Bio-business in brief: the debate over biosimilars

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Biogenerics, or biosimilars, are a contentious subject. Some of the issues in this debate are outlined here such as should they be allowed onto the market or should they not. The biosimilars that have already been approved in India and in Europe are also listed.

Keywords: Biotechnology, biosimilars, drug company, follow on biologics, pharma industry.

IF one picks up an article related to biogenerics it is important to first check the date at the top. Things have progressed in the past few years, and to skip that part is to miss the precise context of the article. It is also true, of course, that some things never change, and arguments from 2000 may be reiterated in 2010. But first, what are biogenerics? In the pharma industry, when the patents on a new therapeutic molecule of an innovator company expire, other companies wish to introduce copies. Such a 'follow on' molecules are called 'generics'. It implies complete identity with the original molecule (Figure 1). This is routinely done for chemically synthesized molecules, and we in India are familiar with this story because our large pharma companies – Ranbaxy, Dr Reddy's Laboratories, Cipla and so on – produce about 30% of the world's generic pharmaceuticals[1].

Biological molecules, however, are much larger and more complicated. A review of biologics that can be produced by recombinant DNA technology and that are in the market as 'original molecules' appeared in these columns a few years ago[2]. In principle, each of these biologics could be produced as a biogeneric or biosimilar by different companies. However, for these large molecules, proving the identity of two molecules is not so simple. There are many possible differences (Figure 1) that could exist. The most common biologics that are discussed are proteins, and the kinds of differences between two molecules fall into two categories: (i) small chemical changes, as by the addition of groups such as phosphate, sulphate, amide and fatty acids and/or (ii) conformational changes where the chemical composition may be the same, but the protein 'folds' differently, at least in part. Apart from simple proteins, there could be those that are decorated with carbohydrates, leading to possible variation in the nature of (i) the constituent sugar units, (ii) the linkages between sugar units, (iii) the conformations of both the individual sugar unit and the entire carbohydrate chain and (iv) further chemical modifications of the sugar units.

As a result of these potential complexities, there has been a debate on what exactly to call the 'biogeneric'. Generic biologicals have come to be known by various words and phrases: biogenerics, biosimilars, follow-on protein products, follow-on biologics, subsequent entry biologics, subsequent entry products, etc. I myself prefer the word 'biosimilar' for the following reasons. First, the larger phrases are unnecessarily clumsy, and a single word should suffice. Second, although most current biologic therapeutics are proteins, there are already two nucleic acid therapeutics in the market, Macugen (from Eyetech Pharmaceuticals) and Vitravene (from ISIS Pharmaceuticals), both for eye-related disorders, and no doubt the future will bring more. Thus 'follow-on protein products' will not suffice to describe the entire category. Third, it is true that although a chemical generic is identical to the original molecule, the same will not necessarily

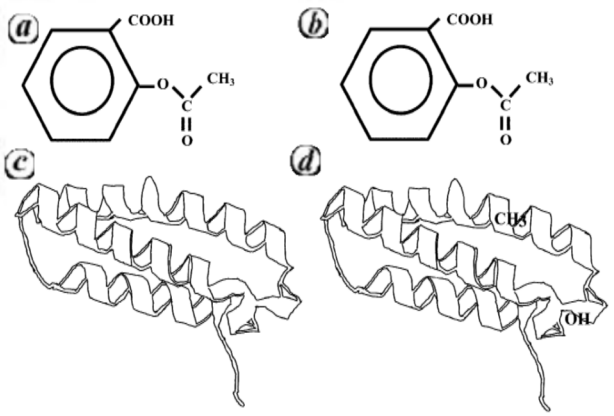

Figure 1. Outlining the differences between original and generic versions of small chemical molecules and much larger biologics. ***a***, An 'original' aspirin molecule. ***b***, An identical generic aspirin. ***c***, An 'original' protein molecule. ***d***, A post-translationally modified version of the protein.

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hold true for the 'biogeneric' which may have minor modifications that do not affect its characteristics as a drug (such as activity, bioavailability or toxicity). So, 'biosimilar' may be the best descriptor. It is the term used in Europe.

Biosimilars and the market

Despite the possible confounding issues, India has been at the forefront of developing biosimilars. By 2008, Indian companies had produced eight categories of molecules, of which several are produced by more than one company[1]: Recombinant hepatitis B vaccine and erythropoietin are produced by six Indian companies each, insulin and streptokinase by three each, and granulocyte colony stimulating factor (G-CSF) by two (Table 1). Interestingly, the monoclonal rituximab from Dr Reddy's Laboratories does not yet have domestic competition. (Although another company, Biocon, has demonstrated the capacity to produce a monoclonal – BIOMab-EGFR – it is not a biosimilar.) Thus, several companies have the skill sets to produce these molecules. Readers specially interested in the topic of monoclonals – a popular category of biologics – may wish to refer to an earlier article in this series[3].

