COST: A COMPLICATED FACTOR IN THE DRUG MANUFACTURING PROCESS

Developing and marketing pharmaceutical products is expensive, but those expenditures exist for a very good reason.

BY JERRY ST. PETER

Risk versus reward calculations are a critical component of the drug manufacturing and distribution process, but they are rarely, if ever, straightforward. Although the safety and efficacy of a compound are the primary factors that must be considered, other elements such as medical necessity, potential to address an unmet need, and value may enter the equation. It can be easily appreciated that safety and efficacy are often definable endpoints in clinical trials, whereas the influence of the other aforementioned factors on the general risk-reward conversation is generally less tangible in nature.

Underscoring this complexity is the fact that drug manufacturers have a complicated yet important obligation to the public. On the one hand, pharmaceutical providers are beholden to their ownership (shareholders in the case of publicly traded entities), so profit is a motivating factor in all research and development activities. Yet, as far as I am concerned, the prime directive of the pharmaceutical industry is to provide products to the market that will safely and effectively treat medical conditions and improve health. In a variety of ways, a pharmaceutical manufacturer's products dictate its viability and ability to remain solvent but only if the interest of the patient is ultimately held to be more important than profit.

COST CONSIDERATIONS

In today's health care environment, cost has crept into the risk-reward calculus involving pharmaceutical products. At one end of the spectrum is the need to stabilize and reverse the rising costs of delivering health care. For patients, cost is sometimes a barrier to health care utilization. These realities help to explain recent reform efforts aimed at reducing health care expenditures while ensuring adequate access.

Nevertheless, cost realities for a functioning health care system are distinct from those affecting the individual. The cost of health care delivery is only partly dictated by drug prices. According to a 2012 report by the Kaiser Family Foundation, prescription drugs accounted for just 10% of overall health care expenditures in 2010.[1] Subsequent reform efforts likely adjusted that percentage, but suffice it to say that other cost factors still probably constitute the lion's share of spending. These issues will not be solved by making cheaper products or by making available products cheaper. It is logical fallacy, then, to assume that efforts aimed at cost correction for the individual (ie, a cheaper drug price) will necessarily yield bellwether change for the system.

It may be the case that systemic cost and cost affecting individual consumers are needlessly conflated. In some instances, this may have dire unintended consequences, especially in the context of regulated drug products. There has been a recent suggestion that regulatory bodies ought to consider cost in their decision-making process or, at a minimum, that certain steps in the regulatory process might be skipped to lower the cost of development.[2] Such a viewpoint, however, may be the first step on a dangerously slippery slope, one that results in fewer consumer protections and reduced confidence in the safety and efficacy of pharmaceutical products.

Under the current regulatory model, drug products are evaluated by four standards: bioavailability, efficacy, sterility, and stability. Each element must be rigorously tested and proven in well-conceived and precisely executed clinical trials, starting in the laboratory before moving to appropriate animal models and, eventually, to human subjects.

The safety and efficacy data that result from this process serve as a reasonable starting point in the risk-benefit conversation. Introducing cost considerations into this already convoluted dynamic would seem to do more harm than good and might be a disservice to patients. After all, if a drug product is proven to be safe and effective, it should really be up to individual patients (and in a more general sense the

AT A GLANCE

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- If a drug product is proven to be safe and effective, it should really be up to individual patients (and in a more general sense the market) to determine if the product's cost (a variable that determines its price) is supportable.
- There are at least two rationales for the availability of compounded pharmaceuticals. On the one hand, compounding pharmacies play a crucial role in making products to address urgent medical need (medicinal necessity) where no such drug currently exists. On the other hand is the desire to use compounding pharmacies to make products for the sole purpose of lowering their cost, but this practice appears to introduce a number of uncertainties, with potentially unfortunate consequences.

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One case in point is the drug market for the treatment of hepatitis C. Some agents cost the system tens of thousands of dollars per administration in drug price,[3] yet they are vital to stopping or slowing liver cirrhosis and to yielding a cure for a condition that is otherwise fatal in a great many cases.

IMPLICATIONS FOR COMPOUNDING

A recent development in the pharmaceutical market is the expanding role of compounding pharmacies. To some, compounded products represent an alternative to the traditional manufacturing process. The assumption is that, because compounding pharmacies are simply taking approved active pharmaceutical ingredients (APIs) and reconstituting them, the final products should be equally safe and effective as each of their constituents.

It may be worth considering whether this assumption is true and whether encouraging wide-scale production outside the vetted pharmaceutical system is in patients' best interest. There are at least two rationales for the availability of compounded pharmaceuticals. On the one hand, compounding pharmacies play a crucial role in making products to address urgent medical need (medicinal necessity) where no such drug currently exists; one example is the compounding of fortified vancomycin to treat methicillin-resistant *Staphylococcus aureus*. In those kinds of ophthalmic situations, the risks introduced may be offset by the reward of treating vision-threatening conditions. In this scenario, a compounding pharmacy can be more responsive to emergency situations than a traditional pharmaceutical manufacturer.

On the other side of the spectrum is the desire to use compounding pharmacies to make products for the sole purpose of lowering their cost. This practice appears to introduce a number of uncertainties, however, with potentially unfortunate consequences. The drug manufacturing process is extremely deliberate, with each component of a compound produced in precise quantities in proportion to other ingredients. Taking APIs and reconstituting them into a new singular compound or mixing multiple APIs together to form a compounded "drug cocktail" has the potential to disrupt the delicate balance, with an unknown effect on the bioavailability, efficacy, sterility, and stability of each ingredient and the final product.

There is an additional complexity to note here: pharmaceutical companies expose themselves to tremendous risk with each development candidate. A drug's price usually must account for hidden expenditures by the sponsor such as the costs of other associated failed clinical trials and development programs. If the market is going to encourage risk taking, it must also provide a mechanism for companies to recoup such costs. Thus, while I appreciate that there may be a place for alternative-development business models to make products that are patient friendly, I am also cautious about their application. I question whether patients' interests are served by placing roadblocks on the path to innovation.

CONCLUSION

Overall, efforts to increase patients' access to needed pharmaceutical products are laudable, but I would prefer to see cost removed from the overall conversation whenever possible. The interests of patients appear to be best served by having products subject to the rigorous FDA process. The regulatory body has already demonstrated a willingness to work with industry to smooth out the procedural steps. In the future, channels of communication that have been opened will likely help to alleviate financial burdens borne by manufacturers. Cutting corners and abrogating the process that ensures the safety of drug products, however, seems to introduce more problems than it solves. ■

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2. Lorezetti L. Is it time for the FDA to consider cost when it comes to new drugs? *Fortune*. http://for.tn/1xis3YF. February 4, 2015. Accessed April 25, 2017.
3. Ramsey L. The 10 most expensive drugs in the US. *Business Insider*. http://read.bi/2oSAtwl. Published September 30, 2016. Accessed April 11, 2017.

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