Biogeneric drugs: Ready or not here they come

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SMALL MOLECULES AND BIG MOLECULES

Therapeutic compounds can be divided into two broad categories: small molecules, which comprise most of the traditional drugs, and biologics. Biologics include medically important substances like erythropoietin (Epo) for treating anemia, Humulin (recombinant insulin) for diabetics and Interleukins for treating Parkinson's disease. This class of therapeutics is also economically important; in 2000 the worldwide market for biologics exceeded $ 12b (Wood Mackenzie, Pharmaceuticals, Feb 2002) and had grown 33.5% from the previous year.
Small molecules, which include chemical substances like aspirin, and psychotropic drugs like Prozac, are typically chemical compounds that are synthesized in the laboratory in a precisely controlled way by a defined sequence of chemical reactions. The nature of these molecules is such that once they are made their exact structure and composition can be determined by sophisticated laboratory tests, ensuring that if a manufacturer sets out to make a precise molecular copy of fluoxetene (Prozac) they can know with certainly whether or not they have succeeded.

BIOLOGICS ARE FUZZY

Biologics on the other hand cannot be made in this way. In most cases, manufacture of biologics relies on engineering live cells growing a laboratory to produce the material of interest and then purifying and characterizing that material. There is an increasing number of sophisticated assays and tests that can be done to characterize the structure, composition and activity of a manufactured biologic. But, unlike with small molecules, these tests by themselves do not guarantee the clinical effectiveness or safety of a biologic. The reason is that while the synthesis of small molecules can be completely controlled to yield a precisely defined entity, the cell-based synthesis of biologics is much more difficult to control. Subtle alterations in cell growth conditions, nutrient supply, and host cell origin can make a significant impact on the composition of the end product.
In some cases the impact may be so great that the assays used to test the manufactured material will pick it up immediately. Sensitive bioassays will reveal if the molecule is not fully active, and precise sizing tests can readily determine if it is smaller or larger than normal. In other cases however, the molecule may appear normal in all of the standard quality tests, but still have a problem. This is possible because there are many important features of a biologic, such as its precise three dimensional shape, or the detailed pattern of sugar molecules added to it during production, that cannot be easily determined. In the case of sugar molecule addition (called glycosylation) for example very subtle alterations in the pattern of addition can have profound effects on whether the manufactured entity is viewed by the immune system as friendly or foreign when administered to a patient.

BIOLOGICS ARE APPROVED ALONG WITH THEIR MANUFACTURING PROCESS

Luckily, the fact that such subtle alterations cannot be easily detected is not typically a problem for biologic manufacturers. This is because manufacturers go to great lengths to ensure that every batch of biologic made is manufactured in precisely the same way, and in the same place, as the last batch. Indeed, review and approval of the manufacturing process and facility as well as the controls used to ensure consistency is an integral part of getting a biologic approved by the FDA. Thus, one might say that for biologics adherence to strict manufacturing protocols becomes a substitute for the rigorous determination of structure and composition that is possible for small molecules.
This procedure works fine of you are the inventor of the manufacturing process, and you know the details and subtleties of your specific biologic. The FDA requires you to have already manufactured a substantial supply of your biologic before you test it in humans, and will have to approve the facility and the process of manufacture. Moreover, they will have to approve the battery of tests to be done to prove that each batch of biologic you make is as much like the last as possible. The principal is that if you have a defined process, and you use the material from that process in a clinical trial and it works then the process and the output of that process and the manner of testing that output are deemed acceptable.

BUT THERE IS SOME FLEXIBILITY

Significantly, if you are the original manufacturer, you can even over time change some of the details of the manufacturing process to improve them or make them more convenient, as long as you prove to the FDA that by the approved quality control tests the new substance is identical to the old. In one case the FDA even allowed a company to move the manufacturing process from one cell line and manufacturing facility to another when *in vivo* human data demonstrating pharmacokinetic equivalence but not efficacy was presented. (Biogen, Avonex).

