EXECUTIVE BRIEFING

Biosimilars in the US:

Evolutionary, Not Revolutionary Thus Far

DECISION RESOURCES GROUP

CONTENTS

INTRODUCTION

After years of legislative roadblocks and slow delivery of regulatory guidance, the world's largest biologics market, the United States, is finally open for business to biosimilars with the entry of Zarxio (biosimilar of Neupogen) and the approval of Inflectra (a biosimilar of Remicade).

With the arrival of the first biosimilar in the US market, some preliminary questions have been answered, but critical questions remain unanswered for biopharmaceutical manufacturers.

KEY FACTS ABOUT THE FIRST US BIOSIMILAR

On March 6, 2015, the FDA approved the first biosimilar in the US named Zarxio (filgrastim-sndz) which is a biosimilar of Amgen's Neupogen (filgrastim). The manufacturer of Zarxio, Sandoz, later launched the product on September 3, 2015.

Sandoz conducted one Phase III trial comparing Zarxio to US-sourced Neupogen in cancer patients receiving myelosuppressive chemotherapy and approval was granted for all five of Neupogen's indications with expired exclusivity.

Both Neupogen and Zarxio can be given by intravenous or subcutaneous injection, although Zarxio is only available in prefilled syringes, whereas Neupogen is available in both vial and syringe forms.

Though Zarxio is the first biosimilar to be approved through the FDA biosimilar pathway, Teva has been selling its own filgrastim product, Granix (tbo-filgrastim), in the United States since late 2013. Teva filed for approval of Granix through the full BLA pathway in 2009 (before the biosimilars pathway had been enacted); although Teva's approach enabled the company to launch its filgrastim product as soon as Neupogen's patent expired, the full BLA pathway does not permit indication extrapolation and therefore, Granix is only approved for the indication it was clinically tested in (cancer patients receiving myelosuppressive chemotherapy).

[1]Neupogen is also approved for patients acutely exposed to myelosuppressive doses of radiation. Amgen holds orphan exclusivity for this indication until March 2022.

Critical Open Questions for Biopharmaceutical Manufacturers Regarding Biosimilars:

- **How should biosimilars-related legislation be interpreted and what is the impact of such legislation to product commercialization?**
- **What are the implications of FDA naming and labeling guidelines for biosimilars?**
- **How will physicians adopt biosimilars into clinical practice, if at all?**
- **What are the market access and distribution implications for biosimilars?**
- **of such legislation to product commercialization?**

KEY FINDINGS

Upon the launch of Zarxio and the recent approval of Inflectra the market has had some initial learnings related to the critical open questions regarding biosimilars. We have begun to outline below what we have learned to date regarding key critical questions and what still remains unknown.

Critical Question 1: How should biosimilars-related legislation be interpreted and what is the impact of such legislation to product commercialization?

Initial Learning: Biosimilars sponsors are not required to disclose their biosimilar dossier but they must provide reference brand companies with 180 days' notice of marketing after FDA approval.

Sandoz's experience as the first user of the US biosimilars approval pathway has forced the courts to clarify how to interpret the Biologics Price, Competition and Innovation Act (BPCI Act) that established the pathway.

"*Winston Churchill once described Russia as "a riddle wrapped in a mystery inside an enigma." That is this statute. In these opinions, we do our best to unravel the riddle, solve the mystery, and comprehend the enigma*."
Circuit Judge Lourie, Amgen vs. Sandoz, July 2015

Amgen filed the following two key complaints against Sandoz's interpretation of the statute:

1. Sandoz acted unlawfully by not disclosing the Zarxio dossier or engaging in the patent-negotiation process
2. Sandoz's notification of intention to market Zarxio was invalid because it was given prior to FDA approval

The case reached the Federal appeals courts which concluded that:

- Sharing the biosimilar dossier and manufacturing information with the reference product sponsor is not obligatory, but if the information is not shared, the reference product sponsor may sue for patent infringement.
- 180 days of marketing notice from the biosimilar sponsor to the reference brand sponsor is only valid after the FDA has approved the biosimilar, not before.

