Paradigms on Biogeneric Drugs - Some views

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Article

The paradigm claimed by brand-name biopharmaceutical manufacturers that “the process is the drug” hence the need for performing clinical trials for introducing biogenerics, is scientifically unsound. It comes to no surprise then, that brand-name biological manufacturers all of a sudden are tremendously concerned on the potential toxicity and potential lower efficacy of biogeneric drugs. This “concern” is traduced in supporting strong regulations including clinical trials, precluding the entrance of competitor drugs in the market despite emerging preclinical and clinical data speak on the therapeutic efficacy and comparable toxicity of biogeneric drugs. Whether all these regulatory affairs for “having effective and safe biologicals” possess a market-driven or a science-driven rationale is a provocative thought, after all, although we must bear in mind that the market of biological drugs will be overwhelmingly superior to that of small-molecule.

Key words: Biopharmaceuticals, biogenerics, paradigms.

Main: Plant-based drugs have been used around the world for thousands of years. Drugs based on chemical synthesis have been with us since the latter half of the 1800s. Now, the era of biologics—genetically engineered protein drugs made in living cells arrived to stay. Recombinant DNA is a form of artificial DNA that is created by combining two or more sequences that would not normally occur together. In terms of genetic modification, it is created through the introduction of relevant DNA into an existing organismal DNA, such as the plasmids of bacteria, to code for or alter different traits for a specific purpose, such as antibiotic resistance. A recombinant protein therefore, is one derived from recombinant DNA technology [1]. The commercial potential of molecular biology and its kindred disciplines was first recognized in the mid-1970s. In the following years capitalist enterprises in the United States and abroad adopted the techniques of molecular biology, a scientific discipline. In the process, molecular biology has transformed an engineering discipline, bioprocess engineering, and spawned an industrial field, biotechnology. Biotechnology as a business arises out of an intersection of the scientific practices of molecular biology—formerly undertaken only in universities — and the engineering practices of biochemical engineering and other technologies necessary to produce biological commodities [2].

One breakthrough in recombinant DNA technology was the manufacture of biosynthetic “human” insulin, which was the first medicine made via recombinant DNA technology ever to be approved by the FDA. Insulin was the ideal candidate because it is a relatively simple protein and was therefore relatively easy to copy, as well as being extensively used to the extent that if researchers could prove that biosynthetic “human” insulin was safe and effective, the technology would be accepted as such, and would open opportunities for other products to be made in this fashion [3]. Thus, the first-generation biopharmaceuticals including insulin are copies of endogenous human proteins, such as erythropoietin (EPO), growth hormones and cytokines. These compounds have revolutionized the treatment of many diseases, including anemia, diabetes, cancer, hepatitis and multiple sclerosis [4]. Biologics now account for 20% of the global drug market, according to market research firm IMS Health. In 2000, only one biologic made the top ten list of worldwide drug sales (Amgen’s recombinant erythropoietin in 4th place). By 2008, five of the top 10 drugs in sales were biologics, and by 2014 biologics are expected to occupy six of the top ten positions, according to EP Vantage [5].

Small molecules or conventional chemical drugs eventually go off patent, as do biologics. This loss of patent protection leads to the introduction of generic drugs, which are usually priced at a small fraction of the cost of the branded drug. These conventional generics are considered to be therapeutically equivalent to a reference, once pharmaceutical equivalence (i.e. identical active substances) and bioequivalence (i.e. comparable pharmacokinetics) have been established and do not require formal clinical efficacy and safety studies. When small molecules lose their patent protection (or their patents are successfully challenged in court), their sellers can lose significant market share within days or weeks when they face a flood of competition from cheaper generic copies. Big Pharma’s solution to the generics issue has been to establish “pay for delay” agreements with generics manufacturers. They pay these companies not to challenge their patents and sell competing drugs, thereby preserving market share. The legality of this practice has come into question, since it is obviously anti-competitive and is designed to
keep prices high for consumers. What about biologics? The barrier to entry in making biogenerics is significantly higher than with small molecules, due to much higher production costs as well as by the legal and regulatory pathways bringing biogenerics to the market. In this regard, the EMEA has forged ahead in providing guidance for national regulatory bodies in Europe. The EMEA guidelines are, however, a work in progress currently being updated (www.emea.eu.int). Some sections of the guidelines are still controversial. For instance, it is stated that comparative clinical trials can be foregone if the biogeneric can be characterized in detail by physicochemical and in vitro techniques, or alternatively that comparative pharmacokinetics (PK) and pharmacodynamics (PD) studies can replace clinical trials. The annex to the insulin concept paper echoes this: efficacy data need not be provided if equivalence can be concluded from PK and PD data. In contrast, the other three concept papers regard comparative clinical studies as a necessity. The emphasis on adequate screening for immunogenicity events is well-warranted, given the incidence of pure red cell aplasia (PRCA). Post-marketing monitoring is an essential component in tracking rare but serious adverse events like these. The guidelines state that immunogenicity analyses should be performed especially in cases where repeated administration is proposed. A useful addition to the guidelines would be to require branding of biogenerics, to allow optimal and accurate pharmacovigilance. Currently, no legal framework exists in the US for the approval of biogenerics, and the FDA has released no guidance documents. The EMEA has provided a valuable base for EU legislation to evolve from. However, if we wish to ensure patient safety with the arrival en masse of biogenerics to the market, it is imperative that their unique characteristics be recognized. Accrued experience will then allow regulatory authorities to optimally match guidelines to the genuine risks and benefits associated with biogenerics.

