

WHITE PAPER

AN OUTLOOK ON US BIOSIMILAR COMPETITION

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INTRODUCTION

The pharmaceutical industry is experiencing change in ways it hasn't ever before. On the demand side, we are seeing an aging population, increased prevalence of "Western" diseases, and a dramatic growth in global access to pharmaceuticals. On the supply side, we are seeing increased competition from emerging market players, and a shift in the way drugs are being developed, manufactured, and delivered. Meanwhile, policy makers are struggling with an inherent conflict between desire to provide improved access to better medicines and the need to curb the growth of healthcare expenditures.

One topic at the center of all of these changes is the US biosimilars market. Biosimilar products will offer competition to some of the most expensive drugs on the market, but also require high investment. The promise of biosimilars in the US is to provide cost savings, increase patient access, and promote innovation. And despite being a market still void of any entrants, the US biosimilars market continues to attract attention.

From a global perspective, the US lags behind other regulated markets, specifically the EU, in terms of biosimilar competition. Some products considered biosimilar in other regulated markets, such as Sandoz's Omnitrope, gained approval in the US before the biosimilar regulations were created. Most recently, Teva's Neutroval, known as the biosimilar Tevagrastim in the EU, received US approval under the 351(a) or BLA route. Since companies have the option between approval routes, the non-regulatory term follow-on biologic is used as a catch-all for non-innovator biologic products yet to be defined by US regulations.

In 2011, the Thomson Reuters white paper 'What You Need to Know about the Follow-On Biologic Market' in the US provided insight on regulatory, competitive and deal making activity in a market still taking shape. Two years later, we have a bit more clarity about the likely players and regulations that will affect this market, although much uncertainty remains.

As a follow up to the 2011 paper, this report will provide updates and changes associated with biosimilar regulations in the US. Additionally, the paper will identify requirements for success, and the likely early entrants in the US market.

REGULATIONS

The decision by the Supreme Court of the United States to uphold the Patient Protection and Affordable Care Act (PPACA) in late June of 2012 put to rest many questions surrounding the future of the US biosimilars market. Title VII of the PPACA includes the Biologics Price Competition and Innovation Act (BPCIA) which amends the Public Health Service Act (PHSA), creating the regulatory framework for an abbreviated approval process for biologic products in the US. Biosimilar applications can be submitted under section 351(k) of the PHSA. As of February 2013, no biosimilar applications had been received by the FDA, although we believe that work is underway to submit applications

Throughout 2012, several regulatory developments in the US, such as FDA draft guidance documents and user-fee legislation, showed continued progress in the yet-to-form biosimilar market. This section of the report provides insight on sections of the Biosimilar User Fee Act (BsUFA), a general overview of the information included in the three FDA draft guidance documents, and analysis as to what additional developments can be expected to emerge in the short term.

BPCIA AND GUIDANCE

The BPCIA grants the Secretary of Health and Human Services the option to create guidance with regard to licensure under the 351(k) approval pathway. The law states the Secretary must provide opportunity for public comment before issuing final guidance. In February of 2012, draft guidance documents were released pertaining to scientific and quality considerations in demonstrating biosimilarity to a reference product. A third document, focused on providing insight on the implementation of the BPCIA through relevant questions and answers, was released along with the other two documents.

In August of 2011, leadership from the FDA authored an article published in the New England Journal of Medicine which suggested an evaluation method that would rely on employing multiple methods of assessment, and integrating all available data to build a full understanding of biosimilar applicants. Guidance pertaining to scientific considerations further echoed this expectation, stating the FDA intended to use the “risk based, totality-of-the-evidence approach,” an existing concept focused on considering evidence supporting effectiveness of a biologic in its entirety.

SCIENTIFIC CONSIDERATIONS

According to the guidance released by FDA, in the United States a stepwise approach should be used by sponsors to demonstrate biosimilarity between a proposed product and a reference product. Assessment of both the proposed and reference product with regards to structural and functional characterization is necessary for comparison. Sponsors should make use of multiple studies to effectively show differences in relative attributes between the two products. Identifying clinically meaningful differences will provide regulators with the data to be used when deciding if and which additional studies may be required. An appropriate number and selection of lots should be used for analysis of both the proposed and reference product. Additionally, analysis of the proposed product should include lots used for both clinical and commercial purpose.

Biosimilar product development programs will be evaluated by the FDA on a case-by-case basis due to the unique and complex nature of the products and the specific factors that may affect biosimilarity. Biosimilar product sponsors are advised to meet with and present a development plan to the FDA. Meeting early in the development process can provide opportunity for sponsors to understand evaluation expectations and create a schedule for future discussions.

QUALITY CONSIDERATIONS

The draft guidance for quality considerations focuses on protein products and defines a protein as “any alpha amino acid polymer with a specific defined sequence that is greater than 40 amino acids in size.” Among the factors manufacturers should consider when assessing if the proposed and reference product

are highly similar range from the expression system used, to the stability of the two products and include comparative physiochemical and functional studies. Similar to the scientific evaluation, various methods of analysis that employ appropriate levels of sensitivity and specificity should be used to characterize the quality of both reference and proposed products.

