Health Affairs Blog

Orphan Diseases Or Population Health? Policy Choices Drive Venture Capital Investments

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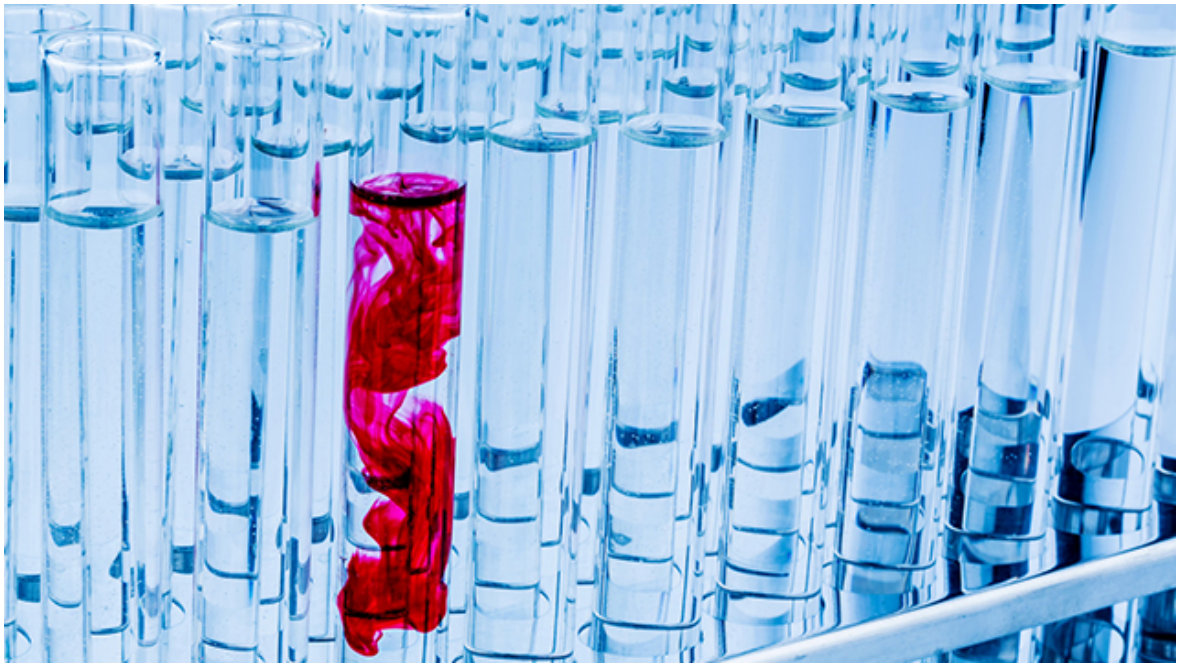

The US exhibits a remarkable pipeline of biopharmaceutical innovation, with 170 new drugs and biologics launched into the market between 2011 and 2015 and another 22 drugs approved in 2016. A striking feature of the pharmaceutical pipeline is the large percentage launched for the treatment of small “orphan” indications, defined by the Food and Drug Administration (FDA) as including fewer than, often many fewer than, 200,000 patients in the United States. Almost half (74) of the products approved by the FDA between 2011 and 2015 were for orphan indications, twice the number (36) approved during the same period by the European Medicines Agency and a remarkable increase over the total of 35 orphan products approved by the FDA in all the years prior to the Orphan Drug Act of 1983. In 2016, 41 percent of the novel drug approvals were for rare diseases (nine of the 22 approvals).

The surge in orphan drugs is a result of public policies that influence development costs and market exclusivity, which in turn influence the prices that can be charged. Early-stage investors in the life sciences pay close attention to policy signals in deciding how to allocate their capital. The policy decisions made yesterday influence investment decisions made today, and hence the direction of innovation tomorrow.

Bay City Capital is a venture capital partnership, founded in 1997, that has invested in over 100 life sciences firms worldwide and currently manages $1.3 billion in capital. In recent years it has focused increasingly on drugs rather than medical devices and diagnostics and, within pharmaceuticals, to those addressing narrow rather than broad patient populations — the firm now mostly looks for biotech startups targeting drugs in indications that can be developed all the way to FDA approval, such as orphan areas that enjoy favorable policy treatment with high revenue potential.

The benefits of venture capital investment in orphan drugs are very important for patients suffering from rare conditions. As investments shift away from treatments affecting large numbers of patients, however, the potential impact of innovation on public health may be reduced. Even modest improvements in therapies affecting cardiovascular disease, diabetes, or other large indications would offer major population health benefits. In the past, for example, some startups financed by Bay City developed cardiovascular treatments up through early clinical studies, but they were unable to secure a partner to finance the large clinical trials necessary for FDA approval.

This post looks at some of the policy and market considerations that encourage Bay City Capital and firms like it to focus their resources on orphan drugs.

Policy Initiatives That Reduce Development Cost

The FDA requires substantial evidence of effectiveness for a new drug approval, with the standard requirement including two adequate and well-controlled clinical trials. However, the FDA uses its judgment to determine the type and quantity of data needed to meet its standards. In reviewing orphan drugs the FDA routinely allows fewer than two controlled studies, smaller studies, and/or studies that use novel endpoints. Between 2009 and 2013, 60 percent of orphan drugs were approved based on a single trial, compared to only 28 percent for drugs addressing more common conditions.

