

# The Emerging Market Dynamics Of Targeted Therapeutics

How the market for high-profile, high-cost drugs differs from that of their traditional counterparts.

by **John E. Calfee and Elizabeth DuPré**

**ABSTRACT:** Targeted biotech drugs that attack specific biological molecules that cause disease are bringing new benefits even as they foment pricing dynamics that are very different from those of traditional drugs. Targeted drugs tend not to compete with each other even when treating closely related diseases, which makes them resistant to price controls. We can expect the supply of expensive new so-called biotech drugs to continue. But the same properties that generate premium prices also facilitate inventing around successful drugs, eventually leading to vigorous competition despite the lack of generic alternatives. [*Health Affairs* 25, no. 5 (2006): 1302–1308; 10.1377/hlthaff.25.5.1302]

SEVERAL NEW CANCER DRUGS HAVE ATTRACTED ATTENTION for remarkable effectiveness, high prices, and, at least potentially, their impact on overall health care costs.<sup>1</sup> Often referred to as “targeted” or “smart” drugs, they include Herceptin, Gleevec, Avastin, Erbitux, and Iressa. These and other targeted drugs all attack very specific biological molecules such as an overactive receptor on certain cancer cells or a kinase or growth factor implicated in a particular disease’s progression. Of course, tightly targeted drugs are not restricted to oncology. Other targeted drugs include Enbrel, Humira, and Remicade for rheumatoid arthritis (RA); Raptiva for psoriasis; and Forteo for advanced osteoporosis.

Most of these targeted drugs are “biologics”—that is, giant molecules produced by genetic or protein engineering—in contrast to traditional “small molecule” drugs that are synthesized through chemical reactions. Virtually all of these large-molecule, targeted biologics were created through the tools of modern biotechnology, usually involving recombinant DNA, molecular cloning, cell culture technology, or some combination. They are often called “biotech drugs,” despite the lack of a clear and consistent definition of that term or even of the word “biotechnology.” Although officials at the Food and Drug Administration (FDA) sometimes refer to “biotechnology drugs,” there is no corresponding FDA category for regula-

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tory purposes.<sup>2</sup> Some targeted drugs are small molecules, however, including the cancer drugs Gleevec, Tarceva, and Iressa. Because their development relied heavily upon biotechnology methods, especially in connection with target discovery, these small-molecule products are also sometimes referred to as biotech drugs (as in the list of biotech drugs maintained by the Biotechnology Industry Organization [BIO]). In this paper, the term “biotech drug” includes such drugs.

### **Essential Characteristics Of Targeted Biotech Drugs**

Our focus in this paper is on pricing and competition. Two aspects of biotech drugs stand out. Their most characteristic feature, obviously, is their ability to address biological targets with unprecedented precision. We emphasize, however, that a narrow biological target does not imply a narrow therapeutic effect. A specific target may play diverse roles in the human body, in which case a drug acting on that target may find multiple uses for very different conditions. Thus, Rituxan, originally approved for cancer, has also been approved for RA. Avastin, approved for cancer, is also prescribed off-label for macular degeneration.<sup>3</sup> Remicade is approved for Crohn’s disease, arthritis, and colitis; and the HIV drug Viread may be effective against hepatitis B.<sup>4</sup>

A second essential feature of large-molecule drugs is the absence of a regulatory pathway to generic substitutes after relevant patents expire. In theory, the 1984 Hatch-Waxman Act, which gave birth to today’s vigorous generic drug industry, could apply to the few older biotech drugs (mainly hormones and insulins) that passed through the FDA’s Center for Drug Evaluation and Research rather than the Center for Biologics Evaluation and Research. As a general rule, however, most biotech drugs are so complex in their makeup and manufacturing that there is no clear way to apply the bioequivalence standard that undergirds generic drug approvals. Nonetheless, patent expirations for the initial wave of biotech drugs have generated considerable pressure to permit competing “biosimilar” drugs to enter the market. European regulators have already approved biosimilar drugs for human growth hormone, while the FDA has yet to make clear how these products could obtain U.S. approval. The FDA appears to be constructing an informal sliding-scale approach, however. While so-called follow-on biologics will not be treated as therapeutically equivalent to pioneer brands, they might not always have to traverse the full sequence of clinical trials required of the pioneer. Rather, clinical trial requirements will vary with products and indications.<sup>5</sup> These circumstances strongly indicate that for the foreseeable future, biosimilar drugs will exert no more than a modest effect on postpatent prices of targeted large-molecule drugs.