Issues addressed by the Questions and Answers document include acceptable variations between the proposed and reference product with respect to formulation, delivery device, routes of administration, presentation, and condition(s) approved. Regarding extrapolation, a biosimilar applicant may use clinical data in one condition of use to support approval in other conditions. Animal and clinical data using a biologic product not licensed in the US can be used as supporting evidence demonstrating biosimilarity between a proposed and reference product.

BIOSIMILAR USER FEE ACT

Of course, the implementation and execution of biosimilar application evaluation has a significant cost. Since the review process for biosimilars is much more comprehensive than small molecule generic drugs, additional resources must be employed to ensure 351(k) applications are processed in a timely manner. Similarly, it is important to ensure sufficient resources exist in the review process so the addition of 351(k) applications will not impede the evaluation and approval of biologics license applications.

Effective October 1, 2012 through September 2017, BsUFA is expected to generate the necessary revenue to fund 351(k) evaluation. The fee rates for applications, supplements, establishments and products are based on those included in the Prescription Drug User Fee Act (PDUFA).

Biological project development (BPD) fees are comprised of an initial fee, an annual fee, and a reactivation fee if the product sponsor has discontinued development and wants to resume participation. Biosimilar product sponsors have the first five days after being granted a BPD meeting by the FDA or upon IND submission to pay the initial fee. Initial fee amount is 10% of the PDUFA fee for an application requiring clinical trials, the same amount of the annual BPD fee. The annual fee exists until the sponsor either submits an abbreviated BLA or decides to cease product development. FDA is required to spend \$20 million in federal funds before it will be able to collect or spend fees from biosimilar applicants.

The FDA has promised to provide timely evaluation and facilitate clear expectations through targeting meetings to help maximize development program success. Performance goals for the FDA to review biosimilar applications will help ensure the resources allocated through BsUFA fees are meeting expectations. According to FDA, by 2017 90% of original and resubmitted biosimilar biological product applications will receive review from the FDA within 10 and 6 months of receipt date, respectively.

12-YEAR EXCLUSIVITY PERIOD

Exclusivity was one of the most publicized topics of debate during the design of the abbreviated approval pathway. Much of the debate focused on identifying an appropriate length of time that would

- Provide innovator companies incentive to develop new therapies
- Offer patients affordable medicine

What has complicated matters more is that the process of identifying exclusivity is designed differently to the data and market exclusivity model associated with US small molecule competition.

Under the BPCIA, no application submitted under the 351(k) pathway can be approved until 12 years after the reference product is approved. Only after 4 years of reference product approval can a 351(k) application even be submitted. The BPCIA does not describe these periods of exclusivity as “data exclusivity” or “market exclusivity”, although they have been described by many in the industry as such. In the small molecules arena, data exclusivity is associated with the New Chemical Entity exclusivity of five years, which bars any NDAs from being referenced. Market exclusivities, such as those granted for orphan drugs and pediatric extensions, typically limit the approval of any applicants relying on a reference product.

Semantics aside, the debate over defining the exact limits of the 12 year period is being continued in a new venue. In mid-September negotiations continued regarding the Trans-Pacific Partnership (TPP), a free

trade agreement between the US and several nations, including Australia, Chile, and Singapore. After 14 rounds of discussion, leaders have yet to define provisions related to biologics and data protection. The significance of how these provisions will be defined is twofold. First, more detail regarding exclusivities of products approved with biologic licensing applications may affect commercial strategies of 351(k), or biosimilar, applicants. Second, and perhaps more significant, the agreement may limit the ability of US lawmakers to amend relevant sections of the BPCIA in the future. TPP negotiations are scheduled to continue in December 2012.

API	Brand Name	FDA will not accept biosimilar applications before	FDA will not approve biosimilar applications before
Adalimumab	Humira	31/Dec/2006	31/Dec/2014
Bevacizumab	Avastin	26/Feb/2008	26/Feb/2016
Canakinumab	Ilaris	17/Jun/2013	17/Jun/2021
Cetuximab	Erbitux	12/Feb/2008	12/Feb/2016
Darbepoetin Alfa	Aranesp	17/Sep/2005	17/Sep/2013
Eculizumab	Soliris	16/Mar/2011	16/Mar/2019
Epoetin Alfa	Epex	25/Feb/2003	25/Feb/2011
Etanercept	Enbrel	2/Nov/2002	2/Nov/2010
Infliximab	Remicade	24/Aug/2002	24/Aug/2010
Natalizumab	Tysabri	23/Nov/2008	23/Nov/2016
Palivizumab	Synagis	19/Jun/2002	19/Jun/2010
Pegfilgrastim	Neulasta	31/Jan/2006	31/Jan/2014
Ranibizumab	Lucentis	30/Jun/2010	30/Jun/2018
Rituximab	Rituxan	26/Nov/2001	26/Nov/2009
Trastuzumab	Herceptin	25/Sep/2002	25/Sep/2010
Ustekinumab	Stelara	25/Sep/2013	25/Sep/2021

FIGURE 1: THE BIOLOGICS PRICE COMPETITION AND INNOVATION ACT GRANTS APPROVED BLAS WITH 12 YEARS OF MARKET EXCLUSIVITY.