The size of the orphan drug trials typically is much smaller than for non-orphan candidates, involving dozens or hundreds, rather than thousands, of patients. For example, Ravicti™, a drug for Urea Cycle Disorder developed by Bay City portfolio company Hyperion Therapeutics, received approval based on a pivotal efficacy trial that included 45 patients and long-term efficacy and safety studies that totaled 100 patients. Drug firms developing cancer treatments increasingly are launching them in small sub-indications demarcated by biomarkers or clinical criteria that improve the probability of showing a therapeutic benefit in a small number of patients.

The FDA has created expedited clinical development programs that benefit orphan drugs more than their non-orphan counterparts. Between 2008 and 2016, 86 percent of orphan drug candidates were approved through Accelerated Approval, Breakthrough Therapy, Priority Review, and Fast Track designations, compared to 35 percent for non-orphan drugs. Under the Accelerated Approval program, for instance, approvals can be based on surrogate endpoints that predict, rather than demonstrate, clinical benefit.

The Orphan Drug Act also offers research grants and tax credits that reduce further development costs. The impacts of these incentives are relatively minor, however, in comparison to the favorable treatment during drug testing and market approval and the resulting ability to charge very high prices.

Initiatives That Increase Profitability

Manufacturers price orphan drugs at levels significantly higher than those possible for drugs treating larger specialty and blockbuster indications. For example, the median price of an orphan drug in 2016 was $140,000 per patient per year, compared to $28,000 for a non-orphan specialty drug. This revenue opportunity is a result of public policies that favor orphan drugs with respect to pharmaceutical intellectual property and market exclusivity.

The 1983 Orphan Drug Act extended the period of regulatory exclusivity, during which no competitor may launch a drug with the same mechanism of action, from the five to seven years. The recently adopted 21st Century Cures Act further enhances the attractiveness of orphan drugs: The Act renews and extends the rare pediatric disease program, granting six months of market exclusivity to firms developing pediatric orphan drugs, over and above the standard seven years. Six months of additional exclusivity imply another $150,000 to $250,000 in revenues per patient for a high-priced orphan drug.

The Cures Act also extends the Rare Pediatric Disease Priority Review Voucher program, which provides to the sponsor of a drug approved for an orphan pediatric disease a voucher to get a future drug application reviewed in six months. Importantly, the vouchers need not be used by the innovator but may be sold to another firm launching a different drug. For example, the priority review voucher obtained by United Therapeutics for dinutuximab, a treatment of neuroblastoma, sold for $350 million to Abbvie in 2015. A priority voucher obtained by Sarepta for the approval of Exondys 51 for Duchenne muscular dystrophy sold for $125 million to Gilead Sciences in February 2017. The possibility of winning, and then selling, a priority review voucher makes investment in pediatric orphan drugs especially attractive for venture capital firms.

In principle, orphan drugs can enjoy longer patent protection than can non-orphans because of the shorter times required for clinical trials and FDA review. Patents are filed at the time of initial molecule discovery, rather than at the much-later date of drug launch. The more limited FDA evidentiary requirements and accelerated review for orphan drugs shorten the interval between patent filing and market launch, thereby leaving a longer interval during which the drug is on the market but protected from generic competitors.

In addition to these policy initiatives, market considerations also make investing in orphan drugs attractive. The small patient populations in ultra-orphan indications dissuade potential competitors from pursuing candidate molecules. However, alternatives will enter larger orphan indications, as patent protection is not forever and the revenue opportunity is alluring. The erosion of price for orphan drugs is not as steep, however, as that experienced by blockbuster drugs. The extent of price erosion depends on the number of generic drugs that enter a therapeutic indication once the branded product has lost patent protection, which in turn depends on the size of the indication. The very small numbers of patients in ultra-orphan indications reduce potential revenues, but this deficit is more than made up for by the exceptionally high prices that can be charged.

The lack of therapeutic alternatives and relatively small number of patients deter insurers from instituting limits on patient access to orphan drugs. Prior authorization and step therapy, so effective in restricting sales volumes for drugs treating large specialty indications such Hepatitis C and statin-resistant elevated cholesterol are less often used for orphan drugs. On top of this, orphan drug firms often only require small numbers of field representatives to bring their products to physicians and patients, compared to the hundreds of representatives needed for drugs

addressing larger specialty indications and thousands needed for primary care indications.

The Future

The combination of accelerated review, low development costs, priority vouchers, high prices, low costs of distribution, and few limitations on patient access generate especially high profitability for orphan drugs, compared to their non-orphan counterparts. A crucial question now concerns the nature and timing of the insurer pushback. The cumulative impact of orphan drugs on insurer budgets is growing fast. Spending on orphan drugs is estimated to double between 2016 and 2022, at which point it will account for 21 percent of global prescription drug sales. This increase may stiffen the resolve of insurers on price and utilization.

For the moment, however, Bay City Capital and many of its venture capital peers continue to invest heavily in orphan drugs, rechanneling funds that otherwise might have been devoted to larger therapeutic markets. New public policy approaches that reduce drug development costs for drugs targeting large therapeutic indications could shift venture capital investments back to include broader public health needs.

DRUGS AND MEDICAL INNOVATION

ASSOCIATED TOPICS: COSTS AND SPENDING

TAGS: ORPHAN DRUG ACT, ORPHAN DRUGS, VENTURE CAPITALISM