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Biogenerics in Developing Countries: *Biotech Boom or Misguided Development Model?*

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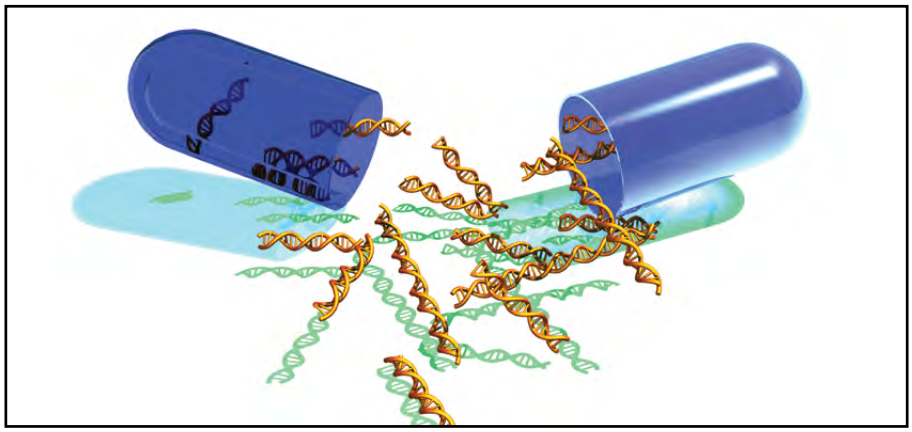

Several developing countries, including India and China, have young biopharmaceutical industries that have based much of their growth potential on the production of what are currently known as "biogeneric" products, or "bioequivalent" versions of biologics that have already been licensed in Western countries. With a disdain for foreign patents, an established philosophy of copying Western innovations, and success in generic pharmaceutical manufacturing, this approach appeared to be the logical way to build a biologic manufacturing industry. However, there are numerous problems with this development strategy. First and foremost is the inherent incompatibility of the very concepts associated with biogeneric products.

Generic pharmaceuticals have been produced for decades and have fostered a thriving industry in Western economies, as well as other geographic areas that are able to support such technology. With pharmaceuticals, physical equivalence of generic versions can be established by demonstrating basic chemical and structural properties, and abbreviated human clinical trials are typically used to demonstrate functional equivalency to the original, licensed product.

But with biologics, simple chemical and structural equivalency is not sufficient to show bioequivalency. Biologics are heterogeneous products by their very nature, and the numerous molecular variations within a particular product are critical to its pharmacodynamics. For example, many different epitopes in a biologic can vary from molecule to molecule throughout a production lot, and the composition of a batch is known to be quite sensitive to slight changes in the production process. Even the most predictive and sensitive potency assay may not pick up subtle product differences that are known to occur with changes in protocol, or with the use of a different manufacturing location.

Biologics are much more complex and difficult to manufacture than chemically synthesized pharmaceuticals. Whereas highly controlled raw materials, a recipe, and a solid quality program can all but assure the identity and function of a "classical" small molecule pharmaceutical, a biologic has many more production aspects that can significantly affect its suitability. For example, the cell line and expression system are critical variables that help define the product.

Cell lines are not only transfected to make them more stable, but they are also typically genetically altered to enhance or define specific performance. And even stable cell lines can change over time or population doublings, and any such change can dramatically alter the resulting product. This is one reason that post-production testing is used to demonstrate cell stability and functionality after the last of the product has been harvested.

The expression vector and technology are also critical, and very small differences in their application and efficiency can result in dramatically different cellular expression levels and batch heterogeneity. In addition, biologic raw materials are far more numerous and often less defined than those used for pharmaceuticals. For instance, animal-sourced materials are especially variable from lot to lot, and can significantly affect product composition, impurities, and safety. Cell culture media are made from many chemicals, and often contain protein additives. Although much work is being done to develop standards and testing protocols for raw materials, assuring consistency among production lots remains a serious challenge.

Of increasing concern is the matter of product immunogenicity. Slight changes in the process, raw materials, or product handling can result

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in product lots that are highly immunogenic. Therefore, immunogenicity assays are now being required for more product types, and must be developed earlier in the development process.