INTERCHANGEABILITY AND NOMENCLATURE

Interchangeability and nomenclature are areas which have yet to be fully addressed by the FDA. Under the BPCIA, products deemed interchangeable will be biosimilar to the reference product, produce the same clinical result as the reference product in any given patient, and show no increased risk in terms of safety or diminished efficacy when switching between reference product and interchangeable product. Future guidance is expected to answer questions regarding safety and quality considerations for interchangeable products.

Despite the lack of guidance for these products from the FDA, some state legislatures are already addressing the substitution policy for interchangeable biologics. Virginia recently passed legislation that grants pharmacies the authority to substitute products deemed interchangeable by the FDA, but only if the prescriber or patient do not say otherwise. Pharmacists must inform patients before dispensing the biosimilar product and also track both the brand/product name and biosimilar manufacturer¹.

Bills in Illinois, Pennsylvania, Texas, North Dakota and Indiana are at various stages of the legislative process that speak to dispensary permission². Further debate is anticipated regarding interchangeable products and substitution policy, both at the state and federal level. Two bills putting limits on the dispensary of biosimilars at the pharmacy level were rejected by the Mississippi state legislature. Biologics manufacturers Amgen and Genentech have proposed the bills to limit interchangeable competition³.

The debate regarding nomenclature challenges establish standards in other regulated markets and patient safety considerations. In the EU, biosimilars currently use the same international non-proprietary

name (INN) as their respected reference product; a system the Generic Pharmaceutical Association believes should stay constant in the US⁴. Conversely, the Biotechnology Industry Organization (BIO) and Pharmaceutical Research and Manufacturers of America (PhRMA) believe unique names for biosimilar products rather than shared INNs will ensure the appropriate pharmacovigilance⁵.

The World Health Organization, during an INN Consultation meeting in October 2012, addressed challenges associated with nomenclature and biosimilar competition. The INN Committee offered consideration for policy changes, including distinguishable non-proprietary names for biologic products, a move that gained support from Amgen⁶.

In late November 2012, the Alliance for Safe Biologic Medicines (ASBM), whose members include Genentech, Amgen, and BIO, released the paper “It’s all about the name: what is the imperative of adopting a unique names for biologic and biosimilar therapeutics?” which provided insight to the ASBMs views on the topic of nomenclature for biosimilars approved in the US. In the report, considerations included the recommendation that interchangeable products should receive distinct non-proprietary names⁷.

REGULATIONS PERTAINING TO CLINICAL TRIALS

Although the FDA’s draft guidance documents for biosimilar approval expand on the BPCIA, there is residual ambiguity concerning product-specific considerations for clinical trials. In contrast, the EMA’s long-standing and comprehensive approach to biosimilar approval delineates clinical trial pathways for each product under their established guidelines. This allows for pre-Clinical Trial Authorization development programs and clinical trial phases to move forward in an efficient and stepwise manner. While the United States employs a similar “stepwise” approach, the lack of documented guidance beyond a general framework necessitates an elaborate collaboration between the sponsor and the FDA during trial development.

Scientific Considerations in Demonstrating Biosimilarity to a Reference Product provides guidance suggesting comparability studies, particularly in safety, efficacy, and immunogenicity, in order to establish biosimilarity between a proposed product and a reference product. Pharmacokinetic studies, and pharmacodynamic studies if there are relevant measures, are suggested as the main comparative assessments between the reference product and the proposed product. The FDA recommends that if pharmacokinetic, pharmacodynamic, or immunogenicity studies fail to show confident similarity, then efficacy and safety studies should be considered. Head-to-head immunogenicity studies are suggested across the board, however the FDA advice is absent as to the time course and assays necessary for each product class. Of particular importance is that the proposed product does not have a higher activity which results in an increased immunogenicity as compared to the reference product; or a lower activity which could result in inferiority.

Overall, the broad scope of the FDA’s draft guidance documents for biosimilar approval provides minimal advice for trial pathways as compared to the EMA. These documents rely heavily on the sponsor to anticipate necessary measures in protocol development and encourage a hand-in-hand approach with the FDA leading up to Investigational New Drug approval and clinical trial operations. In this respect, abbreviated program development may prove difficult; particularly because the FDA’s position is that there will not be a “one-size-fits-all” assessment for products across all classes.

