Opportunities and Challenges for Biosimilars: What's on the Horizon in the Global Insulin Market?

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Ninety years after the discovery of insulin, the therapy remains a staple of treatment for both type 1 and type 2 diabetes. Fueled by the growing prevalence of diabetes and the progressive nature of the disease, the insulin market has grown at a healthy 7% annual rate by volume during the past decade. Meanwhile, global insulin sales reached $16.7 billion in 2011, up 12.5% since 2010. U.S. insulin sales in 2011 totaled $8.3 billion, a 14.9% increase compared to 2010.[1]

Today, five main types of insulin are available: regular insulin, NPH, rapid-acting analogs, basal analogs, and pre-mixed insulin. Both regular insulin and NPH are synthetic forms of naturally occurring human insulin. Regular insulin is short-acting human insulin that is meant to cover mealtime glycemic peaks. In contrast, NPH is an intermediate-acting human insulin that is meant to mimic the baseline insulin secretion of the pancreas and is used for basal insulin therapy.[2,3] Insulin analogs are similar to human insulin but have their amino acid sequences altered to provide desired chemical properties. Rapid-acting analogs are bioengineered fast-acting insulins that are absorbed into the bloodstream more rapidly than regular insulin and thus have a faster onset of action. Like NPH, basal insulin analogs provide glycemic control over a longer period of time. However, they have a more stable profile than NPH and are associated with less weight gain and nocturnal hypoglycemia.[4,5] Finally, pre-mixed insulins are pre-formulated combinations of fast-acting and basal insulins, composed of human insulins or insulin analogs. They provide an approximation of basal/bolus therapy with the advantage of fewer total injections.[6]

Insulin analogs are priced higher than regular insulin or NPH.[7] Consequently, many payors encourage the use of regular/NPH by placing them in more favorable drug formulary tiers or on preferred drug lists.

Although some smaller companies sell insulin only in emerging markets such as China and India, three companies dominate the global insulin market in terms of revenue: Novo Nordisk (41%), Sanofi (32%), and Eli Lilly (20%).[1,8] All three participate in the rapid-acting analog market. In 2011, Novo Nordisk, Sanofi, and Eli Lilly achieved rapid-acting analog sales of $3.9 billion, ~$270 million, and $2.4 billion, respectively. Sanofi dominates the basal analog market; 2011 sales of glargine (Lantus) totaled $5.5 billion, nearly four times that of its main competitor, Novo Nordisk's detemir (Levemir). Eli Lilly does not currently market a basal analog, although it has two in development. Novo Nordisk and Eli Lilly are the largest distributors of human insulin (both regular and NPH), with sales of $2.0 billion and $1.3 billion, respectively.[1]

In established markets such as the United States and Europe, Novo Nordisk, Sanofi, and Eli Lilly have enjoyed exclusive marketing rights for their insulin products because of strictly enforced intellectual property laws. However, the dominance of these companies will soon be tested as the patents for their analog insulins begin to expire (most notably, the patent for glargine in 2014–2015).[9] This change opens the door for biosimilar insulins, which are second-generation "copies" of the original insulin products.

IN BRIEF

Biosimilar insulins are likely to enter the insulin landscape as patents for major branded insulin products start to expire in the next few years. Biosimilar insulins have the potential to reduce diabetes treatment costs, increase the accessibility of insulin treatment, and expand the number of insulin brands available for those with diabetes. However, they will have to overcome numerous regulatory hurdles, meet a variety of commercial demands, and effectively confront competition from both established and next-generation branded insulin products before they can succeed on the global market.

Biosimilar Insulins: A Definition

Biosimilar insulins (hereafter called biosimilars or follow-on biologics) are designed to be highly similar to

the original, or reference, insulin product described in a patent.[10] They are analogous to generic versions of small-molecule drugs and are developed by companies other than the reference product's patent holder. Producers of biosimilars use manufacturing techniques that are similar, but likely not identical to, those used by the original patent holder. Thus, although a biosimilar and its reference insulin product will have the same amino acid sequence, they may differ slightly in their more subtle molecular characteristics and clinical profiles.[9] Insulin glargine is expected to be the primary target for biosimilars producers.[11]

Biosimilars: Promise and Perceptions

With the total 2011 cost of diabetes treatment approaching $201 billion in the United States and $465 billion worldwide,[12] huge incentives exist to drive down diabetes-related expenditures. Because biosimilar producers do not have to bear the costs of research and development and full-scale clinical trials, their second-generation insulin products may be cheaper than the original insulins. Therefore, like generic versions of small-molecule drugs, biosimilars have the potential to reduce diabetes treatment costs, expand market competition, and increase the accessibility of insulin for people with type 1 or type 2 diabetes.

Patients and diabetes educators appear optimistic about using biosimilars, as indicated in a recent survey conducted by the diabetes-focused market research company dQ&A. When 1,637 insulin-using adults with diabetes were asked whether they would use "a less-expensive generic version of their insulin (a biosimilar)" if it were available and their health care provider (HCP) had approved it, 30% said they definitely would, and 37% said they likely would. Similarly, when 415 diabetes educators were asked how likely they would be to recommend biosimilar insulins if they were available in the future, 41% said they would definitely recommend them, and 42% said they would likely recommend them. However, both groups had significant follow-up questions about biosimilars.[13]

Despite this general initial enthusiasm, the rise of biosimilars is not likely to be an easy one. Before entering any major, established market such as the United States, biosimilars will have to meet stringent regulatory requirements that will center on their production and their product's similarity to reference products. Specific skepticism and reservations, described below, must also be addressed before the products are taken up widely. To gain market traction, biosimilars will have to gain widespread reimbursement. Finally, biosimilars will face competition from new insulin products in major companies' pipelines, and they will have to overcome loyalty to existing brands.