When the BPCI Act was first enacted, the information-sharing steps of the biosimilars pathway were seen by many observers as a barrier to use of the pathway. The Amgen vs. Sandoz case has shown that the information-sharing and patent negotiation steps of the biosimilars pathway are not obligatory, but in reality, the court's conclusion is not necessarily a major win for biosimilar manufacturers. Those companies that opt not to follow the steps defined by the statute will still face litigation from the reference product sponsor, potentially against a long list of patents. Furthermore, the reference product sponsor is likely to gain access to the manufacturing information through discovery.

All other biosimilar applicants have opted to submit at least some of their dossier and manufacturing information to the reference product company within 20 days of FDA acceptance and to participate in some, if not all, steps of the patent negotiation process described by the BPCI Act.

As a consequence, the biosimilar applicants Apotex, Pfizer, and Celltrion all argue that they are exempt from providing the reference product sponsor with marketing notice because they participated in the information-sharing components of the biosimilars pathway, unlike Sandoz.

The District Court of Florida and the Federal appeals court have both ruled against Apotex, stating that the 180 days' notification is mandatory, irrespective of whether the information-sharing steps have been adhered to.

The benefits of embarking on the predefined process of information disclosure and patent negotiation include the ability to limit the number of patents included in litigation and an opportunity to negotiate a license or a mutually acceptable launch date. The approach taken should be decided based on the patent estate associated with the molecule and the level of risk deemed acceptable. However, it is now clear that irrespective of whether a company follows the information-sharing process or not, there will be a delay between FDA approval and launch of at least 180 days.

Unanswered Questions: Will current interpretation of the BPCIA be altered by future court rulings?

The Amgen and Sandoz are both seeking a review of the Federal Circuit decision on the Zarxio case, which has been referred to the Supreme Court. This could result in many more months of debate about what the statute was intended to achieve. Furthermore, new lawsuits may be filed in future that challenge different clauses of the BPCIA. As a consequence, some uncertainty regarding the biosimilars pathway persists.

Critical Question 2: What are the implications of FDA naming and labeling guidelines for biosimilars?

Initial Learning: The FDA has developed draft guidance indicating that all biosimilars and reference products have distinct names, but similar labeling.

The FDA's first guidelines for the biosimilars industry were published in 2012, seven years after the EMA produced its first overarching guidance. Guidance specifically related to biosimilar naming and labeling was provided in August 2015 and March 2016 (respectively).

Below is an overview of the draft guidance currently provided by the FDA related to biosimilar labeling and naming:

- *Nonproprietary Naming of Biological Products* (August 2015): Draft guidance proposes that all biologic products' proper names should be suffixed

by a random, four-letter suffix to aid identification.

- *Labeling forBiosimilar Products* (March 2016): Draft guidance proposes that the labelling for biosimilars should only include reference product data (where relevant) and exclude data from clinical trials of the biosimilars. A statement of biosimilarity should identify the product as a biosimilar and state the reference brand.

Similar labeling between biosimilars and their reference products will likely make arguments related to clinical differentiation more challenging for reference drug manufacturers. Additionally, payers may also be more comfortable with preferring biosimilars given the equivalency between the labels.

Unanswered Question: Will final FDA guidelines differ compared to the drafts?

It is important to note that the naming and labelling guidelines are yet to be finalized by the FDA. Additionally, Zarxio's proper name – filgrastim-sndz – and its label are not in line with the draft guidance on these topics, so if the guidance is finalized in its current form, changes to Zarxio naming and labelling would be required. Furthermore, the proper name of all biological products would need to be changed over time, beginning with those that are the target of biosimilar applications. The timeline and process of achieving this safely is yet to be defined.

(Further information on US biosimilars regulations are available in Biosimilars | Access & Reimbursement Overview | Global, Published by DRG in April 2016)

Unanswered Question: What are the data requirements for a biosimilar to gain approval as interchangeable?

Demonstrating interchangeability is an important target for biosimilars applicants as this designation is believed to have an impact on payer coverage and management and physician uptake and acceptance of biosimilars. Most importantly, interchangeable status, may allow pharmacists to dispense interchangeable biosimilars at point-of-sale even if patients have a prescription for the reference brand product (Note: applicable for biosimilars acquired through a specialty pharmacy and/or self-administered). Physicians, therefore, would not have to explicitly prescribe biosimilars.

