

# Why biosimilars will have a smaller competitive edge than generics

Joseph P. Fuhr, Jr.

Erwin A. Blackstone  
jpfuhr@widener.edu

This presentation examines the potential role for biosimilars to reduce the monopoly power of the pioneer biopharmaceuticals.

Biopharmaceuticals have become an increasingly important part of the pharmaceutical industry.

Entry of biosimilars is far more costly than are chemical generics.

The U.S. currently has no means to permit approval of biosimilars.

The early experience is that biosimilars have more difficulty entering and have a smaller impact.

Biosimilars are likely to cut prices by only 20 to 30 percent.

Entry should be allowed if safety and comparability can be assured.

After all there is no substitute for actual market experience.

# Introduction

Controlling healthcare cost is a national priority.

Around 16% of GDP is spent on healthcare, 10% is pharmaceuticals.

Expenditures on pharmaceuticals are increasing faster than healthcare.

Biopharmaceuticals are increasing even faster.

Biopharmaceuticals are more expensive which presents access issues.

Biosimilars decrease the price of biopharmaceuticals but also decrease the incentive to invent.

The higher prices of biopharmaceuticals could still lead to great savings in overall cost.

Innovative drugs have greatly benefited society.

The major public policy issue is the trade off between access and firms being compensated for their risk-taking.

Monopoly profits could last for a long time (beyond the patent period) unless biosimilars are allowed.

The European Union developed regulations for biosimilars.

The major issues are safety and whether biopharmaceuticals can have an identical product.

In 1984 the United States was faced with a similar issue concerning generic chemical drugs.

The Hatch-Waxman (H-W) Act was passed with the intention of balancing competition and innovation.

The H-W Act for the most part has worked but has led to some unintended consequence.

The fundamental problem is to achieve greater competition without reducing the incentives for innovations.

# High Risk

Biopharmaceuticals are a high risk venture.

Biopharmaceutical firms spend around 50 percent of their revenues on R & D compared to about 19 percent for pharmaceutical firms.

Their spending on R & D is 17 times larger than American manufacturing.

Biotechnology is probably the most R & D intensive industry in the U.S. and the world.

Many of the smaller biotechnology firms have negative cash flow.

The industry as a whole is losing money.

In 2006, U.S. biopharmaceutical firms lost \$3.5 billion after losing \$1.4 billion in 2005.

In 2007 the U.S. biopharmaceutical industry as a whole lost \$300 million.

In the same year, the worldwide biotechnology industry lost \$2.7 million.

Also indicative of less than favorable profitability is a negative 1.9 percent return for the S & P Biotechnology Index for 2006 compared to a 13.3 percent growth in the S & P 1500 Super Composite Stock Index.

Over a longer period returns to investment in biotechnology firms have produced poor performance.

A \$1 investment in 1981 in a composite of publicly traded biotechnology shares would have grown to approximately \$8 at the end of 2003 compared to almost \$12 in a risk-free treasury bond and to \$21 for the Dow Jones portfolio.

However, some of the firms are highly profitable.

One can liken a successful biopharmaceutical firm to that of hitting the lottery.

# Development Costs

The cost of development of a new innovative biotechnology drug approximated \$1.2 billion (including unsuccessful or failed drugs), comprised of \$615 million of pre-clinical expenses and \$626 million of clinical expenses.

Further, actual out-of-pocket expenditures per each new biological were \$550 million.

This compares to an estimated \$.5 billion to \$.8 billion for traditional new chemical drugs.

Biopharmaceuticals take 97.7 months to get through the regulation process compared to 90.3 months for traditional chemical drugs.

The cost of developing a simple biosimilar ranges between \$14.5 million to \$17 million compared to between \$.9 million and \$2.6 million for a chemical generic.

The development period for a biosimilar is estimated to be seven years.

The production costs of the biosimilar are 60 percent higher relative to price than chemical generics.

The profit margin is much less for a biosimilar than a chemical drug.

Especially significant are the expenditures required for clinical trials.

Clinical trials for biosimilars in Europe have been estimated to require expenditures of \$26.5 million to \$53 million.

# Manufacturing

Biosimilars have considerably higher manufacturing cost.

One authority notes that “even minor changes at any stage in the process have the potential to impact on clinical efficiency and safety.”

Johnson and Johnson’s had problems with an anemia drug where a manufacturing process change “caused certain compounds to leak out of uncoated rubber stoppers” which resulted in clumping in the bloodstream and a serious anemia.

In epo a small variation in the formulation of the product yielded antibodies that affected both the drug itself and the erythropoietin produced by the body.

This illustrates the potential serious problems that can occur with minor changes in manufacturing.

It often takes in excess of five years to get a new facility licensed to produce a specific biopharmaceutical.

It can even take in excess of three years to get a new contract manufacturer qualified.