Companies elsewhere have also developed a few biosimilars. However, regulatory bottlenecks have served as a deterrent to a larger number of companies taking up such work. In Europe, a regulatory pathway for the approval of biosimilars now exists and biosimilar growth hormone and erythropoetin were approved in 2006 and 2007 respectively (http://www.biopharma-reporter.com/news/ng.asp?n=79482&m=2BPR907&c=ugbhfeyctaievyh). To be noted is that erythropoetin – epoetin in short – is a protein with multiple carbohydrate chains and therefore is a good example of a complex biologic. The fact that even one such complex biologic has been approved in a tough regulatory environment is a significant milestone in the journey of biosimilars reaching the market.

In the US, the biggest market for the biopharma industry, the regulatory scene is more complicated. Although there have been occasional approvals of follow-on products, these have been on a case-by-case basis and the molecules have been considered original products, not biosimilars. If more biosimilars are to see the light of day in the US, there needs to be an abbreviated pathway for biosimilars similar to the abbreviated new drug application (ANDA) that is used for small molecule generics. Notably, ANDA does away with extensive and expensive clinical trials. In 2007–08, no fewer than four bills were introduced in the US Congress, presenting different versions of a possible path for the approval of biosimilars[4]. And President Obama has indicated that he supports biosimilars, suggesting that legislation on this issue might come through soon.

Table 1. Biosimilars brought out by homegrown Indian companies, and approved for sale in India (adapted from ref. 1)

Product	Number
Erythropoetin	6
Hep B vaccine	6
Insulin	3
Streptokinase	3
G-CSF	2
Interferon alpha 2b	1
Anti-EGFR monoclonal antibody	1
Rituximab	1
	23

The pro- versus anti-biosimilar debate

There are two contrary and strongly held views regarding whether or not biosimilars should be marketed and what the conditions for their approval should be. The big pharma companies that are making billions of dollars each year from their biologics do not wish to relinquish this revenue stream. There are others, however, who believe that the science to determine the efficacy of generic biologics is in place. These molecules should therefore be approved, thereby bringing cheaper medicines to market. In 2004, the Food and Drug Administration (FDA) – that regulates the entry of new drugs into the US market – held a workshop where it sought public opinion on this issue.

For an overarching view of the debate, please visit http://www.fda.gov/ohrms/dockets/DOCKETS/04n0355/04n-0355-c000005-01-vol1.pdf representing a pro-biosimilars' view and http://www.fda.gov/ohrms/DOCKETS/DOCKETS/04n0355/04N-0355_emc-000004-02.pdf for an anti-biosimilars' perspective. Given below is a list of most of the topics that were discussed at the workshop.

- Manufacturing-related issues: The agency sought feedback on (i) which were the most important aspects of manufacturing that determined the nature of the final product and (ii) which parts of the entire manufacturing process it ought to focus on to determine similarity between the original molecule and the biosimilar.
- Characterization of the biosimilar: The FDA wished to know the capacity of current and promising technologies to characterize biologics and their ability to predict safety and efficacy.
- Immunogenicity of the biosimilar: Does immunogenicity need to be evaluated for a biosimilar and if so, under what circumstances?
- Preclinical and clinical evaluation: Are there conditions under which animal or human studies should be reduced and substituted by bioassays while testing biosimilar products.

Several respondents at the FDA workshop cited a study[5], which appears to reinforce big pharma's views. In this study, Schellekens obtained samples of epoetin on the market in four countries – Argentina, China, India and South Korea – and put them through various physico-chemical and biological tests. When compared with Eprex (the original epoetin from Johnson and Johnson) as a standard, samples had one or more of the following problems: differences in electrophoresis (SDS-PAGE) profiles, presence of unknown impurities, differences in specific activity from what was on the label, protein concentration – and specific activity – that was too high or too low compared to the standard and so on. In addition, samples purportedly from the same batch behaved differently.

I imagine that the biggest reason for these problems was the lack of quality control in the manufacturing *per se* and that the issue of similarity needs to be discussed after this is sorted out. In a separate incident, a sample of streptokinase from India analysed by the National Institute for Biological Standards and Control of the United Kingdom, has been criticized for having no detectable enzyme[6]. If the relevant companies' manufacturing standards were to be improved substantially, most of Schellekens' concerns, and the arguments based on them, might be addressed.

