NEXT GENERATION OF BIOSIMILARS AND BIOBETTERS
CHALLENGES AND OPPORTUNITIES
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CHALLENGES AND OPPORTUNITIES

The biopharmaceutical market is a rapidly growing class of therapeutics, showing significant potential in oncology, diabetes and other disease areas. Unlike conventional chemically synthesized pharmaceuticals, biopharmaceuticals—also known as biologics—are derived from living organisms, typically using biotechnology.

Examples of biologics include hormones, blood products, cytokines, monoclonal antibodies (mAbs), and vaccines, as well as gene transfer, cell therapy and tissue engineered products.

There are more than 300 mAbs, more than 250 vaccines, and more than 100 other biologics—including cell and gene therapies—currently in clinical development. The global biologics market is expected to reach around $291 billion in 2020 and by 2022, 50 percent of the pharmaceutical market share is expected to be in biologics.

But the future of biologics won’t be focused solely on the discovery of new therapeutics. There is also a significant market for biosimilars, biologic drugs that demonstrate high similarity to an already approved biologic reference drug, and can in turn serve as an alternative to it. Biosimilars are different than generics, which are synthetic chemical copies of their reference drugs and are identical in active ingredients, strength, dosage form and route of administration.

Because biologics are made with living cells and no two molecules can be exactly the same, making a copy of a biologic is a much more involved and expensive process than creating a generic drug. There will always be very subtle differences between the biosimilar and its reference biologic.

There are significant benefits to biosimilars. Biosimilars are a more cost effective way to manufacture biologics, increasing the affordability of life-saving biologics to patients.

They could also increase worldwide regulatory approvals, including with the U.S. FDA. The Patient Protection and Affordable Care Act was signed into law by President Barack Obama on March 23, 2010, amending the Public Health Service Act to create an abbreviated approval pathway for biosimilars that are considered “highly similar” with an FDA-approved biological product.

It is expected that by 2030 the biosimilar market will be a greater than a $240 billion opportunity, as patents on major biologics continue to expire.

To be approved, biosimilars need to prove a high degree of similarity in biophysical properties, safety and effectiveness to the marketed reference product. The agent must demonstrate no meaningful difference in immunogenicity and pharmacokinetic/pharmacodynamic (PK/PD) outcomes in a well-designed clinical trial. However, lower immunogenicity and better safety are acceptable.

Challenges facing the biosimilar market

Despite its potential in cost savings, the biosimilar market still faces hurdles. There are gaps in
knowledge and understanding of biosimilars among the public, and that can lead to challenges with physicians and patients’ perception of the safety and efficacy of the product.

Worldwide there is also a high variability in regulations regarding the approval of biosimilars. In Europe, the regulatory pathway and litigation procedures are much clearer and more defined. In the U.S., however, there are very broad IP and patent laws, which can make patent infringements a major obstacle in effective marketing. This can impact patient access and increase cost.

Health plans and pharmacy benefit managers (PBMs) can also contribute to increased costs, as some require high rebates that block biosimilar access and uptake. Finally, multiple companies also often compete to make the same biosimilar of a biological drug that has recently come off patent, causing stiff competition across the market.

Overcoming these obstacles

To stand out from the competition, companies that make biosimilar products can consider lowering prices or offering high rebates to PBMs. However, this approach is best suited in developing countries with high price sensitivity. In more established markets for biologics, such as the U.S., Europe and Japan, pricing alone isn’t sufficient, as there typically isn’t significant price variety among similar therapeutics.

It is also possible to attempt to differentiate the molecule itself by providing better tolerability. However, regulatory agencies will not typically allow bio superiority to be claimed on a label on a biosimilar product.

One potentially effective way to differentiate a biosimilar is through a novel delivery device or container closure system, which improves convenience, ease of use or patient acceptability of the therapeutic from its reference product. Some design differences in the delivery device or container closure system used with the proposed biosimilar product also may be acceptable for regulatory approval of a biosimilar.

For a proposed biosimilar product in a different delivery device or container closure system, the presentation must be shown to be compatible for use with the final formulation of the biological product through appropriate studies including, for example, extractable/leachable studies and stability studies.

For certain design differences in the delivery device or container closure system, performance testing and a human factors study may be needed.

“Biobetters”

Enhancing a biosimilar with an improved or more convenient delivery system is not the only way to differentiate a product.

Highly differentiated biosuperior drugs, known as “Me-Betters” (after the term “Me-Too” drugs used to describe two highly similar therapeutics) are needed to serve patients who have increasingly become resistant to current therapies/standard of care.

These “Me-Betters” or “biobetters,” are new biologics based on an existing approved biologic. Biobetters can deliver the mechanism of action of potency improvements, enhanced half-life, better safety and immunogenicity, and better and broader efficacy.

These biobetters may serve high unmet medical needs more rapidly than a novel therapeutic, as they often receive shorter review and more rapid approval with better reimbursement.

There are numerous biosimilars and biobetters in development today.

Despite its potential, the biosimilar market still faces hurdles.