As product characterization techniques evolve, companies are learning more about their products, including how heterogeneous their products are and how sensitive they are to minor changes in the production process. FDA documents often imply, or even state, that "the process is the product," which we are learning to be more true by the day. Improved techniques are allowing companies to analyze chromatographic peaks previously thought to be artifacts, and are finding that these peaks may provide important information for defining the effects of slight process changes. So much data is being generated that the developers must now ask, "How much of this new data should I show the regulators, how much should eventually become part of the release specification, and would new data prompt the regulators to require additional clinical work?" On the other side, regulators are seeking this new data to better understand what is being discovered and compare product data submissions.

Even with all the additional data, bioequivalence (i.e., product comparability) is a more elusive goal than once thought. So far, characterization has not proven sufficient to eliminate the need for human clinical data when critical process or manufacturing location changes are made. Even if chemical and structural aspects of the product are equivalent to those of the original product, functionality cannot be adequately determined with existing means. The potency assay will have to be reevaluated and dosing will have to be reestablished.

When a product is made in a different facility, whether owned by an innovator company or a contract manufacturer, bioequivalency issues must be addressed. Even with extensive technical transfer to assure that the process, assays, cell line, and raw materials will be as identical as possible, extensive validation is required to make sure the transferred technology can be repeatedly reproduced. In addition, some clinical trials will be required to make sure the product is equivalent to the one that is already licensed.

What Exactly *is* a Biogeneric Product?

"Biogeneric" is typically meant to describe a product that is equivalent to a licensed product, and is produced without the collaboration of the organization that produced the original product. Such a product requires the manufacturing process to be reverse engineered with whatever information may be available. Certainly, piecing together the process and assays from presentations and papers would leave significant gaps that must be filled in through experimentation. But reproducing a similar cell line and expression construct would be far more difficult, and would require a serious research program. It is hard to imagine that such a product could be licensed without extensive clinical trials, since it would be nearly impossible to show bioequivalence through characterization alone.

If lengthy research, development, and clinical evaluation are needed, then I have a hard time understanding how such a product could be compared to a generic pharmaceutical, or why it would be called a "biogeneric." I would consider this to be a new, but similar, product that is intended for the same indication, or possibly a "bio-similar" product.

Companies enter the biogeneric business to produce a low-cost product without incurring the development and clinical trial costs associated with an innovative new product, and to obtain market share by selling the product at a price substantially below that of the original product. If this new product incurs significant development costs and requires clinical trials, then the advantages typically enjoyed by generic pharmaceutical manufacturers no longer apply and the business model no longer makes a lot of sense.

And there are other problems. For example, once an innovative company has licensed a product, it often starts the process of developing the follow-on, or next-generation, product. By the time a biogeneric product can be developed, the next-generation product may be ready for launch, and would further erode any price advantage a lower-cost bioequivalent product might offer.

Furthermore, companies that rely on copying the products of other firms seldom build their own product development capability and become innovative. Western firms will be reluctant to invest in these companies, or to transfer technology to them, since they fear the loss of intellectual property and the threat of direct competition.

An Alternative Business Model

Some of the more enlightened developing countries are putting significant resources into developing biotech industries, and are adopting more pragmatic business philosophies. One of the biggest driving forces for change is the 1994 World Trade Organization (WTO) Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPs). Under TRIPs, some developing countries were given ten years, or until January 2005, to implement patent protection for biopharmaceutical products. While still excluding certain products, this agreement could help Western companies gain the confidence they need to expand their activities in developing countries.

In addition, some countries are becoming more open to foreign investment, and are allowing foreign firms to make larger investments in their companies. Coupled with better patent protection, this change will encourage more Western firms to establish manufacturing agreements and transfer more technology. In other words, there will be far more opportunities and incentives for Western firms to build facilities, invest in companies that already have facilities, and set up either co-manufacturing or contract manufacturing agreements.

Instead of trying to copy the products of other companies, biotech firms could be manufacturing licensed Western biopharmaceuticals for use in clinical trials, and eventually as approved products. While many products will initially be produced for local markets or a single regulatory authority, manufacturing sites could provide products to other developing regions, and possibly Western countries as well.

To support this growing manufactur-

ing base, there will be an enormous need for a wide range of contract services such as testing, fill-and-finish, clinical trial management, marketing, regulatory affairs, and distribution. As more of a technological base is developed, money will eventually be channeled into contract development, translational research, and ultimately, basic research in the more advanced university systems.

With this business model, developing countries can capitalize on where they currently offer the most value — specifically lower land costs for facility construction, plus lower labor costs for validation, testing, and production. Eventually, these benefits also will become evident for product development and basic research.