Many of the concerns described below, including those about equivalence, testing, substitution, and key stakeholder perceptions, were also raised when small-molecule generics were being introduced,[14,15] and some persist today.[16–18] Nevertheless, use of generics has steadily increased over time; in 2009, generics accounted for 75% of all prescriptions written in the United States, and savings from generics were estimated at $139.6 billion.[19] The manufacturing, regulatory, and commercial issues discussed below pose significant challenges for biosimilar insulins and leave their short- and medium-term success an open question. However, given the widespread adoption of small-molecule generics, these issues will not necessarily preclude the long-term acceptance and uptake of biosimilar insulins.

Biosimilar Manufacturing and Regulation

In contrast to small-molecule drugs, which are produced by chemical synthesis; have uniform, predictable structures that are easy to characterize; and are generally stable, protein-based products such as insulin are produced in living organisms; are larger, more complex, and more difficult to structurally define; and require specific conditions to ensure stability.[9] Minute differences in chemical modifications and higher-order physical structure can significantly alter a final protein product's safety and efficacy.[20,21] Such differences between biosimilar and innovator products have been seen with much larger proteins such as erythropoetin[22] and may be a possibility with biosimilar insulins as well (although no instances of this have been widely publicized so far). Thus, a crucial and difficult goal for biosimilar producers will be to ensure that the molecular characteristics of their drug are as similar as possible to those of the reference product.

Because of the relative complexity of manufacturing protein-based biologics, this high degree of similarity will not be trivial to achieve. Small differences in the design and execution of a manufacturing process can have a large influence on the clinical profile of a final insulin product, raising the need for careful design of manufacturing and quality-control processes.[20]

As background, insulin is manufactured by inserting a gene coding for an insulin product into an expression vector, which is then transferred into a living host (typically yeast, bacteria, or plant cells). This host is then kept in conditions that facilitate expression of the precursor insulin product. This product

is secreted either in biological packets in the host itself or in the culture medium. The insulin precursor must then be captured and purified, chemically modified to create a final insulin product, and then purified again. The final insulin product is then formulated and transferred into vials or other delivery devices.[21]

Variances in a protocol at any of the above-mentioned steps can have important consequences for a final insulin product. For example, depending on the conditions in which an insulin product is expressed, it may contain molecular artifacts, proteins, or other impurities from the host cell and may be differentially oxidized or glycosylated. These differences may increase the insulin's immunogenicity, which can result in hypersensitivity reactions, alterations of the insulin's pharmacokinetic and pharmacodynamics (PK/PD) profile, interference with insulin action, and, in rare cases, hypoglycemia.[9,21,23,24] Alteration of protein structure and introduction of impurities can readily occur during formulation, storage, and delivery, with potentially serious effects on potency and safety.[20,25] This raises the importance of careful vetting of a biosimilar insulin's safety, efficacy, and manufacturing during the approval process, as well as of continued assessment of its production protocols post-approval.

Although the insulin manufacturing process is broadly similar among different companies and products, the details vary significantly. Companies use different organisms, protocols, and reagents at each step. Patent holders are not required to divulge their protocols; many use techniques and materials that are developed in-house. Thus, a biosimilar manufacturer would be unlikely to use the same production protocol as the maker of a branded product.[9,24] Because protocol variations can have a significant impact on a final product, regulatory agencies have established a number of similarity metrics that biosimilar producers will have to meet before their insulins can be marketed.

Regulatory approval pathways for biosimilars

In general, a manufacturer of biosimilars must establish that its product is similar enough to a reference product to invoke the latter's efficacy, safety, and post-marketing data and serve as an alternative to it. Efficacy, safety, and comparative studies are all required and must be performed in a step-wise manner to demonstrate biosimilarity. Sponsors must identify at each approval step any residual uncertainty about their product's biosimilarity and determine additional tests that would alleviate that uncertainty.[20,26,27]

The U.S. Food and Drug Administration (FDA) broadly outlined its requirements for a biosimilar producer pursuing an abbreviated licensure pathway in three draft guidance documents issued in February 2012. In the documents, the FDA asks companies hoping to market a biosimilar for a comprehensive dossier beginning with head-to-head comparisons of the biosimilar's and reference product's structural and physiochemical properties, as well as a rigorous evaluation of the biosimilar's manufacturing and quality-control processes. The agency then considers animal and toxicology studies and clinical studies that evaluate a product's PK/PD profiles, immunogenicity, efficacy, and safety. If the immune response to a reference product is rare, both pre- and post-marketing immunogenicity studies will be required. The pre-market study will be powered to detect major differences between the two products, and the post-market study will be designed to detect more subtle differences in immunogenicity. Sponsors may provide scientific justification if they believe that any type of required comparison between a follow-on biologic and a reference product is not needed or can be minimized. The FDA has emphasized that it will take a "totality-of-evidence" approach to evaluating biosimilars and that companies should closely consult with the FDA while developing their clinical testing programs. The FDA has not yet published guidance on biosimilar insulins specifically or on required pharmacovigilance plans.[10,20,28]