Constructing a new manufacturing facility involves capital cost of \$250 million to \$400 million.

The current constraint on capacity provides bargaining power on the side of contract manufacturers.

This further diminishes the probability of successful biosimilar entry.

# Marketing Biosimilars

An important factor distinguishing chemical generics from biosimilars is the greater reliance on marketing and detailing of biosimilars.

Unlike chemical generic drugs, substitution will not be automatic.

Brand loyalty will be especially difficult to overcome.

The first successful drug may enjoy a strong first-mover advantage, making entry quite difficult.

Biosimilars companies will have to assure physicians (and hospital purchasing authorities) that their biosimilar will be safe and perform as well as the brand name drug.

This will be difficult and require substantial expenditures of time and money, adding to the risk of entry.

Further, some of these biopharmaceutical drugs are administered by physicians.

The sensitivity of a drug's success to small manufacturing differences may make physicians especially reluctant to switch to a biosimilar.

Direct advertising to consumers is unlikely to be successful.

These factors mean high costs for marketing since direct contact with physicians may be required.

# Reimbursement Issues

Biopharmaceuticals are expensive.

Biosimilars are likely to be relatively expensive.

One risk that a new biosimilar entrant will face is the strong cost control efforts by insurance companies in the U.S. and by governments in Europe.

Unless a company can show clear economic value or be the most cost-effective in a category for its product, reimbursement may be troublesome

For example, an institute that advises the British government about what drugs it should cover, recommended against covering Avastin which can cost \$100,000 per year but extend life by only a few months.

The special problem a biosimilar producer faces is the uncertainty that another drug, with far greater economic value will be developed before the biosimilar producer can earn enough to cover its cost.

There is the danger that another biosimilar will be developed that will cut its price enough that it will be placed on a formulary of a managed care company.

In Europe there are five brand-name competitors in the human-growth hormone market and two biosimilar products, Omnitrope and Valtropin.

Buyers including managed-care can play companies off against each other for preferred formulary placement which could make entry risky.

As Standard and Poor's notes the rise of biotech alternatives could create reimbursement problems for higher-priced drugs.

Also, with so many firms (350 public ones alone), the uncertainty that someone will develop a superior drug is ever present, making entry risky.

# Capital Cost of Entries

Capital costs to enter the market will be substantial compared to chemical generics.

Not only will a facility be required (or production contracted out) but substantial clinical costs will have to be incurred as well as marketing expenses.

Post-approval testing may also be required.

For example, the European Union mandates in addition to pharmaceokinetic and pharmacodynamic data, clinical studies, post-approval studies, a year of immune-type data, and periodic manufacturing testing.

# Regulation and Entry

The most important issue facing biosimilars is whether they will be allowed to enter the market.

Firms are reluctant to spend a considerable amount of money on R & D if entry is blocked.

The U.S. is where the biosimilar firms have the potential to make the most profit.

As long as the U.S. market is closed, biosimilar firms will find it difficult to make a profit.

The recent FDA ruling concerning Genzyme and its biopharmaceutical branded Myozyme illustrates the problems facing biosimilars in entering the U.S. market.

A senior vice president for regulatory affairs at Genzyme noted that the company had full access to all the information about the drug and yet could not fully replicate the manufacturing process.

The FDA concluded that Myozyme produced at different plants at different scales should be classified as different products because of actual differences in the product.

This suggests how difficult it will be to receive FDA approval for biosimilars.

Substantial testing (including clinical trials) may be required.

The FDA may required post-approval studies to assure a drug's safety and efficacy practitioners about a drug or impose restrictions on a drug's use.

This adds to the cost and uncertainty of drug development.

Amgen, a leading biotechnology producer, states, "In our experience, obtaining regulatory approval has been and continues to be increasingly difficult and costly and takes many years, and after it is obtained remains costly to maintain."

If studies uncover problems or issues for the innovator, the sales of the biosimilar would presumably be adversely affected as well.

# Patent and Data Exclusivity

A major issue concerning biopharmaceuticals and biosimilars is that of patent protection.

Given that biosimilars are different from the branded biopharmaceutical, there is considerable debate on whether the biosimilars will or will not infringe on the branded biopharmaceutical's patent.

The reference brand (patented biopharmaceutical) may not have patent protection.

If this is true then the issue of data exclusivity becomes even more important.

The absence of data exclusivity means that the branded biologic has no legal protection against competition and it would be very difficult for the branded firm to obtain a return on its investment.

This would make biosimilar entry much easier since the generic company can have access to the data.

The issue of the length of data exclusivity becomes very important in the biopharmaceutical market.

# Biosimilars in the Market

## The European Union

The experience of biosimilars in the non-U.S. market confirms our analysis.

The European Union has approved biosimilars for two human growth hormone, erythropoietin and filgrastim and has denied it for interferon Alpha 2-a.