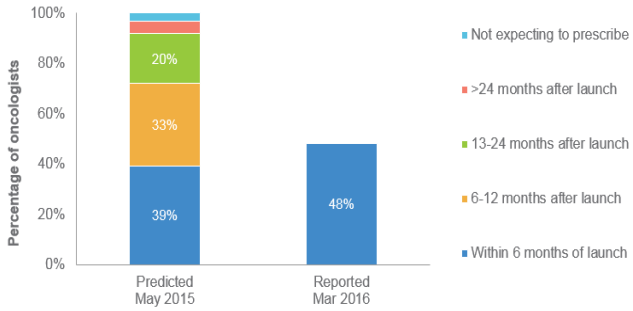
For the third year running, the FDA has indicated that it will publish guidance on demonstrating interchangeability. Without this key document, biosimilar applicants must individually determine the requirements with the FDA once engaged in the formal meeting process.

Critical Question 3: How will physicians adopt biosimilars into clinical practice, if at all?

Key Learning: Initial biosimilar uptake by oncologists has been modest, but is progressing as expected.

Sreejit Mohan, a spokesman for Sandoz, said that gradual uptake of Zarxio was expected: "*This is a physician-driven market, so we fully expected more gradual uptake…What is important is that Zarxio offers healthcare providers a genuinely new option and we continue our sales, marketing and education efforts.*"[2]

US Oncologists' Expected Speed of Biosimilar G-CSF Adoption vs. Actual Uptake



Q. Please assume that biosimilars are approved and that clinical trials have demonstrated similar clinical efficacy compared with the reference brand. Please also assume that the biosimilar net cost is 15-30% below the brand net cost. After launch, how rapidly will you start prescribing G-CSFs? (May 2015: n=61; Actual: n=62) [Source: DRG Biosimilars Insights; LaunchTrends Zarxio Wave 2]

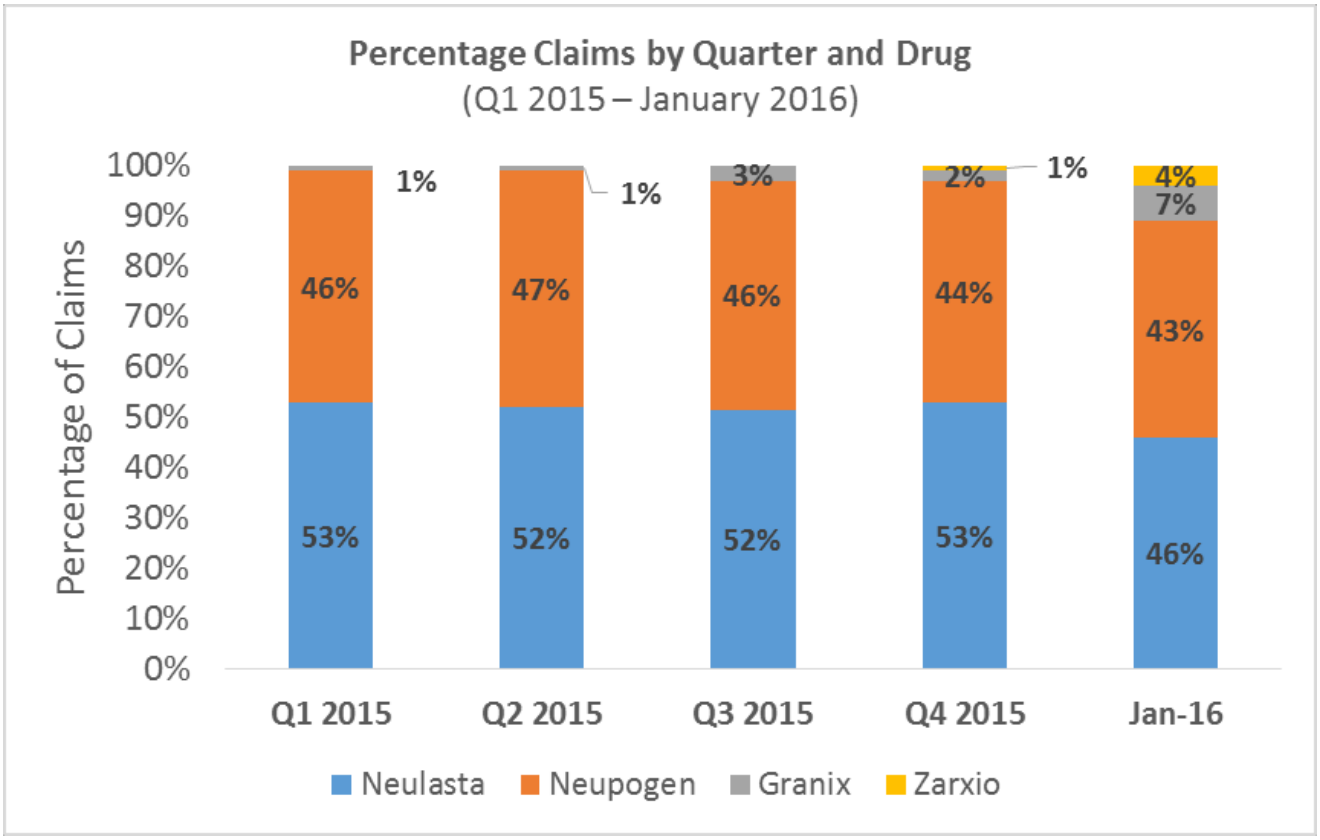
[2]Source: http://www.biopharma-reporter.com/Markets-Regulations/Sandoz-s-biosimilar-Zarxio-gradually-eroding-Amgen-s-Neupogen-sales