### **The Short-Run Implications For Biotech Drug Pricing**

Some biotech drugs are entering large markets to compete like traditional “blockbuster” therapeutics for conditions such as RA and osteoporosis. But, in

general, most targeted biotech drugs do things no other drug can do. Even two biotech drugs for the same cancer may be active against entirely different subsets of that cancer. This suggests implications for foreign price controls. Those controls rely on government exercise of monopsony power, which we would expect to be more effective against sellers of competing traditional drugs within a therapeutic category than against manufacturers of unique biotech drugs.<sup>6</sup>

This is borne out by price data. We obtained price and revenue data from IMS Health for forty-three top-selling drugs in 2004, including seven large-molecule biotech drugs, supplemented by an additional fourteen biotech drugs, of which all but two were large molecules. We also separated modern targeted therapeutics from first-generation biotech drugs, such as human insulin, human growth hormone, interferons, and red and white blood cell-stimulating factors. Most of these pioneer biotech drugs were developed to treat deficiencies of biological substances before scientific understanding permitted the identity of more precise targets. Exhibit 1 compares foreign prices to U.S. prices: first for the thirty-six best-selling traditional drugs in the United States in 2004, then for the full sample of biotech drugs, and finally for a subsample that excludes first-generation biotech drugs. It is apparent that relative to the United States, targeted drugs were priced far higher abroad than nonbiotech drugs and were essentially at parity with U.S. prices in Canada and France. Second-generation targeted drugs tended to be priced somewhat above U.S. levels.

### The Coming Dynamics Of Biotech Drug Pricing

Whether or not biotech drugs will continue to exercise a sort of immunity to ordinary pricing pressures, including foreign price controls, is far from clear. Because the industry is relatively new, there is little reason to think that what we observe today will characterize markets five or ten or twenty years from now. Several partly offsetting forces are at work.

■ **Chasing QALYs.** The ability of biotech drug developers to create tightly targeted drugs, combined with the absence of a regulatory pathway to generics, would

#### EXHIBIT 1

#### Relative Price Indices For Traditional And Targeted Drugs In Five Developed Countries Relative To The United States (U.S. = 1.00), 2004

	Australia	Canada	France	Germany	U.K.
Traditional drugs	0.45	0.50	0.45	0.48	0.54
22 biotech drugs	0.78	0.99	0.94	0.75	0.75
Second-generation targeted drugs	1.15	1.11	1.25	1.13	1.04

**SOURCES:** For thirty-six traditional drugs, J.E. Calfee, M. Villarreal, and E. DuPré, "An Exploratory Analysis of Pharmaceutical Price Disparities and Their Implications among Six Developed Nations," Working Paper no. 06-07, April 2006, <http://www.aei.org/admin/authorpdfs/page.php?id=1265> (accessed 8 June 2006); for biotech drugs (including second-generation targeted drugs), IMS Health.

**NOTE:** Gleevec was deleted from Canadian indices because of anomalous data.

seem to leave relatively little scope for competition. This might be true in the short run. Biotechnology has provided an increasing supply of new drugs that do things that have never been done before, radically altering the treatment of such previously impervious conditions as multiple sclerosis (MS), RA, and, of course, certain cancers. We can expect the supply of expensive new biotech drugs to continue unabated even if payers systematically limit reimbursement to consensus recommendations for how much to pay per quality-adjusted life year (QALY) saved. As long as advanced societies are willing to pay on the order of \$50,000 or more per QALY, creative biotechnology firms will find solutions that meet such standards and will price them accordingly.

