

Less price flexibility, more innovation: the market dynamics of targeted therapeutics

An analysis of how the market for high-profile, high-cost drugs differs from that of traditional counterparts is the subject of a new study published by the Washington DC, USA-based think-tank, the American Enterprise Institute, titled: *The Emerging Market Dynamics of Targeted Therapeutics*. The article's authors, John Calfee and Elizabeth DuPre, found that targeted biotechnology drugs which attack specific disease-causing biological molecules are bringing new benefits to patients, while creating new pricing dynamics.

Dr Calfee and Ms DuPre noted that, unlike earlier types of drug, which tend to employ small-molecule active ingredients that are synthesized *via* chemical reactions, most of the biologics are giant molecules that are produced as a result of gene or protein engineering. These have been created by utilizing recombinant DNA, molecular cloning, cell culture technology, or a combination of these techniques.

The authors found that there is a lack of a clear or consistent definition of the term "biologics" or even "biotechnology" the US Food and Drug Administration also does not have a regulatory classification for this area. This, in turn, has consequences for competition after patent expiry.

Two aspects of biotechnology drugs were said to be noteworthy by Dr Calfee and Ms DuPre: "their ability to address biological targets with unprecedented precision" and "the absence of a regulatory pathway to generic substitutes after relevant patents expire."

Although biologics have a narrow target range, this can have several functions in the human body, so a drug like Rituxan (rituximab), which is marketed jointly by US specialist drugmakers Genentech and Biogen Idec, was originally approved as an anticancer agent but has also been cleared as a treatment for rheumatoid arthritis.

Hatch-Waxman could apply to some biologics

Concerning pricing, the authors noted that, "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."

The problem for generic drugmakers, Dr Calfee and Ms DuPre said, is that "most biotech drugs are so complex in their make-up and manufacturing that there is no clear way to apply the bioequivalence standard that undergirds generic drug approvals."

Considerable pressure is building up over the issue of permitting biosimilar drugs to compete with patent-expired biotechnology agents. The European Medicines Agency (EMA) has already authorized biosimilar products for human growth hormone, with clearance for Omnitrope, the recombinant growth hormone made by Sandoz, the generics subsidiary of Swiss drugmaker Novartis (*Marketletter* February 6).

Meanwhile, the FDA is, according to Dr Calfee and Ms DuPre, "constructing a sliding-scale approach."

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Follow-on biologics will not be treated as therapeutically equivalent to patented products, but they will not be required to undergo the full clinical trial route of the original. However, for the foreseeable future, according to the report, "biosimilar drugs will exert no more than a modest effect on post-patent prices of targeted large-molecule drugs."

Because most targeted biotechnology drugs have capabilities that are unique to that drug, foreign price controls seem likely to become less effective. The AEI authors noted that "those controls rely on government exercise of monopsony [single purchaser] power, which we would expect to be effective against sellers of competing traditional drugs within a therapeutic category than against manufacturers of unique biotech drugs."

Research published jointly earlier this year by the AEI and the New York-based Brookings Institution found that biotechnology drugs tended to hold their market prices better than traditional ones. For "second-generation" targeted drugs, the survey found that these were actually more expensive in Australia, Canada, France, Germany and the UK, than in the USA, despite various forms of price control being enforced in all but the latter country.

Biologics liberated from price control

Peter Pitts, president of the New York-based Center for Medicine in the Public Interest, agrees with this assessment, seeing it as liberating for drugmakers. He told the *Marketletter*: "as we proceed further down the path of personalized medicine *via* both targeted therapies and gene testing, those nations (mostly in the European Union, but also Canada, Australia and - to a lesser degree - Japan) that impose price controls *via* the threat of compulsory licensing will find that what once was a Thor's hammer has become a toy hammer. More and more pharmaceutical firms will simply say 'no' and increasing numbers of patients in these otherwise developed nations will have neither access to nor, for that matter, knowledge about cutting-edge treatments [because of the European Union's direct-to-consumer information ban]."

Mr Pitts added that EU governments would face the choice of paying ever higher prices for targeted drugs, perversely while their prices are relatively stable in the USA, or “they will simply say that there is not sufficient evidence showing that these new, more targeted and safer therapies are of sufficient ‘added benefit.’ Denial is a wonderful thing.”