This “totality-of-the-evidence” approach fails to guide a sponsor through product-specific trial design and implementation as thoroughly or explicitly as the EMA guidelines. As an increased number of sponsors attempt to enter the US biosimilar market and the number of pre-Investigational New Drug development programs are in the works, higher trial design costs and delayed Abbreviated Biologic License Application approvals (due to additional information the FDA may require if the submitted trial data was insufficient) may not allow for a truly abbreviated process.

One point illuminated by the FDA’s draft guidance that may allow US sponsors to circumvent trial design barriers is the acceptance of foreign comparative data. EU guidelines will be changing in early 2013 to allow foreign reference data eliminating the need for redundant and costly generation of reference data in clinical trials. The FDA draft guidance documents suggest that non-US licensed products may be used in comparability studies, if an appropriate bridge can be built to a US licensed reference product. Although

it is unclear as to what this bridging data should consist of, it appears that with this, the FDA is moving towards the global harmonization of the biosimilar approval process. With interchangeability not currently being considered by the FDA, marketing strategies for US biosimilar entrants may have to take into account whether foreign-derived clinical trial data will be a discouraging factor in a physician's decision to prescribe one biosimilar over another. From a marketing standpoint, those with US-based clinical data may have a competitive edge.

GLOBAL REGULATIONS AND HARMONIZATION

Similar to the US, many other markets are establishing regulations for biologic competition with hopes of health care cost containment and increased patient access. While economics and public health realities drive the establishment of abbreviated pathways, safety and efficacy remain at the forefront of discussion. Policy makers will consider domestic needs and global standards to ensure appropriate regulatory requirements. Although strict regulations imply higher cost, the opportunity to bridge studies across different regulatory bodies may incentivize regulators to design biosimilar regulations that are harmonious with those in the US and EU.

In late June, India adopted guidelines for an abbreviated pathway similar to those in the EU. The policy, titled Guidelines on Similar Biologics, uses the term 'similar biologics' to refer to those approved under the abbreviated pathway. Pre-marketing requirements include comparability studies, as well as pre-clinical and clinical studies. China too has moved towards acceptance of biosimilar products. The Chinese State Food and Drug Administration is expected to release regulation on drug registration, and with it, guidelines for biosimilar medicines. Similar to India and other major markets, the push for biosimilar products in China stems from a desired increase in cost savings and patient access. Currently, any similar version to a biologic product must gain regulatory approval in China through the new drug approval process⁸.

As emerging markets align their biosimilar regulations with those of the EU, WHO, and US, it is expected global competition will increase. Until there is regulatory harmonization across all major markets, there will still be opportunity for competition to exist in markets where regulations are less strict. These markets will attract competition from companies that may be able to develop biosimilar versions of biologic products but do not have the means to successfully compete in more regulated markets. Competitors in these markets may also develop products that would not meet the safety and quality standards of more regulated markets. Additionally, companies may commercialize follow-on biologic products in less regulated markets with hopes to attract opportunity to compete in heavily regulated markets later on.

TAKE AWAYS

- Lack of clarity in US regulations is slowing down the development of the biosimilars market
- Significant regulatory costs associated with developing biosimilars – user fees, requirement for clinical data
- Permission to use foreign reference data should reduce the regulatory barriers somewhat

COMPETITIVE LANDSCAPE

Due to the complexity of biologic products and similarly complex regulatory requirements, the biosimilars market requires a combination of capabilities, experience, and capacity which many generic companies are without. This reality has required companies looking to compete in the biosimilars market to either increase in-house capabilities in areas where they currently fall short, or find them elsewhere, often through deal making. As such, the competitive landscape in the biosimilars market will not be aligned with the small molecule market, where the line between innovator and generic companies frequently is quite clear. Instead, the biosimilars market will be filled with additional competitors, including biotech companies and hybrid innovator-generic partnerships.

Likely early entrants in the US market will have access to biologic manufacturing capabilities, experience with running clinical trials, experience in regulated markets, and a strong understanding of relevant intellectual property.

BIOLOGIC MANUFACTURING CAPABILITIES

With small molecule generics, a merchant market exists for active ingredients, which offers a choice among many external suppliers. In the case of biologics, this kind of merchant market does not exist. So, companies need to figure out whether to make the substance in house or enter into a partnership. Either way, competing in the biosimilars market will require an investment to gain access to biologic manufacturing capabilities (BMCs). For many companies interested in biosimilars, this may be the most daunting hurdle due to the high cost associated with commercial scale biomanufacturing. Since the development and manufacturing of biologics requires capabilities not often associated with chemically synthesized therapies, companies currently without BMCs have to decide the scale of manufacturing required to meet demand. Most biological manufacturing efforts happen at the lab, pilot, or commercial level. As the desired output quantity increases from one level to the next, the capabilities required to process the product changes. When quantity level increases, so does the cost and investment risk.