Big pharma has often argued that 'the process is equal to the product'. That is, the exact processes of manufacture and purification of the biologic determines its chemical composition and overall conformation, and therefore only the original innovator company can produce the molecule. It is interesting, therefore, that it was an innovator company, the large biotech company Biogen, that disproved this with its interferon beta, Avonex. Here, two independently developed Chinese hamster ovary (CHO) cell lines produced two interferon products, which were deemed to be therapeutically equivalent and approved by the FDA without extensive clinical trials[7]. An innovator company, Biogen, has been the one to prove that the FDA can approve a product from two different cell lines as the same product.

Overall, however, the FDA seems to have taken a pro-big pharma stand, since even as recently as 2008, it has said that 'the scientific expertise needed to determine interchangeability is at least a decade off, even for the simplest proteins'[8].

Innovator companies and biosimilars

Regardless of their arguments against biosimilars, there are four situations which companies producing biologics (even the original molecules) currently confront, or will soon confront, questions regarding the nature of the manufactured product. First, the manufacturing process involves living cells and is therefore less amenable to control than synthetic chemistry. Just a couple of years ago, up to 40% of the epoetin batch of an innovator company had to be discarded because of misfolded molecules[9]. This means that even regular bio-manufacturing needs constant quality control to ascertain that the product is what it is supposed to be. Second, innovator companies periodically improve their manufacturing process. Each time they do so, they have to convince the FDA of the similarity of the resulting product to the original and it is unlikely that they will argue in favour of extensive clinical trials at every change. Third, in a recent and ironic development, it appears that innovator companies plan to become major players in the area of biosimilars[8]. In case, the regulatory pathway that is ultimately approved in the US is similar to that in Europe, the process for approval is likely to be almost as detailed and lengthy as that for the original molecule, and therefore a company producing biosimilars, in addition to strengths in manufacturing, will also need expertise in clinical trials. Additionally, since the generic players are used to dealing with the Office of Generic Drugs, and this office is unlikely to be handling biosimilar applications, it will take separate expertise to deal with the regulatory authorities for biosimilars. Finally, given the varying opinions over biosimilars, special sales efforts will be needed to convince physicians of the inter-changeability with the original biologic. The expectation, therefore, is that it will take the deep pockets usually associated with innovator companies to go through the entire process of getting biosimilars to the market and to patients, and generic companies may find it too much of a challenge.

So far innovator companies have strenuously argued as to how it is impossible to substitute an original molecule with a biosimilar. One wonders whether the arguments will be tempered as they start producing such molecules themselves.

Heparin contamination and atomic-level characterization

Since even the FDA has argued that it is impossible to characterize a biologic in sufficient detail to determine its interchangeability with another company's product, the following case, reported in 2008, is interesting. Baxter had outsourced the manufacture of heparin to a company in China. Suddenly, and inexplicably, patients receiving Baxter's heparin experienced severe allergic reactions and a drop in blood pressure resulting in over 80 deaths. The FDA contacted Ram Sasisekharan at the Massachusetts Institute of Technology (MIT) who is known for his work on carbohydrates. Sasisekharan quickly brought together different academic groups based on their expertise. Using various nuclear magnetic resonance (NMR) techniques, the culprit was soon identified: a contaminant in heparin that they called 'oversulphated chondroitin

sulphate (OSCS)'[10]. Although it is not clear how the impurity entered the heparin batches, it may have been separately manufactured and deliberately added. Studies on pigs showed that OSCS leads to an allergic reaction and drop in blood pressure. What is important for the larger issue of whether or not biologics can be generic-ized is that the scientists were able to make atomic-level determination of the impurity, including the exact nature of the bond linking the two units of the constituent disaccharide.

Conclusion

We have seen that there is a major disagreement over whether or not 'generic' versions of biological therapeutics can be produced reliably enough to become a regular feature in the market. On one side of the argument are ranged innovator companies and pro-big business governments. On the other side are the biosimilar manufacturers, consumers (especially if they have to pay for their medicines, partially or substantially), insurance companies and governments concerned with reducing healthcare costs and with expanding the availability of affordable health care. As more effective biologics treating conditions that affect larger percentages of the population become available, there will be even greater pressure for affordable therapeutics. More controlled ways of producing biologics and ever more precise ways of characterizing them should end the argument where one side claims that 'the process equals the product'. We are already at a stage where it seems to be more a commercial disagreement than a scientific one. Biosimilars should come to be, for more of the world, at ever lower prices.

Note added in proof: In March 2010, the Obama Administration passed a healthcare bill that provides for 12 years of exclusively for original biologics, but that also provides a legal framework to ensure that biosimilars will reach the US market.

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