In contrast to generic versions of small molecules or conventional drugs which are introduced onto the marketplace without doing clinical trials, running clinical trials are required for biogenerics prior to approval, thus raising the bar higher to keeping out competitors. Even if biogenerics do make it onto the market, they will not be priced as cut-rate bargains like traditional small-molecule generics, because the biologics will cost more to manufacture, and develop. Partly because of their higher prices, biogenerics are predicted to capture much less market share than small molecule generics. As a result, makers of biologics will be much less concerned than makers of small molecules about a potential loss of revenue once the patents expire on their molecules. The main question, therefore, is whether there is genuine interest based on scientific arguments or whether this is solely in the interest of just obey to economical interests of Big Pharma to keep competitors out by raising the bar higher for entrance into the market.

**Paradigms:**

1. The active substance of a biopharmaceutical is a collection of large protein isoforms and not a single molecular entity, which is generally the case with conventional small-molecule drugs. Thus, it is highly unlikely that the active substances are identical between two products.

2. Small changes in, or differences between, manufacturing processes may have a significant impact on the quality, purity, biological characteristics and clinical activity of the final product. Even when biogenerics are produced from the same genetic construct, using the same technique, formulation and packaging as the innovator product, there is no guarantee that they will be comparable with the reference product. Structural differences between proteins may arise for a number of reasons, including oligomerization, modification of the protein primary sequence, glycosylation patterns or the conformational state.

3. The primary safety concern for biogeneric agents is their potential immunogenicity. Although these proteins are designed to closely mimic human proteins, they have the potential to induce an immune response, especially when administered as multiple doses over prolonged periods.

**Facts:** The manufacturing process for biopharmaceuticals is several orders of magnitude more complex than that for small-molecule pharmaceuticals. Conventional pharmaceutical agents are small-molecule chemicals with a defined molecular weight typically between 100 and 1000 Da. In contrast, biopharmaceuticals are large, complex and heterogeneous proteins with more variable molecular weights, commonly ranging from 18 000 to 145 000 Da. Compared to the manufacture of small molecular entities, the manufacture of biopharmaceuticals requires a greater number of batch records (>250 versus <10); more product quality tests (>2000 versus <100); more critical process steps (>5000 versus <100) and more process data entries (>60 000 versus <4000). The molecular size and complexity of biopharmaceuticals and their production in living cells makes the final product very sensitive to changes in production conditions. Changes may occur to the
expression systems used for production, culture conditions (e.g. temperature and nutrients), purification and processing, formulation, storage and packaging. Taken from Shellekens[24,25].

Despite it is beyond doubt that the manufacturing process are different between a conventional chemical drug and a biogeneric [24,25], there is no convincing evidence that current analytical techniques are unable to establish biopharmaceutical equivalence neither in information in most recent techniques for characterization and purification of recombinant proteins has been critically analyzed by brand-name manufacturer supporters [6-16]. The following paragraphs are taken from a statement made by Theresa L. Gerrard TLG Consulting Inc. Committee on Oversight and Government Reform Safe and Affordable Biotech Drugs — The Need for a Generic Pathway, in March 26, 2007 [17].

Every biological product is subjected to rigorous analytical testing. The same would hold true for biogenerics. Analytical testing consists of multiple tests that are used to assess the physical, chemical and biological characteristics of the product. Many more tests are used to assess a biologic than are typically used to assess a drug. This battery of tests is conducted for every batch of biopharmaceutical product manufactured and is also used to monitor the product during the manufacturing process. In the field of biopharmaceuticals both the Food and Drug Administration (FDA) and industry rely on analytical testing to ensure consistency so that every batch of the biopharmaceutical will be deemed safe and effective for its intended use.

Many biologics, including almost all of the biotech products, can be now defined by chemical and physical attributes. This fact can be attributed to two scientific advances. The first is the increasing purity of biological products, especially recombinant biotech products. The production of human proteins through recombinant technology continuously improves, providing ever more highly purified human proteins. The second advance is the increasing sophistication of the analytical technology that allows a very detailed characterization of these products. Although the cells that are used to produce biopharmaceuticals are complex living organisms, all finished biopharmaceutical products used to treat patients are highly purified human proteins that are produced consistently using advanced manufacturing technologies. The large array of sophisticated analytical tools that exist today now allow for the characterization of biopharmaceuticals to ensure safety and efficacy.