In May 2015, before Zarxio launched in the United States, 39% of medical oncologists and hematology-oncologists surveyed by Decision Resources Group's Biosimilars Insights service expected to start prescribing a G-CSF biosimilar within 6 months of launch. When a similar group of oncologists were surveyed at 6 months after Zarxio's launch, we found that 48% of respondents had prescribed the biosimilar to at least one patient, indicating that physician-reported uptake has been slightly better than expected (Source: Decision Resources Group's LaunchTrends: Zarxio (US) Wave 2, May 2016).

While the rate of adoption of Zarxio appears to be tracking well relative to physician expectations, the uptake has underwhelmed most observers. Zarxio's status as the third filgrastim product to market did initially have a part to play; although Granix is only approved for adults receiving myelosuppressive chemotherapy, this indication accounts for ~70% of G-CSF-eligible cancer patients and prescribers were already familiar with Granix when Zarxio launched. However, by 6 months post launch, very few surveyed oncologists indicated that they have not used Zarxio because they have a preference for Granix. Instead, the most common reason for not using Zarxio was the prescribers' preference for Neulasta (Source: Decision Resources Group's LaunchTrends: Zarxio (US) Wave 2, May 2016). Claims data further supports physician-reported data in that the utilization of Neulasta and Neupogen still far outweighs Zarxio and Granix (See below).

Source: DRG Analytics Claims Analysis

Note: Zarxio was approved by the FDA on March 6, 2015 but was not launched until September 3, 2015.