MAJOR BIOSIMILARS AND BIOBETTERS IN DEVELOPMENT

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Source: Biotechnology Information Institute
OPPORTUNITIES FOR BIOSUPERIORS: REDUCE DEVELOPMENT RISK BY FOCUSING ON CLINICALLY VALIDATED TARGETS*

> $1 Billion  $100-300 M  $300 - 1000 M  > $1.5 Billion

Development risk with increasing cost

**Innovator**
- anti-Receptor A
- Receptor A
- Clinically validated target and therapy

**BioSimilar**
- anti-Receptor A
- Receptor A
- No innovation from marketed product

**BioSuperior**
- More protein engineering
- New lead, different epitope, effector function, drug/toxin conjugate, size of molecule
- Innovation in context of original therapy and interface

**Novel**
- anti-Receptor B
- Receptor B
- Target or modality without validation

* Clinical validation of MOA: Positive POC clinical data

MAKING OF INNOVATIVE BIOSUPERIORS

Applying Best Science + Antibody Technologies

mAb (+YTE)  ADC: Ab-drug conjugate  Single-chain immunotoxin  Bispecific Ab

Ab mimetic  T cell  BiTE

Agonist/antagonist mAb  Internalized Ab  Blocks protein synthesis

Release of cytotoxic drug  Induction of T Cell Killing  Enhanced ADCC

Target cell

Next Generation of Biosimilar and Biobetters: Challenges and Opportunities
**Biobetter strategy**

Biopharmaceutical companies have focused on several strategies to develop biobetters. They are only working with molecules that have mechanisms of action (MOA) that are clinically proven or have a proof-of-efficacy that has been established and where addition values can be gained. They are focusing on areas where there are unmet medical needs within a known class of agents, where current drugs or their biosimilars do not already serve well.

They aim to create biobetters where current agents are inadequate to treat refractory patients, relapsed patients, or those that have inconvenient dosing systems or safety concerns. To do this, they are focusing on application of best science and antibody technologies to create highly differentiated and potent biologics within the same general MOA as already established agents.

**Biobetters may serve high unmet medical needs more rapidly than a novel therapeutic.**

**Pros and cons of developing biobetters**

There are several positive outcomes from creating a highly differentiated biosuperior drug. Unlike with a biosimilar, there is generally no need to wait for patents to expire because all biobetters are treated as new molecular entries from a regulatory perspective.

Despite these benefits, developing biobetters does come with challenges. As compared to biosimilars, the regulatory process will be longer and more expensive, as the agent is treated as an entirely new entry. As a result, clinical development cost may not be too dissimilar to innovative drug development.

Biobetters also face fierce challenges for demonstrating superiority in efficacy or safety against established biologics and market leaders, and unless the benefits are superior to biosimilars, the higher costs of biobetters may be questioned. It can be complex to establish biosuperiority, and not every attempt at doing so will be successful.

One example of an extremely successful biobetter is Humira (adalimumab), an immunosuppressive drug used to treat arthritis, plaque psoriasis, ankylosing spondylitis, Crohn’s disease, and ulcerative colitis and other diseases. Humira works by binding to tumor necrosis factor-alpha (TNFα), which normally binds to TNFα receptors, leading to the inflammatory response of autoimmune diseases.

Humira was the third TNF inhibitor, after infliximab and etanercept, to be approved in the U.S. A “biobetter” of the two agents, it was constructed from a fully human monoclonal antibody, which was an improvement over infliximab, a mouse-human chimeric antibody, and etanercept, a TNF receptor-IgG fusion protein.

Humira resulted from collaboration between BASF Bioresearch Corporation and Cambridge Antibody Technology (CAT), which became MedImmune in 2007. The key to Humira’s discovery was the “phage display” method discovered at MedImmune. As of 2017, the drug has made more than 18 billion in the U.S.

One example of an extremely successful biobetter is Humira, an immunosuppressive drug.
Conclusion

Biosimilars have tremendous potential to reduce the high cost of biologics and increase the affordability of biologics medicines. However, there are still barriers to the market’s success on the large scale, including patent limitations and legal challenges, a fractionated market, high discount expectations from PBMs and physician and patient acceptance.

For innovation companies, highly differentiated and technologically advanced biobetters offer the greatest potential to mitigate the risks associated with the introduction of biosimilars, as they can be approved before the patent expires and have blockbuster potential. However, strategy is key, as long development time, high cost, and uncertainty in biosuperiority over existing drugs can hinder the success of a biobetter agent.

For innovation companies, highly differentiated and technologically advanced biobetters offer the greatest potential to mitigate the risks associated with the introduction of biosimilars.
ABOUT THIS TECHNICAL PAPER

This technical paper is adapted from a webinar sponsored by Dassault Systèmes and presented by Advantage Business Marketing.

The webinar featured Rakesh Dixit, PhD, as the speaker, who is an expert in the field of biologics from Medimmune and who presented his insights on the future of the transformative biologics market and helped navigate the webinar discussion.

Laura Panjwani, the R&D Editor with Advantage Business Marketing, served as the moderator.

Rakesh Dixit, PhD, has more than 30 years of experience in the biopharmaceutical drug industry, including at Merck, Johnson & Johnson and Medimmune. At his current role as the Vice President of R&D and Global Head of Safety Assessment-Translational Sciences, at Medimmune, Rakesh is responsible for providing guidance on research and development of biological products, including nonclinical toxicology/safety support for all AstraZeneca-MedImmune biologics products, including monoclonal antibodies and vaccines. Rakesh has published more than 60 papers in renowned international journals and has given over 100 invited lectures, presentations and workshops at national and international meetings. Rakesh is one of the most commonly invited speakers in the biotechnology industry.

Laura Panjwani is the editor of R&D Magazine and rdmag.com. She has broad experience in science journalism, previously serving as a writer/editor for OncLive, a publication for oncologists, and for Water Online, a news website for water and wastewater engineers. She also worked in traditional media for several years as a reporter for The Asbury Park Press and as a copy editor for The Star-Ledger, both in New Jersey. Laura graduated from Michigan State University with a B.A. in journalism in 2009.

The full webcast can be viewed here: https://event.webcasts.com/starthere.jsp?ei=1192416&tp_key=1cd32f57f1