Over the past decade, competitors have gained access to BMCs by either building a new facility or deal making. Many innovator companies have invested heavily in building biologic manufacturing sites across the globe, but especially in Asia. Since 2010, Genentech, Lonza, GlaxoSmithKline (GSK), Novartis, and most recently Amgen have all committed to building commercial plants for biologic drugs in Singapore. Asian players such as Kemwell, Samsung, and Genor Biomanufacturing have also invested in building BMCs of their own.

Contract manufacturing organizations (CMOs) provide opportunity to companies without BMCs that are unable to build their own facility, but interested in competing in the biosimilars market. CMOs with experience in biologic production such as Lonza and Boehringer Ingelheim can fill gaps in capabilities throughout the entire development and manufacturing process. Even companies with limited BMCs may leverage CMO opportunity to scale up production to a commercial level.

Companies most likely to successfully compete in the US market will either already have access to BMCs, or be able to invest in either building their own facility or acquiring through a deal.

CLINICAL TRIAL EXPERIENCE

Under both US and EU pathways for biosimilar approval, comparative clinical trials are required to show biosimilarity. Given that clinical trials, especially in later phases, are very expensive, this makes biosimilars a risky endeavor.

According to Sandoz, a leader in the EU's biosimilar market and currently in Phase III trials for US approval of filgrastim and pegfilgrastim biosimilars, the cost of biosimilar development can range from \$75 million to \$250 million. This is extremely high compared to the \$2-3 million needed to develop small molecule bioequivalent drugs. However, even at \$250 million, the costs of this abbreviated pathway remain much less than the cost of going the full BLA route which is estimated at \$800 million⁹.

Despite the availability of an abbreviated pathway, the possibility of requests for extended or repeated trials by the FDA may decrease the expected cost savings and cause inexperienced companies to consider the exclusivity benefits of a BLA. The FDA's nonspecific ABLA guidance may be a major consideration when companies are strategizing approval pathways for biosimilars. In 2010, Teva's biosimilar version of Roche's rituximab was delayed in Phase III trials by the FDA's request for additional data. Teva's competitors have taken advantage of this delay and moved forward with trials for their own versions of rituximab. Although this occurred prior to the release of the FDA's draft guidance documents, ambiguity remains in the clinical trial pathway, and it may continue to drive the cost of biosimilar development upwards.

In the short term, it appears that cost barriers in the biosimilar market may be overcome by Big Pharma entrants. Companies with the financial capability are willing to take the risk and the list is likely to include those who pioneered the EU biosimilar market. Teva, Roche, Merck, Sandoz, Hospira, and Celltrion are currently conducting global clinical trials for biosimilar candidates. Smaller pharmaceutical companies are partnering to gain a foothold in the biosimilars market. Indian firm Biocon has partnered with US-based Mylan in a \$33 billion deal to develop a biosimilar version of Roche's Rituxin amongst other biologics that are coming off patent. Meanwhile, Roche's Herceptin is being targeted for biosimilar development by a collective effort from Synthon, Amgen, and Actavis; with big names Amgen and Actavis (formerly Watson) assuming responsibility for Phase III clinical trials.

Inexperience may prove to be another barrier for biosimilar development in the US. Clinical trial program development for biological products requires specialty knowledge that those not previously in the market may find daunting. Immunogenicity, rare adverse events, and efficacy are all factors to take into consideration when developing a biosimilar and they can be affected by even the slightest change to a biologic product's molecular design or manufacturing process. Thus, both the EU and the US agree that no 'clinically significant differences' should be detected in comparative studies between a biosimilar and its reference product.

To overcome the knowledge hurdle, companies in the biosimilars arena are partnering with Contract Research Organizations (CROs) and health organizations who have experience with designing and conducting biosimilar clinical trials. Hospira has recently partnered with DaVita, Inc. and Fresenius Medical Care in an effort to efficiently conduct Phase III trials for its biosimilar erythropoietin across 200 hemodialysis centers across the U.S. In 2011, Samsung Biologics partnered with CRO giant Quintiles to develop clinical trials for their biosimilar venture. In turn, Samsung Biologics, with Quintiles in tow, entered into an agreement with Biogen Idec; combining biologic and business expertise to form Samsung Bioepis. Recently, Samsung Bioepis has signed on to develop and conduct clinical trials for Merck's upcoming biosimilar candidates in a move that seeks to overcome the clinical trial barriers present for biosimilar entry¹⁰.

Companies with global experience in biosimilar development, and particularly those who have previously obtained biosimilar approvals under the EMA guidelines, will likely exhibit a competitive advantage in the US biosimilars market. Having already been molded by the EMA guidelines, these pioneers may have an advantage in navigating the murky U.S. approval process, including the steps necessary to overcome cost and experience barriers and move forward with clinical trials. Currently there are several companies running large-scale, global clinical trials who will likely become major players in the US biosimilars market.