Some biosimilars would be entering a market where several branded products compete. This means that profits have been reduced through competition.

The gains from biosimilars would thus be less than in situations where a monopoly producer existed.

Since patent protection arguably may be less adequate in the case of the biopharmaceuticals fewer monopolies may exist.

Omnitrope and Valtropin became the first approved biosimilar in April 2006.

Both are human growth hormones whose reference brand is Genetropin.

Omnitrope was launched in Germany and Austria at a price 20 percent below Genotropin and has been able to gain less than one percent of the European market.

It is standard practice in HGH to maintain patients on the same product.

To gain market share, physicians must be convinced to treat newly diagnosed patients with Omnitrope.

Unlike chemical generics the market for a biosimilar is likely to be relatively smaller, making entry more difficult and risky.

Valtropin has had an even more difficult time.

Even though it demonstrated equivalent safety and efficacy with its reference product.

It has different precautions and warnings than its reference product and is currently not available in the European Union markets.

Also it has had manufacturing problems.

In the epo market 5 biosimilars that have applied in the EU have been approved with Eprex as their reference product.

5 Biosimilar of Filgrastim approved 2008-2009. Reference Product: Neupogen

Epo biosimilars “aren’t expected to make huge inroads right away.”

Hospira’s CEO Chris Begley stated that “Retacrit won’t have a positive impact on its bottom line in the next few years.”

Alpheon an infereon alpha-2a was rejected by the EU's Committee on Medicinal Products for Human Use.

The application was not approved because of problems with characterization, manufacturing and control.

The company admitted that Alpheon had an inferior clinical profile.

There were not enough data on the stability of the drug product.

Also the process used for making the drug had not been adequately validated.

# The United States

In the United States the only biosimilar to be approved is Omnitrope.

Even though the United States has no regulatory mechanism to approve biosimilars, Omnitrope was approved by the FDA in May 2006 under the 505 (b)(2) Pathway of the Hatch-Waxman Act.

A powder form of Omnitrope was launched in January 2007 and a liquid form, Omnitrope Pen 5, was launched in March 2008.

The pen was offered at 35% below the price of the reference brand Genetropin.

Even though no data are available on market share “Sandoz itself has admitted that Omnitrope made a slow start in a challenging U.S. Market.”

# Other countries

Manufacturers in Asia (China and India), Eastern Europe and Latin America have been selling biosimilars for years.

India and China manufacturers would have to fulfill the strict safety requirements of the EMEA or the FDA.

Studies of epoietin manufactured outside the United States or European have had differences in purity, potency and bioactivity which show that differences in the manufacturing process can alter the activity of a biological product.

However, Dr. Reddy is planning on launching one biosimilar a year every year for the next few years and has eight biosimilars in the pipeline and is spending \$20 million to do it

The firm is investing \$30 million to build a biomanufacturing facility in India.

In May 2007 Dr. Reddy was producing two biosimilars.

It plans to attempt to launch each product in Europe.

However, a spokesperson for Dr. Reddy stated that “it will take at least two years for us to get familiar with the different legal requirements on biosimilars in Europe and to wait for the U.S. to come up with a clear regulatory framework for generic versions of biologics.”

This is consistent with the position of most of the CEOs who were at BioAsia in 2007 who note that “most interesting challenge ahead will be to understand and implement the regulatory requirements for biosimilars in order to market them in regulated markets.”

The cost of bringing a biosimilar product to market in India is around \$10-20 million. This is low compared to U.S. and EU.

Sales of biosimilars in India have grown rapidly and will likely expand into the export market.

There are at least 3 companies in India that sell biosimilar insulin. After entry Novo Nordisk decreased the price of some of its insulin products by around 40 percent.

Biocin, an India manufacturer, has been marketing rH1 in the Middle East and Africa and plans to enter the Germany market.

Epo is already marketed in several parts of the world including China.

In China most biological products are biosimilars.

Omnitrope was approved in Australia in Sept. 2004 and launched in Nov. 2005.

Teva has biosimilar R & D facilities in Lithuania, Israel and China.

Teva also acquired Sicor including its biosimilar manufacturing facilities that produce granulocyte colony stimulating factor (G-CSF), interferon alpha 2B and HGH which it sells in Eastern Europe, Africa, and other developing countries.

Other countries could be a good testing ground for clinical trial data for subsequent approval in U.S. and EU.

The advantage of having experience producing biosimilars in other countries where standards may not be as stringent has its downside.

It is possible that a problem with a biosimilar there could make it much less likely for approval of biosimilars in the U.S. or EU.

Indeed, even if biosimilars were approved, an unfortunate incident could make physicians and other decision-makers reluctant to prescribe or permit substitutions of biosimilars.

More branded biopharmaceuticals will be coming off patent and thus in the future there will be greater opportunities for more market entry.