■ **Postapproval research.** The relationship between research and development (R&D) and the lack of generic entry bears emphasis. Research on traditional drugs normally ceases as patent expirations approach. The burden of conducting research on an important therapeutic class is typically assumed by follow-on drugs (as happened most notably with the statins). But a steady succession of patent expirations and generic entries will eventually deplete research incentives, as happened with the important class of nonsteroidal anti-inflammatory drugs (NSAIDs) until the COX-2 inhibitors (such as Celebrex) were developed in the late 1990s.<sup>7</sup>

The situation with most biotech drugs is different. Without the prospect of generic entry, research investment on a pioneer drug does not face a natural endpoint. Absent overwhelming inventing-around, as discussed below, we can expect research to continue almost indefinitely on the extraordinary potential of a drug like the angiogenesis inhibitor Avastin, which in principle could act against many forms of cancer.<sup>8</sup>

■ **Pricing conundrums.** Although introductory prices have commanded most of the attention, the dynamics of biotech drug pricing can raise difficulties as research and medical practice evolve. For example, the colon cancer drug Avastin was demonstrated to be effective for breast and lung cancer, but at roughly twice the dose and presumably twice the price.<sup>9</sup> In contrast, the HIV drug Norvir was first used as a primary treatment but is now mainly prescribed as an adjuvant in small doses to improve the action of other HIV drugs. A large price increase preserved the nexus between price and value but generated intense criticism of the manufacturer. Comparable price changes and additional controversy may arise as other biotech drugs come to be prescribed as adjuvants or preventatives or for intermittent usage.

There seems to be no easy way for manufacturers to avoid such conundrums unless they can set different prices for different uses of an identical product. One might think that these difficulties are not related to R&D incentives, but in fact they are. Research incentives arise from the full range of a drug's potential uses including those explored after approval. The inability to practice price discrimination among uses could greatly undermine incentives for both initial development and postapproval research.

■ **Competition through faster inventing-around.** So far, our reasoning suggests

that tight biological targeting by biotech drugs allows manufacturers to resist competition (and therefore pursue more postapproval research). But biotech drug targeting can also facilitate competition. The classic inventing-around process that expanded traditional drug categories such as cholesterol-reducing statins and glitazones for diabetes can be refined and accelerated for biotech drugs after “proof of principle” has been established for a biological pathway. New drugs can exploit a proven target in a way that avoids patent infringement while retaining a reasonable prospect of success in clinical trials. This is because a deeper understanding of complex biological pathways that cause disease can greatly increase the number of promising therapeutic targets. For example, a drug that treats cancer by disrupting the interaction between a growth factor and its receptor usually achieves its effect by interfering with an assembly line of proteins, which pass a signal from one to the next, ultimately altering a biological process like cell growth, division, or death. Once one protein is implicated in disease progression, the entire pathway becomes a source for therapeutic intervention. In addition, after a pioneer drug has established proof of principle through clinical trials, new drugs can often be developed for the same ultimate target (such as a receptor or dysfunctional enzyme) while employing a different mode of action.

Thus, the astonishing success of Herceptin—a monoclonal antibody that treats certain breast cancers by blocking the human epidermal growth factor receptor 2 (HER2)—motivated a surge of drug development targeting the same receptor with greater potency, other members of the HER family, or one of the many proteins downstream from HER2. Iressa and Tarceva, currently on the market, selectively inhibit HER1, while others in development such as Lapatinib and Pertuzumab interfere with HER2’s ability to collaborate with other HER receptors. A recent *Nature Biotechnology* article described the incipient competition that Herceptin could soon face, listing a total of ten targeted drugs currently in either Phase II or Phase III trials for breast cancer.<sup>10</sup>