MARKET EXPERIENCE

Another barrier to biosimilar market entry is associated with established market presence. In the US, biosimilars do not receive automatic substitution like generic drugs, so uptake will have to rely heavily on pricing, patient and physician education, and marketing. While companies with experience in launching a brand product in regulated markets will have a leg up on those that do not, it is expected companies that have current biosimilar launches in other regulated markets could have the likely success.

For many of the innovator companies entering the US biosimilars market, this barrier could be minimal, as long standing relationships with physician and patient groups can permit access to educate decision makers on their biosimilar therapies. Big Pharma companies such as Pfizer and Amgen also have access to marketing budgets due to their novel drug programs. This experience can be used to gain a competitive advantage against competitors without brand recognition or US marketing experience.

Companies with biosimilar market launches outside of the US will bring a unique experience to the US biosimilar competition. Major generic companies with regulated biosimilar launches such as Sandoz, Teva

and Hospira could have a competitive advantage over companies that have only launched in less regulated markets. Currently, Teva has regulated market launches of both an EPO product, as well as a filgrastim product in the EU, as do both Hospira and Sandoz. Human growth hormone product somatropin, considered a biologic in the EU, has competition from both Teva and Sandoz.

Competitors that have only launched follow-on biologics in less regulated markets will benefit from understanding distinctions between different market expectations. Both Dr Reddy's and Ranbaxy have multiple less regulated follow-on biologic launches, as well as small molecule generic regulated market launches. Many other strong generic companies from India are claiming follow-on biologic development, but few may successfully compete in regulated markets in the short term.

The strongest competitors will be able to bring experience in all areas of market experience. There are few that have all attributes required to successfully overcome the marketing barrier, but deal activity could continue to create opportunity for more. Biologics innovator Amgen's partnership with Actavis brings together the strong brand recognition and biologic market establishment of Amgen with the generic market understanding and savvy of Actavis.

Companies that enter the US biosimilar market initially will have the chance to become an established competitor and a gain benefit in the long term. Celltrion, the first mover in Korea's monoclonal antibody market, will likely have an advantage against future competitors due to brand recognition.

PATENT EXPERIENCE

The patent challenge process for products BLA approved products, along with the biosimilar pathway, has yet to be tested in the US. Without an understanding of the realities of the process, uncertainty still surrounds the topic within the industry. The patent exchange process has been scrutinized due to the requirements for biosimilar applicants to share sensitive information with competitors. This type of exposure is not familiar to generic companies accustomed with the paragraph IV patent challenge process.

Although there are many differences between the patent challenge process for products approved under the BLA and NDA routes, the experience gained by companies involved with paragraph IV patent challenges is likely to help rather than hurt. Through December 2012, Teva leads the list of groups with the most patent challenges on record with 169. Amgen biosimilar partner Actavis ranks second with 132, with Mylan rounding out the top three with 131 challenges. Novartis, the parent company of Sandoz, is fourth overall with 125 patent challenges on record¹¹.

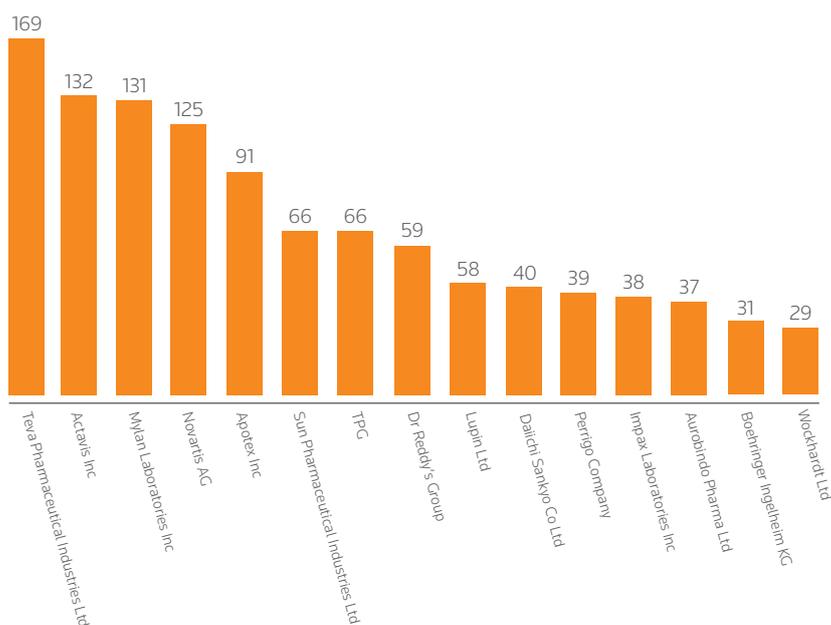


FIGURE 2: GROUPS WITH THE MOST PATENT CHALLENGES ON RECORD THROUGH DECEMBER 2012

Intellectual property experience isn't limited to understanding the patent landscape of a specific reference product or patent litigation. Owning patents associated with a biologic product, such as a process patent, can be a strong indicator of which companies have strong IP capabilities, but also which companies are future competitors in the biosimilar market.