No biosimilar manufacturers have yet submitted a product under this guidance, so uncertainty persists about its interpretation and implementation. The first companies to submit biosimilar products will almost certainly encounter surprises during the regulatory process, which some have suggested could be quite controversial.[11]

Biosimilar Commercialization: Key Issues

Once a biosimilar has met regulatory requirements, separate considerations will determine whether it succeeds commercially. Perhaps the most important will be the unfamiliarity of key stakeholders (patients, providers, and payors) with a biosimilar. After a biosimilar overcomes this key concern, its commercial success will rely on many other factors, including its pricing, the clinical experience surrounding its use, the reliability of its manufacturing, the reputation and capabilities of its distributor, and how it is reimbursed.

Clinical record

The extent of clinical data available for a biosimilar will strongly influence how much confidence

clinicians have in the product and how willing they are to prescribe it[29] (A. Merron, personal communication). In the aforementioned dQ&A survey, diabetes educators said they would need extensive information about a biosimilar's action profile, storage, stability, expiration once in use, predictability of absorption from injection site, and bioavailability before prescribing it. Many also noted that they would want to see evidence that a biosimilar is "equivalent" to a brand-name insulin in all aspects.[13]

Meanwhile, a BioTrends Research Group survey found that a majority of endocrinologist respondents (n = 77) would ideally want to see data from three phase 3 trials, an immunogenicity study, preclinical comparability assessments, and an approved manufacturing process before they would feel comfortable prescribing the product.[30] On the immunogenicity front, physicians are likely to accept that only a certain level of immunogenicity testing can be done before approval. However, in the long term, they will expect long-term tracking data that elucidate any rare events associated with the product (A. Merron, personal communication).

A biosimilar's clinical record will also be important to payors, who have said they will place concerns about safety and efficacy before cost savings in making reimbursement or management utilization decisions.[31] There is not a consensus on how much and which type of data payors need to feel comfortable with a biosimilar in these areas. In a survey by the BioTrends Research Group, 55 U.S. pharmacists and medical directors and 10 payors and leading payor consultants said payors would require a higher level of clinical evidence than the FDA (specifically, more patients studied; trials focused on demonstrating safety and efficacy and not just biosimilarity; and numerous head-to-head randomized, controlled trials) before covering a biosimilar (A. Merron, personal communication). However, according to an Industry Standard Research survey (n = 30), payors know they may have to rely on the FDA's conclusions about safety and efficacy, even if they believe more stringent data would be ideal (A. Schafer, personal communication). For immunogenicity data, payors, like physicians, will likely demand long-term tracking for events in addition to the preapproval head-to-head trials suggested by the FDA (A. Merron, personal communication).

The demands discussed above underscore the importance of manufacturers conducting thorough clinical testing, providing as much data as possible in submission packages, and clearly communicating findings to payors and physicians, particularly through peer-reviewed literature (which, along with government regulations, endocrinologists consider the most reliable source of information on biosimilars)[30] and through presentations at major scientific meetings.

Although many of the aforementioned data demands will be met in the clinical trials used for gaining approval of a biosimilar (at least in the United States),[20] some may not be. If this were the case, it is possible that companies would have to consider conducting additional clinical tests to address provider and payor concerns.

This approach may not be necessary for payors, who would likely defer to the FDA and cover a biosimilar once it had been approved (even if all the data they wanted were not available). However, additional data might be valuable for HCPs. It is possible that physicians and other HCPs would trust the FDA and prescribe a biosimilar product once it had been approved, but they may wait until the product had been on the market for some time or start it only in a limited subset of patients if they had any hesitations. There also may be a subset of HCPs who would choose to preferentially prescribe a branded insulin over a biosimilar insulin specifically because the former had more clinical evidence backing it (G. Rogan, personal communication). To gain the support of these HCPs, biosimilar manufacturers may find it valuable to conduct additional clinical trials beyond those required by the FDA.

Interchangeability with reference products

In addition to wanting robust clinical data, some stakeholders may want to see that a biosimilar is interchangeable with its reference product. According to the U.S. Biologics Price Competition and Innovation Act of 2009, a biologic is considered interchangeable if it "can be expected to produce the same clinical result as the reference product in any given patient." Biosimilar products that are taken more than once or as continuous treatments are considered interchangeable if switching between them and a reference product poses no additional risk beyond that of the reference product alone.[32]

A designation of interchangeability may make physicians view a biosimilar more positively and allow the market for biosimilar insulin to expand beyond new users.[33,34] It may also ease the concern of HCPs who are hesitant about switching patients currently taking branded insulins to biosimilars that are not interchangeable because of immunogenicity concerns.