The advances in analytical characterization and the ability to assess the specified or well-characterized biologics by analytical tests allowed FDA to develop scientific policies on comparability in the early 1990s. These policies gave brand manufacturers the ability to change the manufacturing process without the need for clinical trials if the new product was shown to be comparable to the previous product. Prior to this time, every change in a manufacturing process necessitated the need for new clinical data. It was the innovator biotech manufacturers who pressed FDA for this change, because they rightly claimed that their biopharmaceuticals were so well characterized. They proved this through their ability to identify potential product changes with analytical testing technology.

The brand companies fought for these policies because the need to make manufacturing changes for biotech products was common and manufacturers wanted to make changes to the manufacturing process without the need to repeat clinical trials. FDA agreed that the nature of the products allowed manufacturing changes to be assessed predominantly by analytical testing for characterization. In fact, and this is a critically important point, FDA recognized that analytical testing was far more sensitive in the ability to detect product changes than a typical clinical trial. For the past 15 years, manufacturers of well-characterized biopharmaceuticals have been able to make manufacturing changes without repeating clinical trials if they demonstrate that the product made after the manufacturing change is comparable to the product made before the change.

It is therefore at least surprising that now, brand-name companies of biotechnological medicinal products point on the need of performing clinical trials for biogenerics to demonstrate efficacy and safety. If it is assumed to be true (that small differences in the process require clinical trials to demonstrate equivalent therapeutic efficacy), then the same would apply for “innovator” products as small changes in the process of manufacturing are likely to occur, as well as potential changes on subsequent steps (storage, transport, etc) occurring from the process of manufacturing until the product is administered to the patient. Nevertheless, the regulatory processes favor the “reference” product. In fact, the commonly cited example of the impact of variability between biological products on safety is the large increase in the incidence of Antibody-mediated PRCA (Pure Red Cell Aplasia) that occurred between 1998 and 2003 in chronic renal failure patients using the reference epoetin alfa Eprex® marketed by Johnson & Johnson [17-20].

There is no reason for giving by granted that the “reference” product is free of immunogenicity or any
other potential serious side-effect therefore identical regulatory issues and quality testing should be applied to reference and biogeneric products particularly when the reference biological has been evaluated in distinct populations. Although any two humans are 99.9% identical at the nucleotide sequence level many phenotypic differences are apparent in individuals within the same and from distinct human populations. Genetic diversity underlying the remaining 0.1% nucleotide differences has been postulated to contribute to phenotypic diversity among humans, and to population-specific susceptibility to disease and variability in the response to pharmacological treatments [21-23].

So far, there are several biogenerics approved or in clinical trials. These include a number of epoetins and granulocyte-colony stimulating factors, interferons, activated factor VII, and ready-to-use liquid formulations of human growth hormone. Against all concerns, all these products have demonstrated safety and efficacy with no unexpected adverse events, comparable to the reference biological product [26-44].

**Conclusion**

Brand-name biological manufacturers that essentially are the same that develop “small-molecule” drugs all of a sudden are tremendously concerned on the potential toxicity and potential lower efficacy of biogeneric drugs. This “concern” is translated into supporting strong regulations that preclude the entrance of competitor drugs into the market despite that emerging preclinical and clinical data speak of the therapeutic efficacy and comparable toxicity of biogeneric drugs. Whether all these regulatory affairs for “having effective and safe biologicals” derive from a market-driven or science-driven rationale is a provocative thought; after all, one should be reminded that the biologicals market is going to be overwhelming superior to that of the small-molecule. The following paragraphs taken from “The Scientist” journal is an straigthforth evidence for thinking on the issues raised before.

Manufacturers say they need the longer protection to earn a profit on biotech drugs, which can take over $1 billion and a decade to bring to market. Generic companies say waiting that long would discourage them from developing competing products and would keep drug prices high. The lobbying battle has so far been one-sided. That dominance is partly due to a huge disparity in money, according to the nonpartisan Center for Responsive Politics and the Senate Office of Public Records. Representing biotech companies, the Biotechnology Industry Organization has spent $3.7 million lobbying so far this year. Their ally, Tauzin's association of drug makers, has spent $13.1 million — the second most of any group that lobbies in Washington. The main group opposing them, the Generic Pharmaceutical Association, has spent $1.1 million lobbying this year. Another group, a coalition of generic drug companies, insurers and large employers, has spent another $180,000. Individual biotech companies like Amgen are also easily outspending their generic rivals such as Teva Pharmaceuticals USA, Inc. The one-sidedness extends to campaign contributions, too. The biotech organization contributed $192,000 to federal candidates in the two-year 2008 election cycle, the pharmaceutical association $155,000. The generic association: $51,000 [49].

What appears to be clear is that Big Pharma has the advantage in this game, not to mention that in addition to tight regulations, this leaves little room for competition by domestic pharmaceutical industries, particularly within developing countries. This kind of legislations discourages local research and development, increases drug importation, and decreases local self-reliance in dealing with disease.

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