These are far from the only examples of inventing-around, which is rapidly becoming a central feature in biotech drug development. Others include the tumor necrosis factor (TNF) inhibitors for RA, angiogenesis-inhibiting cancer drugs put into development in the wake of Avastin’s success, and follow-ons to Gleevec.<sup>11</sup>

■ **Competition through new uses.** A second route to competition through targeting is through postapproval research on how a drug’s activity against a specific target may extend to other therapeutic areas, generating new uses for the drug.<sup>12</sup> Expanded uses for multiple drugs can easily overlap, creating new competitive forces. Avastin is now in clinical trials for more than twenty different forms of cancer, including some that are now treated by competing targeted drugs.<sup>13</sup> More generally, a targeted drug might turn out to be not a “cancer” drug per se, but rather a drug that addresses a certain pathway that is involved in seemingly unrelated conditions, as we noted for Rituxan. This possibility invites a broad research agenda. It has become common knowledge, for example, that a drug that works for RA (as several

TNF-alpha inhibitors do) should be tested for Crohn's disease, psoriasis, and other inflammatory conditions, all of which may result from related dysfunctional pathways. In fact, TNF-alpha inhibitors such as Humira and Enbrel are already widely prescribed for some of these conditions.

The phenomenon of drug resistance also opens opportunities for competition. Complex diseases generally result from a number of aberrant and redundant mechanisms. A drug that pinpoints a single molecular target may therefore be at major risk for developing resistance. Already, Sprycel has been approved by the FDA to address resistance to the cancer drug Gleevec, and more such drugs are in testing.<sup>14</sup>

■ **Drugs that are just better.** Finally, a third form of biotech drug competition parallels the most familiar mode of competition in the traditional pharmaceutical market. Research can aim simply at improving existing therapies. Some next-generation biotech companies are expanding upon existing monoclonal antibody technology by developing longer-lasting and more potent antibodies that are cheaper to manufacture for targets that have been well validated by science and the market (like TNF-alpha and epidermal growth factor receptor, or EGFR). The follow-on research we described on Herceptin and its incipient competitors includes, for example, the development of smaller and more stable antibodies for the HER2 receptor, some with dyes and radiotoxins attached.<sup>15</sup>

## Looking Forward

We cannot provide a concrete forecast of biotech drug prices, but certain trends are likely to be important. We can expect the rapid accretion of what might be called QALY-driven drugs: drugs that provide large benefits, especially for previously poorly treated conditions, but at high prices and, often, significant total expenditures. This does not rule out, however, a new generation of old-style blockbuster drugs as manufacturers learn more about exploiting biological mechanisms that fill diverse roles in the human body.

Competition will become a more powerful force as manufacturers exploit biotechnology's remarkable ability to invent around successful drugs. At the same time, pricing will become ever more challenging as drugs find multiple uses involving different doses and regimens.

One unpredictable element is the FDA, which is under great pressure to bridge the gap between the potential of new research methods and a regulatory regime that is in many respects slow to change.<sup>16</sup> Targeted drugs often confound traditional methods for designing FDA-approved clinical trials.<sup>17</sup> There is a need to explore new biomarkers, validate surrogate efficacy and safety endpoints, and encourage more adaptive and flexible clinical trial designs. Some of this could emerge from FDA changes, especially from the agency's Critical Path initiative and its vision of collaboration among the FDA, private nonprofit organizations, and the drug industry.<sup>18</sup>

Finally, our discussion of biotech drugs' apparent resistance to foreign price controls does not carry over to the prospect of price controls in the United States. Because there would no longer be a large market in reserve to provide payoffs from innovative research, domestic price controls could work very differently from those in smaller nations.

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*Jack Calfee has consulted for some biotechnology and pharmaceutical companies. The American Enterprise Institute receives a small portion of its funding from pharmaceutical companies.*

## NOTES

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