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EVERYTHING GOES OFF PATENT

This all has the appearance of a well run system. Define how you will determine the identity and activity of your biologic and adhere to a rigid manufacturing protocol and keep talking to the FDA about any changes you wish to make. What's the payoff for all this effort? Sales of the top three biologics exceeded $ 5b in 2000. What keeps biologics manufacturers up at night? Look at what generic manufacturers did to the sales of Lilly's blockbuster drug Prozac whose sales fell more than 70% in 2002 due to the introduction of generic knock-offs. The biotechnology industry has good reason to worry about the scenario of a generic manufacturer producing a duplicate biological molecule, using sophisticated tests to show that it is the same as the original, and then referencing the original manufacturers clinical tests to demonstrate efficacy.
This last part hasn't happened yet for two good reasons. First only a few biologics have gone off patent (including Abbott's Urokinase, AZs and HMRs Streptokinase, and most recently, Schering-Plough's Intron A, and Biogen's Avonex, interferon beta 1a). Second, for those that have there are currently no unambiguous FDA guidelines on how generic manufacturers should approach approval beyond starting from scratch with a new full blown and expensive clinical trial, a process which would reduce but not eliminate the cost savings associated with a generic.

GLOSSARY

ANDA
Abbreviated new drug application. To obtain an ANDA, the sponsor of a generic must show a complete set of chemical, manufacturing and control data demonstrating analytical comparisons to the innovator product.
As the ANDA process simply enables the generic maker to incorporate the innovator's clinical results by reference, the generic manufacturer also must demonstrate bioequivalence, which in this case is interchangeable with therapeutic equivalence, and is defined as the same rate and extent of absorption as the innovator compound when administered at the same molar dose under the same conditions. For an ANDA, this is normally achieved through a PK/PD study in about 30 healthy volunteers.

Biologic
Generally drugs or therapeutic materials including antibodies, hormones, enzymes, and growth factors, produced by a living organism.

Hatch Waxman Act section 505(b)(2)
The Hatch-Waxman Act, which established procedures for the approval of generic drugs, does not apply to products regulated as biologics, but FDA has suggested that it interprets the law to permit generic versions of biologics that are regulated as drugs. The ANDA requirements establish a base onto which the agency could require varying amounts of additional preclinical and clinical data.
To address follow-on biologics under its purview, the Center for Drug Evaluation and Research (CDER) has been contemplating the use of section 505(b)(2) of Hatch-Waxman, which allows a company to supplement the conventional ANDA with data from scientific literature and/or clinical data. A 505(b)(2) application allows a new applicant to use previous FDA rulings of safety and efficacy for a previously approved drug product without requiring the new applicant to have the permission of the original applicant. The new applicant must also provide any additional clinical data necessary to demonstrate the safety and effectiveness of the new generic drug in relation to any differences between it and the original drug.

CONFLICTING VIEWPOINTS

It is at this juncture that multiple interest groups are converging to do battle. The FDA has issued statements that suggest that it may be amenable to some form of abbreviated approval process for generic biologics, following the principles of the Accelerated New Drug Approval (ANDA) process currently used for small molecule drugs that go off patent. The FDA has also indicated that this new process may take advantage of section 505(b)(2) of the Federal Food Drug and Cosmetic Act (FDCA) which allows FDA applications to reference data and material to which they do not necessarily have access. Such material could include for example the safety and efficacy data filed by the original manufacturer of the biologic. The implication is that if (and this is a big if – see below) a new manufacturer can prove that they're manufacturing the same entity as the original manufacturer, they could simply reference the safety and efficacy data of that manufacturer for the original material which is in the hands of the FDA and seek approval without having to conduct lengthy and expensive clinical trials.

BIO WEIGHS IN

Understandably, this is a scenario that has set the biotechnology industry and in particular its association, the Biotechnology Industry Association (BIO) howling. Pioneer manufacturers of biologics would face the same threat to their monopolies and economic well being that manufacturers of small molecule drugs now face. BIO has recently submitted a 67 page petition to the FDA (BIO Citizen Petition (21CFR 10.30) Follow-on therapeutic proteins) objecting to recent statements made by the FDA about generic biologics and requesting public hearings to review the process by which follow-on or generic biologics must be approved.

NOT DIFFERENT BUT NOT THE SAME

The arguments presented in this petition are many and complex but center on one important element. They challenge the application of 505(b)(2) to biologics by stating that for biologics specifically the agency lacks the authority to rely on one sponsor's data in support of another's application. The reason for this is that 505 (b)(2) requires that new therapeutic molecules first be shown to be identical to the pioneer molecules which they mimic. BIO's petition makes the statement "Because of the scientific complexities of therapeutic protein products it is virtually impossible to isolate much less compare, the active ingredients of two of these products." A statement that might well cause considerable anxiety in patients who rely on these products for their survival.
How much truth is there in this statement? If assays that are good enough to document batch to batch identity to the FDAs satisfaction exist, why can't

