Despite the US Court of Appeals for the Federal Circuit's ruling in *Amgen v Sandoz*, significant uncertainty concerning two key provisions of the BPCIA remains, as Steve Coyle and Leslie-Anne Maxwell of Cantor Colburn describe.

AMGEN V SANDOZ: THE BIOSIMILARS SAGA CONTINUES

Sandoz's launch of Zarxio (filgrastim-sndz) on September 3 began a new phase in the continuing biosimilars saga. It was the first biosimilar product to be licensed under the Biologics Price Competition and Innovation Act (BPCIA). The BPCIA permits a biosimilar drug applicant (known as a section 262[k] applicant) to rely on the safety, purity, and potency data of a reference product already approved by a more stringent process required for innovator products. Zarxio has successfully navigated the BPCIA's abbreviated, though convoluted, path to market and a number of additional biosimilar products are in the approval pipeline.

However, significant uncertainty concerning two key provisions of the BPCIA remains. It is still unclear whether biosimilar applicants will be required to divulge their biosimilar application and manufacturing information to the reference product sponsor (RPS) and whether a 180-day

notice of commercial marketing must be given after the biosimilar product is licensed, despite the US Court of Appeals for the Federal Circuit's ruling in *Amgen v Sandoz* on July 21 addressing these issues.

The federal circuit's opinion, written by Judge Lourie, was highly fragmented with no two judges agreeing on all issues. Amgen and Sandoz have both filed petitions for a rehearing *en banc* and a number of *amici* briefs supporting a rehearing on the 180-day notice of commercial marketing issue have also been filed.

The decision

In *Amgen v Sandoz*, the federal circuit affirmed the district court's holding that Sandoz did not violate the BPCIA's section 262(l)(2)(A) by failing to disclose its application and manufacturing process to Amgen within 20 days of filing its biosimilar drug application. The court adopted Sandoz's argument and agreed with the district court that the BPCIA permits a biosimilar product applicant the choice of providing its application and manufacturing information to the RPS or potentially facing an immediate patent infringement suit by it.

According to the federal circuit "the BPCIA explicitly contemplates that a section 262(k) applicant might fail to disclose the required information by the statutory deadline". The court held that the BPCIA sets forth the consequence for this failure: that the RPS may immediately bring an infringement action against the biosimilar product applicant. The court also held that a patent infringement action under section 271(e)(2)(C)(ii), title 35 of the US Code is the only remedy available to an RPS against a biosimilar product applicant that fails to provide the information required by section 262(l)(2)(A) of the BPCIA.

Judge Newman's dissent and Amgen's petition for a rehearing *en banc* both urge that the BPCIA's provision for an infringement action against a biosimilar product applicant that fails to provide the information required by section 262(l)(2)(A) does not excuse the applicant from complying, and is not the sole remedy available against a non-compliant applicant.

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How much notice?

The question regarding the BPCIA's 180-day notice of commercial marketing provision is even more uncertain. Here, the federal circuit reversed the district court's holding that the 180-day notice could properly be given before the biological product's licence is approved. All three judges agreed that Congress meant for notice to be given after such approval. The scope of a biological product licence is not known until a biological product licence is approved. The applicant may change its manufacturing process, or the Food and Drug Administration (FDA) may approve the licence for only some of the requested therapeutic indications. So, the court reasoned that notice must follow licence approval.

The court also held that the 180-day notice of commercial marketing was mandatory, but the judges did not all agree on this point. Judge Chen vigorously dissented, arguing that as with the section 262(l)(2)(A) disclosure requirement, the 180-day notice of commercial marketing requirement is optional and the BPCIA provides a remedy to the RPS against a biosimilar product applicant that fails to provide the 180-day notice.

According to Chen, the BPCIA provides the RPS with the same remedy against a biosimilar product applicant that fails to provide the 180-day notice of commercial marketing, as it does against an applicant that fails to comply with section 262(l)(2)(A)—the immediate right to file a patent infringement action against the applicant. To hold otherwise, according to Chen, gives the RPS a 180-day injunction beyond the 12-year exclusivity period established by Congress.

The 180-day delay for biosimilar market entry established by the federal circuit's decision is strongly opposed by Sandoz and all *amici* writing in support of a rehearing *en banc*. In its petition for a rehearing *en banc* Sandoz argued that the BPCIA's 180-day notice provision is a 180-day pre-marketing provision that the court has misinterpreted as a 180-day post-approval provision. Sandoz said that public policy is strongly against keeping less expensive biosimilar products off the market for an additional 180 days beyond the 12-year exclusivity already granted by the BPCIA.

In practice, whether the 180-day notice provision is found to be a pre-marketing or post-approval notice will likely be of little consequence to many biosimilar product applicants. The BPCIA permits the filing of a section 262(k) application four years after the reference product is initially licensed. In most cases, therefore, the section 262(k) application will be approved long before the 12-year exclusivity period for the product has run out. The biosimilar product applicant with an approved licence in hand will simply give notice 180 days before the end of the 12-year exclusivity period.

For older products such as filgrastim that have long exceeded the 12-year exclusivity period, the interpretation of the 180-day notice provision remains vital. Biosimilar products will probably be only moderately less expensive than their reference product counterparts. Zarxio entered the market costing 15% less than its reference product Neupogen. While the difference is modest, Neupogen is widely used and costs several hundred dollars per syringe. The impact of the 180-day notice provision on the market and consumers is considerable.

> "THE FEDERAL CIRCUIT REVERSED THE DISTRICT COURT'S HOLDING THAT THE 180-DAY NOTICE COULD PROPERLY BE GIVEN BEFORE THE BIOLOGICAL PRODUCT'S LICENCE IS APPROVED."

Given that the *Amgen* case is a matter of first impression, the fragmented nature of the federal circuit's decision, and the importance of a clear interpretation of the BPCIA, a rehearing *en banc* on at least one of the issues presented to the federal circuit is likely. Therefore the effect of the section 262(l)(2)(A) requirement in forcing a biosimilar product applicant to disclose its application and manufacturing information and the timing and mandatory nature of the 180-day notice of commercial marketing provision is not fully resolved. Should the federal circuit deny a rehearing *en banc* the parties will inevitably appeal to the Supreme Court.

Guidance on names

In a separate BPCIA development, the FDA published its long-awaited draft guidance on "Nonproprietary Naming of Biological Products" on August 27. The guidance proposes using the same core non-proprietary name for related biological products and a unique suffix for each. The purpose of the unique non-proprietary names is to prevent inadvertent substitution of related biological products that have not been deemed interchangeable. The proposed rules are applicable to both biological products licensed under section 262(a)—the traditional approval pathway for biological products—and biosimilar products licensed under section 262(k).

The FDA requires only that the suffixes in the core name have four lowercase letters, be unique, and be devoid of meaning. In FDA parlance the non-proprietary name is also referred to as the 'proper' name. The FDA has provided a few hypothetical examples of acceptable proper names. For a hypothetical monoclonal antibody with the core name replicamab, the reference product could be named replicamab-cznm and the biosimilar replicamab-hixf. Zarxio entered the market with the non-proprietary name filgrastim-sndz, but the FDA considers this a placeholder name that could ultimately change.

The FDA suggests that applicants submit no more than three proposed suffixes for a new biological product at either the Investigational New Drug or the Biologics License Application submission stage. The FDA is seeking comment on whether a biological product deemed interchangeable may have the same non-proprietary name as its reference product. ■

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