Will Biosimilars Gain Momentum?

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Abstract
Biosimilars, also known as follow-on biologics, continue to be an area of great interest in oncology because of the potential cost savings and improved access related to their use, yet significant confusion remains regarding their introduction in the United States. The regulatory and legal hurdles remain poorly defined, and companies producing branded products have been battling their introduction. The European Union provided a pathway for approval in 2004, with various agents reaching the market since that time. It is important to understand the nuances of the discussion and experiences and for clinicians and policy makers to take an active part in defining the role of biosimilars. Several outstanding questions remain, including the degree to which physiochemical, biologic, quality, and clinical end points must be demonstrated in clinical trials compared with the use of analytic data for approval; whether off-label indications should be embraced; and the regulatory rules around areas such as marketing and interchangeability. This article highlights tbo-filgrastim, an agent currently marketed as a biosimilar in Europe, because its pending introduction in the US market provides insights into the potential of these agents. (JNCCN 2013;11:1291–1297)

Background
Biosimilars, also known as follow-on biologics, continue to be an area of great interest in oncology because of the potential cost savings and improved access related to their use, yet significant confusion remains regarding their introduction in the United States. The European Union (EU) provided a pathway for approval in 2004\(^1\) and has since provided guidance on, and seen the approval of, various biosimilars, including erythropoietins,\(^2,3\) granulocyte colony-stimulating factors (G-CSF),\(^4\) growth hormones,\(^5\) and insulin.\(^6\) Despite having agents on the market, uptake in the EU has been limited and, in some cases, is decreasing, as has been seen in the case of filgrastim (Neupogen, Amgen, Thousand Oaks, California), which had an 8.6% market share in Denmark in 2009 that declined to 2% by 2011.\(^7\) The regulatory and legal hurdles in the United States have made the potential impact of biosimilars difficult to define. However, as the originator biologics approach patent expiration and health care reform continues to progress, it is important to understand the nuances of the discussion and for clinicians and policy-makers (eg, FDA, Centers for Medicare & Medicaid Services, payers) to be active participants in defining the role of biosimilars. This is especially true at a time when efforts at the local and state levels are attempting to preempt federal regulatory actions.

As detailed at length in the authors’ 2011 publication on this topic\(^8\) and the subsequent NCCN White Paper,\(^9\) biosimilars represent a field of significant interest and controversy. Biologics refer to diagnostic or therapeutic agents manufactured using biologic pathways as opposed to traditional chemical processes. They are integral to modern cancer management, often in the form of monoclonal antibodies for cancer treatment and growth factors used for supportive care, such as G-CSF agents. Because of the complexity of manufacturing these agents, biologic equivalents cannot be produced easily when the original agent comes off patent. Issues regarding comparability, bioequivalence, and immunogenicity are at the center of these concerns.\(^10–11\) Several outstanding questions remain, including the degree to which physiochemical, biologic, quality, and clinical end points must be demonstrated in clinical trials.
Analytic processes whereby the structure of biologics can be studied in a laboratory setting have advanced a great deal over the past few years. The FDA has gained considerable experience using these assays to assess physiochemical and functional attributes related to changes in manufacturing processes since the 1990s. They also have experience with abbreviated applications in which generic agents are submitted for approval under an Abbreviated New Drug Application to the Office of Generic Drugs at the FDA’s Center for Drug Evaluation and Research.\(^\text{17}\) Once approved, a generic can be marketed as a “safe, effective, low cost alternative to the American public.”\(^\text{18}\)

Unfortunately, the analytic capabilities are not yet adequate to fully appreciate the comparability of agents. Trials are needed to understand the physiochemical and biologic properties of these agents, starting with pharmacodynamic and pharmacokinetic parameters. The degree to which clinical safety and efficacy end points will need to be demonstrated remains unclear. For some agents, surrogate end points may be a useful link between that surrogate and clinically meaningful benefit. As an example, the demonstration of efficacy for G-CSF agents may include absolute neutrophil counts, CD34\(^+\) cell counts, the duration of severe neutropenia (neutrophils <500 cells/μL), and rates of febrile neutropenia. However, surrogates may be difficult to define for new agents, such as monoclonal antibodies.