However, newly patented second generation biopharmaceuticals may be developed that will decrease markets, especially in U.S. and Europe.

The experience in the U.S. and in other countries suggests that biosimilars will have a smaller relative impact than chemical generics.

Nevertheless, they could be important in lowering prices somewhat and in encouraging greater competition to develop new biologics since profitability on older ones will be reduced.

# Implications and Conclusions

The biopharmaceutical industry as a whole is losing money.

Entry into the biopharmaceutical market is risky with the cost of development of \$1.2 billion plus the added cost of actually bringing the product to market.

Biosimilars have and are attempting to enter the market to compete against the branded biopharmaceuticals.

Currently in the United States there is no regulatory process to approve biosimilars.

The FDA and Congress are looking at various methods to allow for generic entry in the biopharmaceutical market.

The European Union has a mechanism for approval of biosimilars but the regulatory process is more costly than that for chemical generic drugs because of the need for clinical trials and post-approval studies.

However, various safety and economic issues must be resolved.

In particular are biosimilars safe and will they achieve the same results as the branded referenced biopharmaceutical product?

In terms of economics, the issue is how to balance lower prices and competition with the incentive to invent.

The issue of patent rights and data exclusivity must be resolved in addressing these economic issues.

A Congressional Budget Office study suggested that allowing biosimilars would reduce total expenditures on biologics by about \$25 billion over the 2009-2018 period or about .5 percent of total national spending on prescription drugs.

Entry into the biosimilar markets may even be more risky than entry into the biopharmaceuticals as a whole.

The cost of developing a biosimilar is estimated to be between \$14 and \$17 million.

A new manufacturing plant is estimated to cost between \$250 and \$400 million.

Constructing a new plant gives the firm control over production which is very important in the biosimilars market.

The cost would be lower in underdeveloped countries but production there would raise more safety issues.

There is a lack of capacity which gives bargaining power to independent manufactures.

Clinical trials are estimated to cost between \$26.5 and \$53 million.

This does not include the cost of getting the biosimilar approved through the regulatory process and the cost of marketing and detailing.

These could add an additional \$10 to \$20 million.

A conservative minimum cost estimate would be \$50 million and \$300 million with a manufacturing plant.

The relatively small market for many biosimilars because of the reluctance of physicians to change drugs makes entry quite risky.

Biosimilars have greater costs and risks than chemical generics and they are not likely to be the solution to high pharmaceutical prices.

They may be helpful in moderating prices and reducing health care cost.

Given the difficulties that biosimilars are likely to face, their entry will probably not have the impact that generic chemical drugs have had.

Nevertheless, if their safety and comparability can be assured their entry should be allowed.

In addition to somewhat lower prices, reducing the profitability of branded biopharmaceuticals may even encourage pioneers to do more R & D to continue to earn economic profits.

Foreign biosimilar producers might be encouraged to try to secure FDA approval to market in the U.S.

In any event, since the U.S. market is the largest and unregulated until a mechanism for entry is established the market will be slow to develop.

Although the early experience with biosimilars has not been particularly promising, we should try to encourage competition but at the same time provide incentives for innovation.

Since biosimilars can avoid much of the research and development costs, they have room to compete.

Indeed, our estimates suggest that they might avoid on average almost a billion dollars of R & D expenses.

Although we expect biosimilars to have a smaller competitive edge than chemical generics, only the market should eventually determine their impact.

There is after all no substitute for actual market experience.

# Recent Developments

Ranbaxy manufacturing biosimilars Filgrastim for Zenotech.

Recently FDA accused Ranbaxy of falsifying data and test results.

IBPL only biopharmaceutical plant in India to comply with EU Good Manufacturing Practices.

Omntrope and Epo selling at 25-30% discount in Europe

Supply side issues are being resolved.

Next, demand side issues: Will doctors and patients accept biosimilars?

Benocrit (Sandoz) received same INN as Amgen's Eprex in EU

Legal issue: Does identical INN allow for substitutability as in chemical?

Obama in favor of biosimilars, law passed 2010, first approval 2012

Burrill claims 2008 Industry earned profit for first time but mostly due to large profits for a few.

In 2009 this has all changes with economy.

Difficult to raise capital.

Small and medium companies are in trouble and some being bought out or bankrupt.

U.S. had competitive edge in Biotech

Other countries coming to aid with biotech funding from stimulus package

Should biotech be part of U.S. stimulus package?

To answer this, one needs an analysis of the economic impact of putting stimulus money into the biotech industry.

## Full cost of Medication of Biosimilars

Dose penalties: More of drug is required to achieve same therapeutic effect

More frequent dosage of biosimilars

Biosimilars in same class are one product from same manufacturing plant but licensed to different companies.

### Unintended Consequences of H-W

1. Review of Patent Infringement settlements for possible anticompetitive effects.
2. Issue of Market Exclusivity for first filer resulting in delay of entry.