The interchangeability of a biosimilar will also drive how it is reimbursed and managed at the insurance level. According to a

descriptive study of managed care organization (MCO) personnel, MCOs will have a much easier time driving the use of biosimilars if they have been deemed interchangeable. Products not deemed interchangeable are likely to be treated like branded entries into the class, which would make formulary inclusion more difficult and reimbursement less probable.[35] Regarding other types of private insurance, whether or not a biosimilar is designated as interchangeable will determine the specialty tier in which it is placed or what type of utilization management it will be subject to. In general, payors are enthusiastic about reimbursing interchangeable biosimilars, particularly because of their potential to drive down costs through automatic substitution. However, they acknowledge that the first tier of biosimilars will likely not be interchangeable, and thus they will be willing to reimburse non-interchangeable ones (A. Merron, personal communication).

Demonstration of interchangeability will not be easy. Companies will need to conduct crossover trials in which patients switch between products over time, and in the United States, they will likely have to apply separately for biosimilarity and interchangeability designations. (U.S. interchangeability guidelines have not yet been released.) Both of these factors are expected to raise the cost of demonstrating interchangeability far beyond those of demonstrating biosimilarity.[33] On the other hand, companies whose products achieve an interchangeable rather than just a biosimilar designation may have to bear relatively fewer marketing and education costs because their products are likely to be viewed as true "generics" rather than just somewhat less expensive branded products.

Necessity of education

Given their influential roles in prescribing insulin, influencing patient decision-making, and encouraging payor support of biosimilars, HCPs will need to have a thorough understanding of the clinical profiles of biosimilars and how they diverge from reference molecules. To facilitate this understanding, companies commercializing biosimilars may have to provide clinician education similar to that currently provided for branded products.[29,36] One of the main ways HCPs learn about new branded products is through company-sponsored continuing medical education programs, on which billions of dollars are spent each year.[37,38] Companies commercializing biosimilars may have to sponsor this type of education as well, at a significant cost.

Education about biosimilars will also be crucial for patients, especially for initial uptake. In the aforementioned dQ&A survey on biosimilars, a vast majority of patient respondents stressed that they would use biosimilar insulins only if they were identical to current insulins in safety, efficacy, action profile, and/or quality. These data suggest that patients will, at the very least, expect their HCPs to address their concerns that biosimilars are identical, and many may even want to review the data themselves.[13] Additionally, informing patients about a biosimilar's immunogenicity risk and any ways in which it diverges from the reference product would better prepare patients to monitor for signs of immunogenicity.[39] Thus, unlike the makers of small-molecule generics, biosimilar producers may need to make significant investments in brand-specific education materials.[36] (A. Merron, personal communication)

Interestingly, according to a survey conducted by the BioTrends Research Group, biosimilar educational campaigns targeted at payors will also be necessary for increasing this group's familiarity with the products (A. Merron, personal communication).

Pricing issues

Price will be another strong determinant of interest in biosimilars. Just as generics are cheaper than their patented chemical reference products, it is hoped that biosimilars could be cheaper than their reference biologics.

A biosimilar's price discount may determine how many people who would otherwise use reference products would be willing to switch to a biosimilar, as well as how many people who previously could not afford insulin now could. In the United States and most established markets, patients who have had good outcomes with a reference product would presumably be unlikely to switch to biosimilars if differences in their out-of-pocket costs were not significant. Newly diagnosed patients who rely more heavily on physicians in their decision-making may be relatively more likely to initiate or switch to biosimilars, even if cost differentials are only moderate.[34] Of course, uptake will also be heavily predicated on reimbursement and coinsurance design in the United States because these factors will determine a biosimilar's relative out-of-pocket cost.

A biosimilar's cost difference versus a reference product will also strongly influence reimbursement, specifically by determining whether it is placed on formularies and preferred drug lists and how its use is controlled.[35] Although payors are not expecting price reductions for biosimilars to approach those of chemical generics, they have suggested that a minimum 20% discount will be needed before they consider the products. However, a significantly greater

discount will be needed to stimulate uptake (A. Merron, personal communication).

Unfortunately, the expenses associated with executing a biosimilar's complex manufacturing process and clinical evaluations may limit how much its price is reduced compared to that of a patented product. In contrast to a chemical generic, which requires about a $1–2 million investment before approval, the cost of bringing a follow-on biologic to market could be anywhere from ~ $30 to $150 million.[33,40] Per-unit manufacturing costs for insulin are ~ $50–75 per gram versus $5 per gram for chemical drugs. Consequently, price reductions for biosimilars are only expected to be ~ 20–40%, with some reduction estimates ranging as low as 10% and as high as 70%.[21,30,33,34]

Although this discount is far less than the 90% seen with small-molecule generics,[21] it still has the potential to make insulin treatment (particularly insulin-analog treatment) more affordable and accessible. However, high development, approval, and manufacturing costs may also mean that only one or two companies will have the expertise and scale to discount biosimilars enough to promote uptake (S. Garg, personal communication) or that biosimilar manufacturers will end up seeking full biological license applications to make their investments worthwhile.[41,42]

Patient and provider experience

Generic companies are largely able to count on generation of demand through the significantly lower price of their products. However, companies commercializing biosimilars will also have to provide optimal patient and HCP "experiences" to help promote uptake, especially given that the price differential will likely be smaller than for chemical drugs. A biosimilar insulin's delivery device, associated support systems, associated marketing strategies, and naming will shape these experiences.