Another critical concern in the regulatory approval process for biosimilars is the potential for immunogenicity. Instances have occurred in which hypersensitivity to an agent has led to unintended consequences. The most recent example was seen with peginesatide (Omontys; Affymax, Palo Alto, CA and Takeda, Osaka, Japan).\(^\text{19}\) Omontys was a peptide erythropoietin mimetic approved by the FDA for the treatment of anemia in patients with end-stage kidney disease on dialysis. After approval, 19 cases of hypersensitivity reactions and 3 deaths from the agent were reported. The reactions were more severe than those seen in the preapproval trials, leading the sponsors to voluntarily remove the agent from the market in early 2013.

Epoetin alfa (Eprex, Janssen-Cilag, North Ryde, Australia) provides another example in which simple changes in the production process for this erythro-
The importance of regulatory considerations related to biosimilars in the United States cannot be overstated. As of 2010, the 3 agents with the highest revenues in the outpatient oncology setting were biologics: bevacizumab (Avastin, Genentech, San Francisco, CA), rituximab (Rituxan, Biogen Idec, Weston, MA), and trastuzumab (Herceptin, Genentech, San Francisco, CA). These 3 agents accounted for nearly $4.3 billion in expenditures and more than 50% of the charges for the top 20 drugs in outpatient clinics. This trend is likely to become more dramatic, as biologics represent the majority of oncology products under development. Unlike generics, biosimilars will not be sold at a substantial discount, because of the complexity and cost of development, yet they are a step in the correct direction. They will likely be priced at a 20% to 40% discount compared with the innovator agents. Given the total costs associated with the biologics, this still represents a substantial savings.

A battle is currently being waged between the companies manufacturing branded biopharmaceuticals and those attempting to bring biosimilar agents to the market. A recent editorial discussing the polarization in the field warned that “the brand biotech industry is erecting barriers to biosimilars that will slow market entry and torpedo price competition.”

Although some companies are pursuing strategies as both an originator and the developer of biosimilar agents, incumbents are erecting impediments to uptake.

Battles are occurring at several levels. Recent headlines in The New York Times highlighted efforts to enact state legislation that would make it more difficult to substitute biosimilars for branded agents. Although specific requirements vary by state, proposed provisions include a requirement to notify patients and prescribers before exchanging a biosimilar for a branded product, a mandate that pharmacies maintain records for at least 5 years documenting any substitution decisions, and a prohibition against the substitution of biosimilars for off-label indications. As an example of the legislation passed in Florida, the amendment to Florida Statute 465.0252 states that “a pharmacist who practices in a class II or modified class II institutional pharmacy shall comply with the notification provisions of paragraph (2) (c) by entering the substitution in the institution’s written medical record system or electronic medical record system.” Legislation has already been passed in Colorado, Maryland, Florida, and Virginia, with many other legislatures considering similar action.

The state concerns and other actions, including attempts to constrain the language that can be used in marketing biosimilars, are preempting the ongoing regulatory discussions, yet progress is slowly occurring on the regulatory front. Regulatory progress was first made with the passage of the Biologics Price Competition and Innovation Act as part of the Patient Protection and Affordable Care Act in 2010. This act provided a pathway for biosimilar approval, much as the Hatch Waxman Act did in 1984 for generic drugs. In the bill, biosimilarity was defined as ensuring a product was both “highly similar to the reference product notwithstanding minor differences in clinically inactive components” and that “no clinically meaningful differences” existed in terms of “safety, purity and potency.” It went on to explain that the agent must have a similar delivery attribute and mechanism of action. This was further supplemented by guidance regarding scientific and safety considerations from the FDA in 2011, accompanied by an editorial on the topic in The New England Journal of Medicine. Although both provided further information about the specifics of the pathway for developers, the recommendations

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were vague. The authors of the editorial state that “it’s unlikely that a ‘one size fits all’ systematic assessment of biosimilarity can be developed.” They argued that animal and clinical studies will be needed for the foreseeable future, with the hope that the requirements can decrease with time. Before advising developers on the required animal and human studies, the FDA will review all of the analytic and in vitro results that are available. In March of 2013, the FDA released draft guidance on 5 types of meetings that they anticipate having with sponsors as part of the development process. Although reliance on a case-by-case basis is understandable, this has made it difficult for manufacturers to move forward with development, because they have limited confidence regarding the steps needed for regulatory approval. Despite numerous pre–Investigational New Drug meetings as of April of 2013, no submissions have been made for regulatory approval to date in the United States.