Once the infrastructure has been put in place for manufacturing and development, then the biotech industries in developing countries will be ready for true innovation in which they develop their own products.

However, for innovation to take place, major changes are needed for many government ministries, regulatory agencies, and universities. Some progress is already being made to harmonize regulatory requirements among the agencies of various governments, and some countries are starting to reorganize their university systems to make them more competitive for industry research funding, and to make them more conducive to entrepreneurial endeavors. As witnessed in the United States, private universities, such as Stanford in Palo Alto, CA, have been successful in stimulating innovation among their faculty, and in encouraging the formation of private ventures.

Finally, some developing countries are quickly developing Western-style stock markets and venture capital communities, which are making vital funding available to start-up firms. Still, investment and collaboration by Western companies will provide the best means through which their biopharmaceutical industry can grow.

Summary

The "biogeneric" business model does not make sense for developing countries. Biologics are far more complex than pharmaceutical products, and even slight process changes require clinical trials to prove bioequivalence. Then, when a biogeneric manufacturer has to reverse engineer the process and assays, plus attempt to duplicate the cell line and expression system; the cost of research, development, and clinical evaluations erase the advantages typically enjoyed by generic pharmaceutical companies.

Products that require significant development and clinical evaluation should be thought of as similar, but nonetheless new products for the same indication. The term "biogeneric" is truly a misnomer when it is compared to "generic pharmaceutical."

The TRIPS Agreement and more relaxed restrictions on foreign investment will make a more pragmatic business model available for developing countries to develop a biopharmaceutical industry. To become innovative, firms will have to develop intellectual property protection for their own products and respect the international patents of other companies. This action will encourage Western companies to invest money and transfer technology. Manufacturing growth will be through co-manufacturing and contract manufacturing, as well as corresponding growth in the services that support biotech manufacturing.

With the harmonization of regulatory requirements, Western firms will be encouraged to conduct more clinical trials in other geographic areas, plus produce and test the products locally for these trials.

Eventually, Western money will also be channeled into translational and basic research. However, many university systems will have to be reorganized so that they promote innovation and encourage entrepreneurial endeavors. Private university models in the United States have been particularly successful at this.

With manufacturing and service infrastructure in place, and a supportive university system, companies in developing countries will then be more capable of developing their own products.

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Business Model for Developing a Biotech Industry

Focus on Strengths

- Inexpensive labor
- Well-educated technical workforce
- Relatively inexpensive land and building materials
- Established information technology industry
- Large populations for clinical trials

Satisfy Needs of Established Companies to Build Infrastructure

- Clinical trial management
- Manufacturing capacity
- Lower cost manufacturing
- Lower cost testing services
- Regulatory affairs and coordination
- Distribution and marketing
- Lower cost process development and research

Focus on Products That Make the Most Sense

Product Type	Devel. Stage	Leading Issues	Strength
Viral Vaccines	Mature	• Efficacy (Trials) • Cost	• High • High
Antibodies and rProteins	Late Stage	• Comparability • Capacity	• Low • High
Viral Gene Vectors	Early Stage	• Characterization • Potency	• Low • Low
Cell Therapies	Infancy	• Defining Product • Everything	• Low • Low

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*Assumes an average yield of 1 x 10^5 cells/cm^2 from a 100% confluent culture. Yields may be significantly higher or lower depending on the cell line and culture conditions used.

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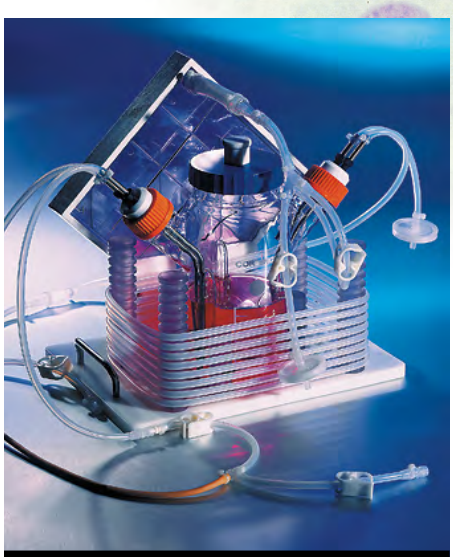
- **Cell yields from 6.3 x 10^7 to 2.5 x 10^9***



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