Currently, multiple non-innovator companies hold process patents for potential biosimilar targets rituximab, etanercept, trastuzumab and adalimumab. Two Indian based companies, Avesthagen and Zydus-Cadila Healthcare Ltd, hold process patents for trastuzumab, as well as each holding a process patent for etanercept and rituximab (respectively). Chicago based Therapeutic Proteins International holds process patents that cover rituximab, trastuzumab and etanercept. Sandoz also holds a process patent for rituximab.

LIKELY EARLY ENTRANTS

The list of companies that will successfully compete in the US biosimilars market in the short term is limited due to the high barriers associated with capabilities and experience required. The existing competitors have invested heavily both internally and externally to fill the gaps in capabilities and experience, and it is expected that other companies will do the same as the costs to enter decrease. As the biosimilars market becomes more established in the US, the number of companies will increase as long as there is enough financial incentive to compete.

In the short term, the list of products that will be targeted for competition will also be limited. It is expected the US biosimilars market will include competition for both recombinant protein and monoclonal antibody products. Because of both regulatory and patent expiry timelines, as well as challenges inherent with manufacturing, recombinant protein biosimilars will most likely be the initial products to have biosimilar competition in the US market. That being said, many companies entering the biosimilars market have committed to the development of MAb biosimilars such as rituximab, trastuzumab and adalimumab. The most successful biosimilar companies will be able to compete in both recombinant protein and MAb biosimilars.

RECOMBINANT PROTEIN COMPETITION

Companies, such as Hospira, are already developing biosimilar versions of recombinant proteins. Similar to monoclonal antibodies, biosimilar versions of recombinant protein products are also challenging to manufacture and require high levels of investment. Unlike monoclonal antibody biosimilars, some regulated markets, such as the EU, already have experience with biosimilar versions of recombinant proteins like erythropoietin (EPO), filgrastim and human growth hormone. Hospira is currently in late stage trials for an EPO product for the US market and has a biosimilar filgrastim launched in both the EU and Australia.

Innovator companies such as Amgen, based in Thousand Oaks, CA, are taking steps in anticipation of biosimilar competition. The company announced a plan to stop manufacturing its anemia product Epogen next year. Epogen is currently manufactured in Building 20 at the company's Longmont facility in Colorado, which will become idle after a 12 month increase in production of the active ingredient. With the building remaining idle, manufacturing can resume if necessary. Epogen loses US patent protection in 2013, and competition is expected by biosimilar versions of epoetin alfa as well as class competitors such as Omontys (peginesatide) from Affymax. Teva's G-CSF product Tbo-Filgrastim, a rival for Amgen's Neupogen, received FDA approval in mid-August. Under BPCIA, Tbo-Filgrastim will receive 12 years of exclusivity before any biosimilar version of the product can be approved, because it was approved as a BLA. Under the terms of a settlement agreement reached with Amgen in July 2011, Teva may launch Tbo-Filgrastim by November 10, 2013, almost 4 years after it first submitted its BLA for the product in November of 2009¹².

Since Teva's G-CSF product will not be a biosimilar, competition in the filgrastim market may be unique, especially if an interchangeable version of Neupogen eventually competes. Companies will employ different strategies based on pricing and marketing to build success and drive revenue for their biologic product. Teva may also try to gain a competitive advantage through differentiating delivery devices used with biosimilar products¹³. The FDA permits variation in delivery device used for biosimilar products to provide opportunity for improved and innovative products.

Although Biocon and Pfizer discontinued their partnership for insulin products¹⁴, the Indian based biomanufacturer is still developing similar biologics (EPO, filgrastim), insulins (glargine, lispro, aspart) and is a leader in developing novel biologics products as well. In 2012, Biocon entered an agreement with Bristol Myers Squibb for a novel insulin product (IN-105) currently in phase II clinical studies. Biocon's experience with both novel and similar biologic therapeutics offers portfolio diversity that may prove to be a competitive advantage in global markets.

It is expected that companies such as Shainghai Citic Pacific Guojian Pharmaceutical and Shanghai Celgen Biopharmaceutical, both with launched versions of Amgen's etanercept (Enbrel) marketed in China, will continue to be leaders in the domestic market. Novel biologic products are also expected to be a focus for Chinese biomanufacturers for both the domestic and global markets.

MAB COMPETITION

Competition in the short term for biosimilar monoclonal antibodies (MAbs) in regulated markets will most likely be dominated by few companies. Sandoz (Novartis) has been a pioneer in biosimilar competition and will likely be an early entrant in the US market. A phase 3 trial for Sandoz's biosimilar rituximab (GP-2013) in the treatment of patients with previously untreated, advanced stage follicular lymphoma began at the start of 2012 and is estimated to be completed at the end of Q14. Sandoz currently has multiple biosimilars launched in the EU including a biosimilar somatropin and filgrastim. The company will be able to leverage their regulatory and market experience with biosimilars in the EU to be a strong initial competitor in the rituximab biosimilar market.