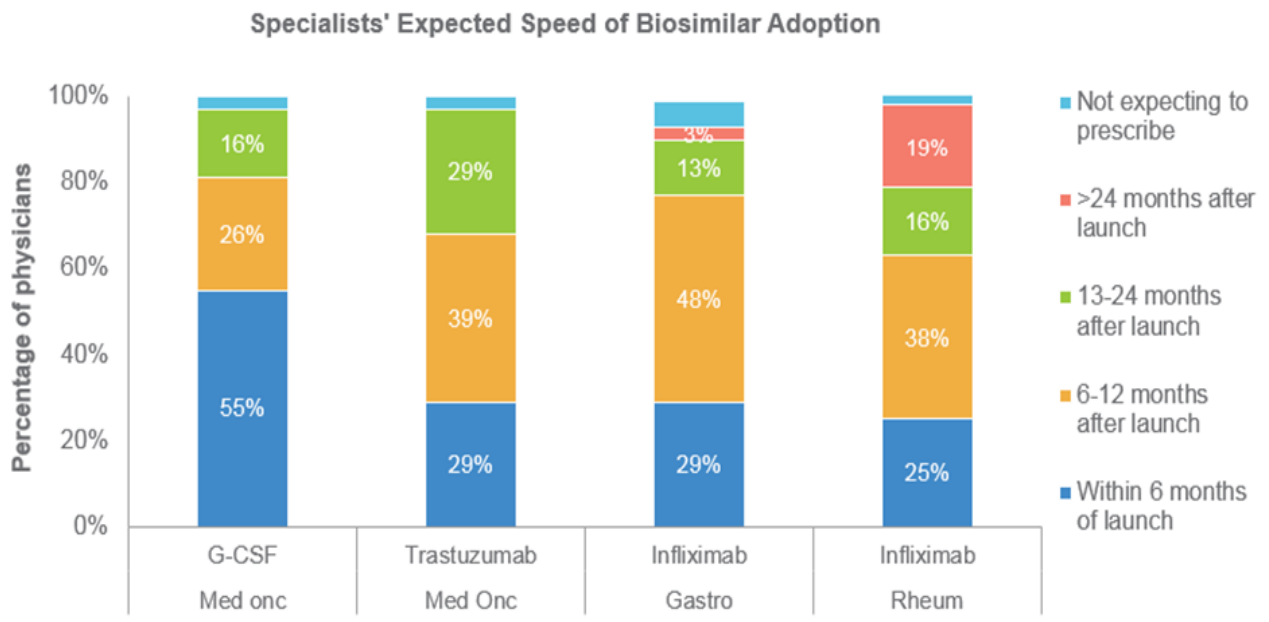


Unanswered Question: How will uptake of biosimilar monoclonal antibodies compare to G-CSF?

Decision Resources Group's Biosimilars Insights service found that less than 30% of rheumatologists and gastroenterologists surveyed in May 2015 expected to start prescribing an infliximab biosimilar within 6 months of launch; this suggests that uptake of monoclonal antibody biosimilars, such as infliximab, is likely to be slower relative to filgrastim.

However, even among oncologists, attitudes toward uptake can vary depending on the type of biosimilar; only 29% of medical oncologists expect to start using a trastuzumab biosimilar with in the first 6 months, compared with 55% who report the same for a G-CSF biosimilar.

There are a multitude of reasons why physicians have differing opinions about uptake rates of biosimilars, including treatment intent, treatment duration, and perception of similarity to the reference product. Physician-reported differences in expected uptake rates underscore that it is not appropriate to extrapolate the performance of a single biosimilar product such as Zarxio to all biosimilar products. However, Zarxio provides a real-world benchmark for US physician uptake of biosimilars which, based on Decision Resources Group's data, suggests that uptake of monoclonal antibody biosimilars will be even slower, unless significant uptake drivers emerge.



Critical Question 4:

What are the market access and distribution implications for biosimilars?

Initial Learning: Biosimilar uptake and preference by US payers is not a guarantee.

To date, there is little evidence of managed care organizations (MCOs) aggressively driving use of Zarxio through utilization-management tactics. The most obvious explanation is the relatively modest differential in the wholesale acquisition cost (WAC) of Zarxio compared to Neupogen (syringe) (Zarxio priced ~11-15% lower than Neupogen syringe[4]). Pharmacy and medical directors surveyed by Decision Resources Group in April 2016 indicated that in order for their MCO to cover and preferentially manage a biosimilar, they expect the net cost of the biosimilar to be ~35% less than the cost of the reference brand.

Sandoz's discount for Zarxio falls short of surveyed payers' expectations, although the company does offer a more generous patient-assistance program for eligible patients and may choose to negotiate discounts relative to the wholesale acquisition cost to improve competitiveness.[3]

[3]Source: Decision Resources Group's Biosimilar Insights, July 2016

[4]Source: RedBook

FINAL THOUGHTS

As Zarxio was the first biosimilar to gain FDA approval it is an imperfect analog to be used to determine how the US marketplace will likely respond to new biosimilars in the next 12-36 months. Despite being an imperfect analog, the Zarxio experience has provided clarity on the importance of payer management and physician demand to drive the uptake of biosimilars. The market's experience with Zarxio has also guaranteed that more questions will rise to the surface as biosimilar and reference brand manufacturers gain more experience with interpreting and acting on FDA guidelines.

Inflectra, a biosimilar of Remicade, was approved in the US in April 2016. If we extrapolate findings from Zarxio, we can surmise that interpretation of the FDA legislation will continue to be fluid. If Celltrion can mirror the distribution channels of Remicade, meet payers' discount expectations, and engage with physicians to assuage their concerns about initial use of biosimilars, Inflectra has the opportunity to take advantage of its first-to-market position, if Celltrion can dislodge patent-infringement claims.

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