European Experience

The first biosimilar was approved in the EU in 2006. The approved agents have been less complex, including classes such as erythropoietins, G-CSF, and growth hormones; however, the pathway is evolving, with the recent release of guidance for low-molecular-weight heparins. Despite the defined pathway in the EU, the uptake and use of biosimilars has been limited. In a recent analysis based on registry data from Denmark, filgrastim uptake has never surpassed 10% and erythropoietins have not exceeded 1% of the market. Because of a product shortage, somatropin use rose in 2011, but this was not replicated for the other biosimilars in the EU. The authors of the analysis concluded that the limited uptake was from an “expression of uncertainty” as to the true comparability of the agents and lack of large-scale approval trials. This uncertainty exists despite the fact that regulatory agencies in the EU believed that adequate evidence was available, as demonstrated in the European Public Assessment Reports on G-CSF and other agents, which clearly presents the evidence leading to approval. Another argument is that uptake has been low because the introduction of biosimilars caused manufacturers of the originator products to cut their prices to remain competitive, thereby maintaining their market share. Clearly, several forces are at play.

Forthcoming discussions in the EU will focus on the approval of monoclonal antibodies, because the first agents in the class will soon come off patent and represent a more complex development and approval process. These agents lack intermediate end points that can be used as meaningful surrogates, such as the absolute neutrophil count and duration of severe neutropenia highlighted for G-CSF. If full approval trials are required, as occurred for the approval of innovator agents, it will be an enormous hurdle to overcome.

Use Case: Tbo-Filgrastim

Tbo-filgrastim serves as a test case of the issues being considered, because it represents a new form of G-CSF that is likely to be introduced in the United States in late 2013. The first agent in this class was filgrastim, a bacterially synthesized nonglycosylated recombinant methionyl form of human (r-metHuG) G-CSF, which was approved in the United States in 1991. Lenograstim (Granocyte, Chugai Pharmaceuticals, Tokyo, Japan) was the second recombinant G-CSF, although it was only approved in the EU and was produced using hamster ovarian cells. Tbo-filgrastim reflects the third agent in the class to be approved and the second r-metHuG G-CSF. It has been available in the EU as a biosimilar to filgrastim, sold under the trade name Tevagristim. No biosimilar regulatory pathway was available at the time of its submission to the FDA, so a full BLA was pursued and ultimately attained in August of 2012. During the development process, Amgen sued Teva for patent infringement and won an injunction through November of 2013, at which time Amgen’s patent is set to expire. It is expected that Teva will be ready to launch the agent when the injunction is lifted. The critical question is whether clinicians and payers will switch to tbo-filgrastim. Studies published in 2008 and 2009 demonstrated safety and efficacy data, as shown in Table 1. The studies were conducted in breast and lung cancers and hematologic malignancies, all showing the agent to be superior to placebo and noninferior to filgrastim.

To evaluate the potential economic impact of switching to tbo-filgrastim, an industry-funded study was conducted by Aapro et al in 2012 comparing the cost-effectiveness of filgrastim, biosimilar filgrastim, and pegfilgrastim across EU countries. The cost of filgrastim ranged from €128.16 for 1 day of therapy...
to €1794.30 for 14 days of therapy, compared with €95.46 and €1336.46 for tbo-filgrastim. The cost savings of the agent therefore ranged from €32.70 to €457.84. This represents a 26% to 34% cost savings over filgrastim under the assumption of equivalent efficacy and safety. The authors also found that the biosimilar would yield a cost savings compared with pegfilgrastim. Based on European cost estimates and findings of noninferiority, a strong case seems to exist for the use of tbo-filgrastim. The test will be to see how it performs in the market.

Conclusions

A true conclusion cannot yet be drawn about the exact role of biosimilars in the United States because of the many remaining uncertainties. As the FDA reviews agents on a case-by-case basis, hesitation to be the first to test the potential for regulatory approval has occurred throughout the industry. Concern over growing evidentiary requirements has resulted in companies reconsidering development altogether.32 For those that do move forward, the cost of development may limit the ability to price the agents at a sufficient discount to drive broad uptake. The potential also exists that those marketing originator products would drop their prices to remain competitive, thereby displacing the potential market for the biosimilar agents. Likewise, based on the EU experience, how broadly the US oncology community and patients will embrace biosimilar forms of G-CSF is unclear. Finally, state legislative activities are already placing barriers in the way of those that ultimately market biosimilars.