Delivery devices. Delivery devices are important facets of patients' experiences with insulin,[29] affecting comfort, convenience, adherence, and outcomes. The three main insulin companies have developed devices that enable significantly less painful and more precise insulin administration.[43] Thus, the device through which a biosimilar insulin is administered may serve as a key market differentiator, even if it is chemically and clinically equivalent to the branded product.

Biosimilar companies may not be able to match the device innovation of current manufacturers, and they will not be required to commercialize their products in the same devices in which reference products are delivered.[28] But they will be expected to commercialize functional, reliable pens, as well as easy-to-use vials. Patients, HCPs, and payors will expect that a biosimilar's delivery method does not impose additional burdens on patients compared to that of a reference product.[35] Providers presumably will be less interested in adopting a biosimilar product if it is less convenient to use than a reference product and could therefore decrease adherence to insulin therapy (A. Merron, personal communication). They may additionally expect that a biosimilar product will not require more effort on their part for administration education.

Patient support and financial assistance programs. Patient support systems are established parts of the patient experience offered for originator biologics.[29] In light of concerns about similarity and immunogenicity, as well as the significant risks associated with any insulin, companies that make biosimilars should also provide robust support systems, which may help establish patient comfort and confidence with these novel products.

All of the major insulin companies also have financial assistance programs for their products.[44–46] If biosimilars are not priced or reimbursed competitively, financial assistance may be expected.[29] The availability of financial assistance may determine the initial uptake of biosimilars and, in the long run, may shape brand loyalty. Whether companies developing biosimilars are willing to bear this cost has yet to be determined.

Marketing. Given current levels of physician concern and limited prospects for price discounting, biosimilars may need to be marketed to physicians in a manner more similar to branded products than to generic drugs.[36] This may involve employing strong sales forces and forming "reputation bonds" with HCPs, as the top insulin companies currently do.[47] Companies will also need to effectively communicate brand value to physicians, whether through publications, advertising, or education programs.[29,33]

Marketing to payors will be equally, if not more, important. Communicating value to payors in a way that effectively addresses their expectations, needs, and motivations is central to gaining coverage of biologics such as insulin.[48]

Implementation of robust promotional strategies for both of these groups can be expected to further raise the cost of marketing biosimilars beyond that of generics.

Naming. Regulatory agencies have not yet adequately addressed the naming of biosimilars, but this could have a significant impact on patients and providers. Currently, the World Health Organization assigns one international nonproprietary name (INN) to both a reference product and its generics.[49] It has not yet been determined whether this scheme will

also apply to biosimilars and their reference products.

Some have suggested that biosimilars and their reference products need distinct names for recognition purposes and for the monitoring of product-specific safety and immunogenicity concerns. Others have argued that distinct naming would help improve the accuracy of patient records. It could also aid in avoiding unintentional substitutions, help physicians properly differentiate among brands, aid patients in identifying which products are branded and which are biosimilars, and increase confidence in biosimilars.[29, 50–52]

Distinct naming of biosimilars could also help alleviate automatic substitution concerns. In the context of insulins, automatic substitution entails a pharmacist dispensing a biosimilar product in place of the original insulin without the physician's knowledge or approval. This is typical with chemical generics[53] and is a major determinant of the cost savings that allow generics to drive down health care spending.[54] However, the above-mentioned BioTrends Research Group survey of endocrinologists found that they would be uncomfortable with this practice for biosimilars.[30] At the 11 May 2012 FDA public hearing on biosimilars, speakers from the Alliance for Safe Biologic Medicines and the National Kidney Foundation also voiced concerns about this practice.[50] Giving biosimilars distinct names would pave the way for policies that allow physicians to prescribe specified insulins without the possibility of substitution.[55]

On the other hand, key stakeholders have suggested that referring to both a reference insulin and biosimilars of that insulin by the same INN could decrease confusion, lower marketing costs for biosimilars, and obviate inadvertent dual prescribing of the same type of insulin.[50,51] It would also facilitate automatic substitution, thereby enhancing the ability of biosimilars to drive down diabetes-related health care costs.

Product labeling

The information provided on the labels of biosimilars will be a strong determinant of physician comfort with the products. Although guidelines about packaging and labeling of biosimilars have not yet been set, speakers at the recent FDA public hearing on biosimilars agreed that these labels should include clear, informative, and unique information. For physician ease and patient comfort, labels should include information about how clinical data for a biosimilar were obtained (e.g., how many trials were conducted and what information was extrapolated from the reference product), whether the biosimilar is interchangeable (and a warning against substitution if it is not), and whether data were extrapolated from other indications. Moreover, a biosimilar should be clearly labeled with tracing information to facilitate adverse event reporting.[50]

Reliability of manufacturing

Given the significant therapeutic importance of insulin, all insulin producers should have sufficient production capabilities to meet demand and ensure a sufficient, constant supply. Failure to meet demand could pose serious public health problems and would undermine key stakeholder trust in the product, with important commercial consequences. Because doctors will likely not feel confident switching patients from a noninterchangeable biosimilar to a reference product or another noninterchangeable biosimilar, having sufficient capacity to constantly meet demand and back-up production capabilities will be particularly important for companies whose products are not interchangeable. Experts familiar with biologics manufacturing have suggested that even once an insulin manufacturing process has been perfected on a small scale, scaling up production on demand while maintaining the product's integrity may prove challenging for companies new to insulin manufacturing[56] (L. Heinemann, personal communication).