those same assays be used to certify identity of a new version of the biologic from a different manufacturer in a different manufacturing facility? The FDA has already answered this in principle in approving Avonex manufactured in the US. So what's the big problem?
The problem is that as we noted earlier, biologics are in fact complicated to make and no one really believes that all the assays used to prove batch to batch comparability guarantee molecular identity. Indeed, as noted in the BIO petition "Scientifically, one never demonstrates sameness, rather….the absence of differences according to a set of tests and criteria." Turn the process over to a new group of people in a different plant and even though they may be following the same manufacturing process as the original manufacturer and using the same characterization and release assays there's no guarantee they're making the same thing. Even worse, have the new group make the biologic by a process different from the original and the concerns become even more acute. The complexity of biologics requires a degree of caution beyond that applied to chemicals.

A PATH FORWARD

Some think that it is inevitable that some form of guidance for the manufacture and sale of generic biologics is inevitable. Ken Kaitin, Director of the Tufts Center for Drug Development believes that "..economic and political conditions will force a serious discussion of mechanisms for achieving this" and says that eventually "generic biologics will happen." Support for this belief is expected to come from patient advocacy groups, particularly those with diseases that require costly therapies such as Genzyme's Cerezyme which currently costs about $ 200,000 per year.
Everyone agrees that the prevailing attitude must be one of caution. However, when caution has a major economic impact on the affordability of health care the degree of caution must be evaluated, and creative solutions much be sought.
As noted above the FDA has shown that it can accommodate to complex medical and economic realities. In approving US manufactured Avonex the FDA showed considerable flexibility on one cautionary principal, that of associating manufacturing details with approval, while retaining another, that of manufacturing know how. Is it un-reasonable to ask that if the FDA approved transfer of manufacture to a different site and a new cell line operated by certified manufacturers, that it might also allow transfer of those manufacturing skills from one group to another? And then to yet another site, etc? In fact why not require that the original manufacturer of a biologic whose patent has expired make all the details of the manufacturing process available to those who would wish to manufacture generic versions of the compound? And why not compensate such companies for their effort by extending their patent protection by one year, using the same principle that was applied in the orphan drug act to encourage manufacturers to work for the public good.
All of this assumes that manufacture of generic biologics could be done at significant cost savings, and that there is manufacturing capacity available, both questionable tenets. However, these are economic factors and not legal or regulatory ones. Whether it is practical and economically beneficial to produce generic biologics should have no bearing on the decision to make it legally possible to do so, and in a manner that can best benefit health care consumers and manufacturers alike.
What is the path forward for such approvals? Some have suggested that biologics can be grouped into classes, each requiring different levels of comparability data depending on the expected consequences of subtle alterations in protein structure or modification. The simplest class would be those proteins for which such alterations have been shown to have little or no effect on activity, as in the case of glycosylation of human growth hormone. For this class of biologics only animal studies and human pharmacokinetic data might be sufficient to demonstrate comparability. More complex cases in which minor alterations or differences in composition may compromise activity or induce severe immunogenicity would likely need to be treated as a new chemical entities. Intermediate classes of biologics with correspondingly intermediate levels of comparability data can also be defined. It is just this kind of detailed ranking of potential generic biologics that the pharmaceutical and biotechnology industries need to get involved in as soon as possible.
Who besides the consumer will benefit from such a process? Clearly manufacturers of generics will benefit provided that they can acquire or contract for the facilities needed to manufacture biologics. Given that current estimates indicate that biologic manufacturing capabilities are operating at maximum capacity this suggests that new facilities may need to be built and that companies that do so pro-actively may be in a position to benefit from a biogeneric policy once it is approved.

CONCLUSION

Each of the stakeholders in this discussion have important contributions to make to its resolution. However, each must also avoid taking positions that polarize the discussion, exaggerate consequences or minimize hurdles. The FDA must tackle the problem head on but must involve the manufacturers of existing biologics as well as those who hope to manufacture biogenerics. BIO should step back from the legal nit picking which is the prevailing theme of its Citizen's Petition and focus squarely on helping to develop workable guidance for the industry. Finally, advocates for biogenerics must take a realistic and scientific view of the challenges involved in making biogenerics. Statements like those of Roger Williams, executive vice president and chief executive of U.S. Pharmacopeia who is quoted as saying "What do you think about a 747 – pretty complicated, right?... Do you think somebody could make a 747 beyond Boeing? Of course they could" (http://www.mult-sclerosis.org/news/Dec2000/BiotechDrugsPatents.html) add little to resolving a complex and important issue.