Tbo-filgrastim represents a limited-use case for this class of agents. Judging by the price differential in the EU, it will test the willingness of clinicians and payers to move to a “generic agent” that could drive cost savings. As health care reform continues to gain momentum and costs play an increasingly central role in clinical, reimbursement, and health policy decisions, the role of biosimilars may gain traction even if the savings are not dramatic. Unlike other biosimilars that may follow, more clinical evidence supports the use of tbo-filgrastim than will be true of subsequent agents, because it moved through a full FDA approval process. If tbo-filgrastim does not garner uptake, it may well be a warning sign to other biosimilar developers.

The issue of biosimilars is an important one, because the costs of health care, including oncologics and supportive care agents, is considerable. Regardless of the FDA’s decision on evidentiary requirements, any biosimilars coming to the market will need a high level of evidence supporting their appropriate use in order to overcome hesitation to replace previously used and known effective therapies. Because cost savings do not necessarily directly benefit providers or patients in the current health care system, it is unlikely these stakeholders will be willing

Table 1 Studies Comparing XM02 and Filgrastim

<table>
<thead>
<tr>
<th>Trial</th>
<th>Cancer Type</th>
<th>N</th>
<th>Trial Design</th>
<th>Results</th>
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<tbody>
<tr>
<td>Lubenau et al,29 2009</td>
<td>Healthy subjects</td>
<td>124 total</td>
<td>Received X; F at intravenous and subcutaneous doses of 5 or 10 μg/kg</td>
<td>Mean serum concentration profiles and ANC and CD34+ counts similar</td>
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<td>PK &amp; PD end points within bioequivalence range</td>
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<tr>
<td>Engert et al,37 2009</td>
<td>Non-Hodgkin’s lymphoma</td>
<td>92 total: 63 (X), 29 (F)</td>
<td>Randomized, daily injections for between 5 and 14 days</td>
<td>DSN: 0.5 (X), 0.9 (F) days; FN: 11.1% (X), 20.7% (F) in first cycle (P=.12)</td>
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<tr>
<td>del Giglio et al,36 2008</td>
<td>Breast</td>
<td>348 total: 140 (X), 136 (F), 72 (P)</td>
<td>Randomized, daily injections for between 5 and 14 days</td>
<td>DSN: 1.1 (X), 1.1 (F), 3.9 (P) days; FN: 12.1% (X), 12.5% (F), 36.1% (P) in first cycle (P=.23)</td>
</tr>
<tr>
<td>Gatzemeier et al,38 2009</td>
<td>Lung</td>
<td>240 total: 160 (X), 80 (F)</td>
<td>Randomized, daily injections for between 5 and 14 days</td>
<td>DSN: 0.5 (X), 0.3 (F) days; FN: 15.0% (X), 8.8% (F) in first cycle (P=.23)</td>
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Abbreviations: ANC, absolute neutrophil count; DSN, duration of severe neutropenia; F, filgrastim; FN, febrile neutropenia; P, placebo; PD, pharmacodynamics; PK, pharmacokinetics; X, XM02 (tbo-filgrastim).
to accept significant uncertainty or risk in order to change to potentially less-expensive agents. However, the use of approaches such as bundled payments, in which lump sum amounts are provided to cover a given episode of care, would provide incentives to choose less-costly agents and reward savings by providers. Furthermore, a new trend is being seen for large provider organizations (eg, Accountable Care Organizations, Integrated Delivery Networks) to assume the risk of cost overruns. This may dramatically change the marketing strategy of the pharmaceutical industry, including the role of biologics. Carefully defining the appropriate regulatory process and finding the right balance to move biosimilars forward in an acceptable fashion is critical to the future of providing effective and efficient cancer care.

References


36. del Giglio A, Eniu A, Ganea-Motan D, et al. XM02 is superior to placebo and equivalent to Neupogen in reducing the duration of severe neutropenia and the incidence of febrile neutropenia in cycle 1 in breast cancer patients receiving docetaxel/doxorubicin chemotherapy. BMC Cancer 2008;8:332.