Boehringer Ingelheim, one of the world's strongest biologic contract manufacturers, has also invested in biosimilar MAb development. A biosimilar rituximab phase III program commenced in 2012 with primary completion is expected in April of 2015. The company has also started trials for a biosimilar version of Abbott's adalimumab (Humira). Adalimumab will be one of the most targeted products for biosimilar competition due to high worldwide sales and approval for multiple indications.

Two infliximab biosimilar applications were submitted in the EU during 2012. South Korea's Celltrion submitted an application for its candidate CT-P13 (Planetra), which finished phase III comparison studies to Johnson & Johnson/Merck's Remicade product for the indication of rheumatoid arthritis in early 2012. Celltrion is also continuing early stage trials for infliximab in the indication of ankylosing spondylitis. Celltrion's infliximab biosimilar received approval in South Korea in late 2012, the first monoclonal antibody to receive biosimilar approval in a more regulated market.

Chicago based Hospira has marketing and distribution rights for multiple MAb products developed by Celltrion, including the infliximab biosimilar. The deal grants Hospira rights to market in the EU, the US, and other North American markets. Hospira has positioned itself to succeed in regulated markets through a diversified portfolio of both licensed products, like those from Celltrion, and in-house programs.

Biologics innovator Amgen partnered with Actavis to develop its own biosimilars. Thus far, the partnership has yielded a deal with Netherlands-based Synthon. Synthon and Actavis came to terms on a global licensing agreement for the Dutch firm's trastuzumab biosimilar. The deal grants Actavis and Amgen global rights to the marketing and manufacturing of Synthon's product. The companies will work together to transition the development of the trastuzumab biosimilar to Amgen/Actavis for worldwide development and Phase 3 clinical trials. Recently Amgen announced plans to launch biosimilar versions of six MAb products starting in 2017¹⁵.

One of the first Indian companies to be associated with follow-on biologic development, Dr Reddy's Labs, has had versions of both monoclonal antibody and recombinant protein products in less regulated markets for over 5 years. Their experiences with follow-on biologics lead to a partnership with Germany's Merck KGaA to develop and commercialize biosimilar products. The two companies will co-commercialize products for the US market, while Merck will take the lead in other markets globally.

Reliance Life Sciences currently has multiple follow-on biologic therapies launched, including versions of filgrastim, epoetin, and interferon products. Additionally, the Indian based company is aiming to compete in the infliximab market with a similar version of Remicade, currently in clinical trials. As with regulated markets, a major driver for competition for biologic products in India and other emerging markets is to

reduce the high cost of biologic medicines. It is reported Reliance's version of infliximab could provide patients up to 50% cost savings¹⁶. Continued competition for biologics is expected in India following the adoption of guidelines regarding the approval process for similar biologics.

Meanwhile, originator company Roche has planned to market its two blockbuster biologics, trastuzumab (Herceptin) and rituximab (Rituxan), at a reduced price to compete with the expected lower-cost similar versions. Roche signed an agreement with Indian manufacturer Emcure permitting the development and manufacturing of both trastuzumab and adalimumab biosimilar for the Indian market. The strategy, similar to that of an authorized generic, can help ensure the brand products retain market share and also increase patient access.

TAKE AWAYS

- The list of early entrants in the US market will include companies with access to biologic manufacturing capabilities, experience with running clinical trials, experience in regulated markets, and a strong understanding of relevant intellectual property
- As the US biosimilars market becomes more established, the risk to enter will reduce and more competition can be expected
- Long term competition will include increased global competition as regulations across markets become harmonized

LOOKING FORWARD

Specific hurdles limit US biosimilar competition, which gives interested parties a clear path to enter the market. Companies with the attributes required to enter the market will still contend with the most challenging barrier, which is uncertainty regarding market expectations. But even here, certain companies can manage the level of risk associated in competing in a market with many unknowns.

Major generic companies Sandoz, Teva and Hospira all have biosimilar market experience in the EU, as well as strong generic market experience globally. Due to their in-house manufacturing capabilities and global brand, it is expected Sandoz will continue to be a leader in biosimilars and one of the first entrants in the US market. Teva's biologic regulatory experience in the US will provide useful in both understanding the FDA's expectations for large molecule products, and perspective on the strategic opportunities between the 351(a) and (k) pathways. The combination of Hospira's market experience and Celltrion's capability makes the partnership one of the strongest for US competition.

The alliance between Amgen and Actavis promises success if Amgen is able to manage the legal and regulatory balance required to be a force both with 351(a) and 351(k) approvals. Samsung Bioepis/Merck could potentially be a strong biosimilars entrant, but perhaps not in the short term. It is likely industry leader Pfizer will be able to leverage brand recognition to be a strong competitor in the short term. Boehringer Ingelheim will most likely be a strong competitor in the biosimilars market.

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