Distributor reputation and capabilities

The companies that dominate the U.S. and global insulin markets have established reputations and are trusted by clinicians, patients, payors, and regulators. They additionally have significant worldwide manufacturing and marketing capabilities. A successful distributor of biosimilar insulins will have an easier time gaining the trust of key stakeholders if it is well regarded. Furthermore, a firm with relatively established brand recognition and large production capabilities will be in a stronger position to address all the considerations discussed above that influence commercial success, from provision of robust clinical data to provision of optimal patient and provider experiences.

Well-established companies are also expected to have an easier time gaining coverage for their biosimilar products. Payors have suggested that, if multiple biosimilars were available, they would only reimburse a few of them from well-known generics companies or widely recognized companies that have experience with biological drugs; they would choose not to reimburse products from less well-known companies that do not have pharmaceutical experience (A. Merron, personal communication).

Although many of the companies currently eyeing the biosimilar space do not have such reputations

or capabilities, they may be able to gain these through strategically chosen partnerships. This approach has already been explored among biosimilars companies[57] and is likely to increase as interest in biosimilar insulins grows.

A notable example of this is Biocon's recently terminated partnership with the U.S. pharmaceutical company Pfizer. Biocon is an India-based company that markets two biosimilars, Insugen (a recombinant human insulin) and Basalog (a biosimilar insulin glargine), in 25 countries worldwide (J. Deviprasad, personal communication). (Biocon does not report sales for these products.) From October 2010 to March 2012, Biocon partnered with Pfizer to distribute its biosimilar insulins. Under the partnership's terms, Pfizer received worldwide rights to Biocon's insulin portfolio, with the exception of a few locations.

Pfizer's worldwide reach, established brand name, and strong marketing apparatus had the potential to enhance Biocon's position in some of its weaker areas. Reflecting this, the two companies launched separately branded versions of Insugen and Basalog under Pfizer's name (Univia and Glarvia),[58] with the purpose of expanding the Indian insulin market (J. Deviprasad, personal communication).

The companies probably expected that certain segments of the Indian population—those who were not previously interested in their biosimilars—would be interested in products sold under the Pfizer corporate name. Had the partnership persisted, it might have allowed Biocon to enter the U.S. and E.U. biosimilar fields earlier than some competitors and with more brand-name recognition. However, Pfizer's exit now suggests that biosimilars might be more complicated and less lucrative than previously expected, especially in the United States. Biocon is currently seeking a new partner to commercialize its insulins in the United States and European Union by 2015 (J. Deviprasad, personal communication).

Biosimilar insulin coverage and utilization management

In the United States, biosimilars must be widely covered if they are to be viable treatment options. In deciding whether to reimburse for a biosimilar and by how much, payors will consider several of the metrics described above, including a product's cost, quality of clinical data, interchangeability status, and its manufacturer's reliability. They will also assess product-specific characteristics affecting patient adherence, including delivery device and patient-support systems, and look for the support of the medical community and opinion leaders[35] (A. Merron, personal communication; A. Schafer, personal communication). Payors are likely to strongly consider physician and patient perceptions of a product's safety and efficacy before making coverage decisions.[35]

As noted above, safety and efficacy will be the highest considerations, with manufacturers needing to show, at a minimum, comparative data on both. Price will probably be the next major driver of payors' coverage decisions, with a minimum 20% discount expected. The reputation of a biosimilar's manufacturer will also hold strong weight. Factors such as the device a biosimilar is delivered in and its interchangeability status will be relatively less important for coverage decisions, although not ignored (A. Merron, personal communication).

Once they have decided to reimburse a biosimilar, payors can influence its uptake through their pharmacy benefit and utilization management techniques. They are most likely to employ step therapy, prior authorization, and placement in preferred drug tiers or controlled drug lists[33,35] (A. Merron, personal communication).

Established Competition for Biosimilars: Brand Loyalty and Innovation

In addition to the regulatory and commercial issues biosimilar insulin manufacturers will have to consider, they can expect to face significant competition from existing insulin manufacturers. Eli Lilly, Sanofi, and Novo Nordisk have all worked to differentiate their current insulins in ways that solidify brand loyalty. Additionally, all three companies are developing novel insulins to expand their product portfolio. These upcoming products have the potential to provide clinically meaningful benefits that make biosimilars relatively less appealing.

Sanofi products

Sanofi markets two insulins: the basal analog glargine and the rapid-acting analog glulisine (Apidra). Glargine is the world's top-selling basal insulin and top-selling diabetes medication. It generated $5.5 billion in revenue in 2011, and sales continue to grow at a healthy rate (between 15 and 20% year-over-year growth for each quarter in 2011).[1] Its European and U.S. patents expire in 2014 and 2015,[25] respectively, and it is likely to be the main target of biosimilar competition.[11] Glulisine, meanwhile, netted $266 million in sales in 2011, putting it in third place among fast-acting analogs.[1]

Glargine's delivery devices and its unique claims may help retain loyalty to the brand, even if biosimilars turn out to be much cheaper. The compound is delivered in a disposable, pre-filled pen called SoloSTAR,

in a reusable pen called ClikSTAR, or from a vial and syringe.

