. These discussions can help define the details for developing the estimate, as well as raise questions to adequately define the elements, such as number of individuals for the clinical trials. It will also help foster discussions about how much of the product is needed, how long a shelf life is desired, and discuss any surge or increase demand scenarios to appropriately define the quantity to be procured.

Summary

Estimating the cost of a pharmaceutical product is not as difficult as it may seem. Working with the medical and scientific experts the estimator can create a sound and defensible estimate that can adequately capture the cost to develop, produce, and field an effective product. Unlike a major weapon system, there is usually little published data regarding the cost to develop and license a pharmaceutical product.

Therefore, the estimator must be able to have a good understanding of the pharmaceutical process to create as complete as possible estimate structure, and the ability to communicate and work with the experts to capture a true picture of the product being estimated. There is a lot of back and forth that benefit both the estimator and expert. Being able to develop a good rapport will help ensure that the process is well defined, the risks are identified, and mitigation strategies proposed, and the uncertainties are discussed. Obviously the final estimate is just reflective of estimator and expert experience, but discussing those experiences will help bound the risk dollars, as well as bound the expectations of all the stakeholders.