Few generic drugmakers can make biosimilars

When asked about the potential for biosimilar competition, Meir Pugatch, from the University of Haifa’s Intellectual Property Policy and Commercialization of Knowledge Assets department, in Israel, told the Marketletter: “there are currently few generic companies, such as [Israel’s] Teva and Sandoz that are going to be able to produce biosimilars. In terms of price elasticity, I agree the price of biosimilars will be likely to be less flexible and perhaps closer to the original price.”

Dr Pugatch added that, if the therapeutic features of the branded biotechnology drug are superior to biosimilars (it seems plausible that it extensive clinical trials would be required to demonstrate otherwise), then the former would tend to have a longer market life. However, both the AEI study’s authors and Dr Pugatch point out that arbitrary price controls could distort the price dynamics.

The Marketletter asked Dr Calfee about the effects of recent Medicaid price controls enacted by the US state of California (*Marketletter* October 9), especially given the impact of the most populous state on the rest of the US drug market. He said: “the California law will be tested in the courts, which could take two to three years. At some point there may be more convergence between prices in the Medicaid system and prices elsewhere. The kinds of drugs we wrote about will tend to generate their own pricing structure as manufacturers set prices after taking into account all parts of the US system including Medicaid discounts, etc.”

Dr Calfee also noted that “we can expect more manufacturer resistance to exceptionally low prices in poorer EU nations such as Greece and post-Soviet economies. It is entirely possible that firms will refrain from marketing in such nations. Note that Gilead and others have held off marketing of innovative drugs in Canada in the face of price ceilings substantially below prices next door in the USA.”

Six forces pushing biologics competition

The AEI report also considers the longer term effects of biotechnology drug pricing. These are heavily dependent on a number of external issues beyond the control of drugmakers. For example, the absence of a regulatory procedure for generic entry into the US market, could change with several outcomes possible. Dr Calfee and Ms DuPre list six forces that they consider may change the biologics’ market dynamics. They list these forces as: chasing quality-adjusted life years; post-approval research; pricing conundrums; competition through faster inventing-around; competition through new uses; and drugs that are just better.

In the short term, tightly targeted drugs that face little threat from generics would seem to imply a lack of competition. The study’s authors said: “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* QALY saved.” Provided that developed countries are willing to pay in the region of \$50,000 or more *per* QALY, incentives to innovate will exist for firms that meet such standards and can price their products accordingly.

For traditional drugs, the patent duration determines the length of time a drug company is willing to undertake R&D on a product, including research into other uses. With biotechnology drugs, unless there is considerable “inventing-around,” the study proposed that “we can expect research to continue almost indefinitely.”

Pricing conundrums will emerge as biotechnology drugs are found to have several uses. The study found that Genentech’s Avastin (bevacizumab), originally used for cancer of the colon, at twice the dose is effective against breast and lung cancer. US drug major Abbott Laboratories’ Norvir (ritonavir), on the other hand, is now mainly prescribed at low doses but higher prices as an adjuvant for other HIV drugs, as opposed to its earlier primary use. Restrictions by regulators and payers on price discrimination among uses could “greatly undermine incentives for both initial development and post-approval research.” However, pricing decisions such as the one performed by Abbott for Norvir did cause an outcry.

The inventing-around process could stimulate competition, because a better understanding of complex biological pathways that cause diseases can increase the number of therapeutic agents. “After a pioneer drug has established proof-of-principle through clinical trials, new drugs can often be developed for the same ultimate target,” according to Dr Calfee and Ms DuPre.

They cite the success of Swiss drug major Roche’s monoclonal antibody Herceptin (trastuzumab), which has prompted such a wave of research that, according to a recent article in *Nature Biotechnology*, the drug faces potential competition from 10 targeted drugs that are currently in either Phase II or Phase III trials for breast cancer.

The emergence of new uses for biologic drugs creates competitive forces: Avastin is in clinical trials for more than 20 different forms of cancer, meaning that, in many instances, it is competing against other drugs. Drug resistance too, provides opportunities for competing agents to enter a targeted market. Finally, the most familiar form of competition in the drug market is the development of improved remedies.

The Emerging Market Dynamics of Targeted Therapeutics appears in the September/October issue of the AEI’s Health Affairs journal and can be read on-line at: www.aei.org.