Sanofi management has suggested that patients who are happy with the SoloSTAR are unlikely to be displaced easily. They attribute 51% of first-quarter 2012 glargine sales in the United States to the SoloSTAR, up from 44% a year ago.[59]

The company's recently introduced BGStar and iBGStar blood glucose meters may also help cement loyalty.[60] Sanofi is developing an integrated advice capability for glargine dosing into the meters, which would presumably allow patients to manage their diabetes better and make the insulin appealing to users of blood glucose meters.

The company has also discussed plans to provide patients with related tools for diabetes management.[61] These efforts to create a comprehensive user experience have the potential to make people more likely to choose glargine.

Glargine is the only basal insulin officially approved for use with all of the currently available glucagon-like peptide-1 (GLP-1) receptor agonists—exenatide,[62] exenatide extended-release,[63] and liraglutide.[64] Given the significant popularity of the GLP-1 class, glargine would likely be at a significant advantage versus biosimilars if their distributors do not perform the appropriate studies or provide the correct justifications for similar claims. Finally, recent results from the Outcome Reduction With Initial Glargine Intervention (ORIGIN) study, which demonstrated a neutral effect of glargine treatment on cardiovascular outcomes and cancer in people with early diabetes, impaired fasting glucose, or impaired glucose tolerance (median follow-up 6.2 years),[65] may marginally aid the glargine franchise to the extent that the ORIGIN results are not considered applicable to follow-on glargine biosimilars.

Glulisine could retain users through its delivery in the popular SoloSTAR pen and through its approval for use in children as young as 4 years of age.[66] Presumably, a biosimilar version of the product might not automatically get this indication.

As further insurance against potential competition, Sanofi is developing a novel glargine product and a combination glargine/GLP-1 product. The novel glargine product is in phase 3 trials, is expected to have a flatter PK/PD profile and a lower injection volume, and may require fewer injections than currently marketed basal insulins.[67] So far, Sanofi has not released sufficient data on this new product to indicate whether its characteristics are indeed appealing enough to merit preferential use over a biosimilar glargine.

Sanofi's combination glargine/GLP-1 product will be delivered via a "fix/flex" pen, which administers a fixed dose of Sanofi's once-daily GLP-1 candidate lixisenatide along with a variable insulin dose.[68] This product has the potential to build loyalty among patients who appreciate the ease of glargine/GLP-1 joint dosing, especially if it hits the market before the introduction of biosimilars.

Eli Lilly products

Eli Lilly's current insulin offerings span the human insulin and analog spaces. In 2011, lispro (Humalog), its rapid-acting analog, brought in $2.4 billion in sales, while its human insulin brand (Humulin) netted sales of $1.3 billion.[1] Among the two, lispro is expected to be the main target of biosimilar competition because it is an analog and is priced higher than human insulin. Its patents expire in 2013.[9]

Brand familiarity, appealing indications and delivery devices, and pricing may drive continued use of lispro. Because the product was the first insulin analog when it was introduced in 1996, some patients have been using it for more than 16 years as their primary rapid insulin.

The insulin is additionally delivered in popular devices. In a recent survey of 442 insulin pen users, Eli Lilly's lispro KwikPen received the highest satisfaction rating from among all pens used to deliver analogs.[69] Lispro can also be delivered in the Memoir pen, which features a digital display and a memory function that saves the time, date, and dosage of a patient's 16 most recent doses. These features are particularly advantageous for children and elderly patients.

Lispro's other advantages include labeled indications for pediatric patients (≥ 3 years of age) and for use in insulin pumps (up to 7 days in the pump reservoir, which is longer than for the other analogs).[70] Uncertainty remains as to whether or when biosimilar versions of this product will have these claims.

At the corporate level, one of Eli Lilly's recent competitive strategies has been aggressive price-lowering. For example, during 2011, Eli Lilly gained significant market share from Novo Nordisk through aggressive pricing strategies that helped it garner several key U.S. contracts.[71] Implementation of these strategies for lispro could make it harder for biosimilar versions to compete.

On the innovation front, Eli Lilly is positioning itself to enter the basal analog space as lispro's patents move closer to expiring. Toward this end, the company has partnered with Boehringer Ingelheim (BI) to develop both a novel basal insulin and a new version of glargine. The new glargine product, LY2963016, is in phase 3 trials[72] and is expected to be submitted for approval in 2014.[73] It is not yet clear what will differentiate this candidate from glargine,

although some likely areas include its clinical profile, the device in which it is delivered, and its price.

Although Eli Lilly characterizes this product as a "new glargine" and not a biosimilar, many in the health care system will likely perceive it as a biosimilar. However, in contrast to a biosimilar, the product is expected to go through a full range of phase 2 and 3 studies, which will likely give it the most clinical data of any glargine comparator. These data will not only provide Eli Lilly insurance against strict regulatory guidelines, but also serve as reassurance for providers, patients, and payors who are looking to see whether follow-on insulin analogs can be safe, effective, and tolerable.

The Eli Lilly/BI novel basal insulin analog (LY2605541), thought to be a pegylated version of lispro, entered phase 3 testing in late 2011. Eli Lilly management has said that the company hopes to differentiate the compound from glargine on clinically meaningful outcomes, including less hypoglycemia, differences in body weight changes, and possibly even more effective glycemic control.[74] In phase 2 studies in both type 1 and type 2 diabetic patients, the compound has provided glycemic control similar or superior to glargine, while reducing nocturnal hypoglycemia. It has also been associated with reduced intraday glycemic variability and reductions in weight compared glargine.[75–77]

The Eli Lilly/BI partnership also includes two oral drugs for type 2 diabetes (the dipeptidyl peptidase-4 inhibitor linagliptin[78] and the sodium-glucose transporter-2 inhibitor empagliflozin[72]), giving the two companies a broad range of treatment approaches for diabetes. Some have speculated that Eli Lilly seeks to become a "one-stop shop" for diabetes management, a still-unproven strategy that, if successful, could be especially useful in negotiations with payors.

Novo Nordisk products

Novo Nordisk also provides both human insulin and insulin analogs. Detemir, the company's basal insulin analog, brought in sales of $1.4 billion in 2011. Aspart (Novolog) is its rapid-acting analog, which annualized at $2.4 billion in 2011. The company also sells a pre-mixed combination of the analogs aspart and intermediate-acting protamine aspart (NovoMix) that netted $1.5 billion in 2011. The company also offers several human insulins, of which total sales were $2.0 billion last year.[1]

With expirations for their various patents having already occurred or impending,[79] aspart and detemir are both potential targets for biosimilar competition. However, several factors are expected to drive the continued use of the two products.

At this time, detemir is the only basal analog that has a category B classification for pregnancy.[80] Additionally, it is approved for use with liraglutide, a long-acting GLP-1 receptor agonist that showed triple-digit sales growth in 2011 (versus exenatide's continued sales decline in this period).[1,64] If these indications are not passed on to biosimilar detemir products, they could be key differentiators for detemir.

Like lispro, aspart also has specific labeling for dosage in pediatric patients (≥ 2 years of age),[81] which biosimilar aspart insulins may not receive right away. Novo Nordisk's proprietary delivery technologies include the FlexTouch (the first prefilled pen for which injection force is driven by an inner spring rather than the thumb, allowing delivery of any insulin dose with the same pressure), the NovoPen Echo (a pediatrics-focused pen with a built-in memory function), and NovoTwist (a needle designed for simplified pen attachment).

In contrast to Sanofi and Eli Lilly, Novo Nordisk's innovation efforts do not involve glargine. It has focused on developing differentiated novel insulins that will generate new interest in its branded product offerings. Most notably, Novo Nordisk is developing an ultra-long-acting basal insulin candidate called degludec. Degludec has a half-life of > 24 hours (compared to glargine's 12.5-hour half-life), which allows the compound to be dosed less frequently than glargine.[82] Degludec has a PK profile that is closer to peakless and less variable than that of glargine. In clinical trials, it has demonstrated significantly less overall hypoglycemia and nocturnal hypoglycemia than glargine.[83–85]

Building on the potential of degludec, Novo Nordisk is also developing degludecPlus, a fixed-dose combination of degludec and the company's rapid-acting analog aspart. Novo Nordisk filed for approval of degludec and degludecPlus in the United States in late September 2011, and an FDA decision is expected in late October 2012. The company is also developing a fixed-dose combination of degludec with the once-daily GLP-1 receptor agonist liraglutide that is currently in phase 3 testing.[86]

Some have suggested that degludec has the potential to lessen demand for biosimilar insulin. They argue that if degludec is preferred by patients and providers and has a better clinical profile than that of glargine, it might make biosimilar glargine appear less attractive (S. Garg, personal communication). Were degludec and degludecPlus to get approved 2 years in advance of glargine's patent expiration, as some have predicted, they could potentially gain significant market traction far earlier than com-

panies start engaging in marketing, education, and other commercialization activities for biosimilar glargine.

To round out its novel insulin portfolio, Novo Nordisk is also developing an oral insulin candidate and an ultra-fast-acting insulin analog. Both are in phase 1 development.[86] Given the need for more convenient insulin dosing and analogs with more physiological PK profiles, both of these products have the potential to be game-changers that keep users loyal to the Novo Nordisk brand, even once long- and fast-acting biosimilar insulins are available.

Conclusion

The expected entry of biosimilars onto the insulin market could significantly change the insulin landscape in the coming years. These products could have a notable impact on diabetes treatment costs, accessibility of insulin, insulin market competition, and the number of insulin choices available to patients. However, biosimilar companies will face major challenges on regulatory, commercial, and competitive fronts as they seek to enter this market.

Given these hurdles, along with the inherent complexity and costs of producing insulins, it appears unlikely that multiple biosimilars will emerge in the United States in the near future. However, as time progresses, the availability and acceptance of biosimilars may significantly increase as the regulatory landscape becomes clearer, manufacturers scale up production to lower costs, reimbursement is established, and key stakeholders gain confidence in the products. Already, manufacturers, regulatory agencies, and the medical community are anticipating the arrival of biosimilars, and interest is only expected to increase as various first-generation insulin analogs move closer to their respective patent cliffs.

Looking ahead at the biosimilar landscape, a broader and deeper understanding of the manufacturing, regulatory, and commercial issues these products will face will help the many stakeholders involved better prepare for the introduction of biosimilars.

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