Supreme Court Decision on “Obamacare” Leaves Abbreviated Biosimilars Licensure Pathway Intact… and Puts the Spotlight Back on the FDA

On June 28, 2012, the Supreme Court issued its decision in *National Federation of Independent Business (NFIB) et al. v. Sebelius* (567 U.S. ___ (2012)), leaving the Patient Protection and Affordable Care Act (PPACA), also known as “Obamacare”, mostly intact – including the portion of the PPACA referred to as the *Biologics Price Competition and Innovation Act of 2009* (BPCIA). The BPCIA amended the Public Health Service Act (PHSA) to permit the Food and Drug Administration (FDA) to license follow-on biologics, or biosimilars, in a manner analogous to the FDA’s authority to license generic small molecule drugs under the Drug Price Competition and Patent Term Restoration Act of 1984 (commonly called “Hatch-Waxman”).

While the BPCIA was not challenged directly, the BPCIA was implicated in *NFIB v. Sebelius* because the Court agreed to address the question of whether the various provisions of the PPACA were severable from one another. Confident that Congress did not intend that the provisions of PPACA stand or fall together, the Court declined to hold the PPACA unconstitutional in its entirety. In view of yesterday’s Supreme Court decision, the FDA must continue its work on implementing the BPCIA’s abbreviated licensure pathway. As part of that work, the FDA will address stakeholder questions and concerns raised in response to three Draft Guidance documents released earlier this year.

Under the authority conferred by the BPCIA, the FDA issued its Draft Guidance to provide interested parties with insight into the FDA’s thinking on scientific and quality considerations in establishing biosimilarity with an innovator’s FDA-licensed reference product, as well as providing the FDA’s views on several provisions of the BPCIA. The Draft Guidance documents elicited extensive comments from many industry and public stakeholders, culminating in a public hearing on May 11, 2012. Copies of the Draft Guidance documents and written comments are available using the following links: Questions and Answers, Quality Considerations, Scientific Considerations.

Highlights of the current status of the abbreviated biosimilars licensure pathway:

**Exclusivity**

In order to reward innovators for the arduous and costly process to bring biologic medicines to market, the BPCIA provides that a biosimilar, or “351(k)”, application (Section 351(k) of the PHSA) may not be submitted to the FDA until four years after its reference product is first licensed and may not be approved for at least another eight years after that. Notably, the BPCIA fails to define whether this “exclusivity” period refers to data exclusivity or market exclusivity. If it refers to the latter – as innovators contend – then 351(k) applicants would be unable to rely on innovator data to support their 351(k) application until the twelve year exclusionary period expires. If it refers to the former – as the generic drug industry contends – then 351(k) applicants would be able to rely on innovator data after the four-year exclusionary period expires. While the FDA has sided with the former interpretation, resolution of this issue is not a subject considered by the Draft Guidance documents, and the definitive answer will likely await consideration by the courts.

Another related topic is the issue of “evergreening” of biologics; i.e., the use of patents, regulatory pathways and business strategies to keep other companies from introducing a competing product into the market. In order to prevent innovators from evergreening by obtaining additional exclusivity periods, the “first licensure” provision of the BPCIA denies exclusivity to supplemental biologics license applications (BLAs) and subsequent BLAs...
from the innovator or related entities that support a clinical change (e.g., indication) or structural modification that does not alter the reference product’s safety, purity, or potency. However, at least one stakeholder’s comments raised the possibility that – depending upon on how the italicized “or” above is interpreted – innovators might be able to circumvent the BPCIA’s safeguards by coupling a clinical change with a structural modification (no matter how minor).

The FDA also garnered some attention by stating that innovators could submit a request for reference product exclusivity in their BLA, backed up by adequate data and information supporting the request. Several stakeholders were quick to opine that the FDA’s position was inconsistent with the PHSA because exclusivity automatically attached to a licensed reference product by operation of law.

**Clinical Trials**

Although the BPCIA requires at least one clinical study that is sufficient to demonstrate safety, purity and potency in at least one condition of use, the FDA has discretion to waive this requirement for 351(k) applications. In exercising this discretion, the FDA espoused its view that, at a minimum, pharmacokinetic (PK) and pharmacodynamic (PD) studies and at least one clinical immunogenicity study would generally be expected prior to approval.

In response, at least one stakeholder suggested that clinical trials should only be required if they contribute new and actionable data, whereas another stakeholder expressed its opinion that nothing short of Phase III clinical trials would suffice to assure the public that biosimilars are safe. Particulars aside, the greatest concern from stakeholders appears to be that if the requirements for clinical trials are onerous enough, industry will forego using the abbreviated licensure pathway altogether.

**Use of Non-U.S. Comparator Data**

There were substantial comments and criticism in response to the FDA’s proposal that a 351(k) applicant be permitted to use non-U.S.-licensed product data (e.g., animal or clinical studies) under certain circumstances to help establish biosimilarity to an innovator’s reference product.

Stakeholder opinions on this proposal ranged from acknowledging the appropriateness of using this data, with certain caveats, to allegations that using this type of data to establish biosimilarity exceeds the FDA’s statutory authority under the PHSA. Even if the FDA maintains this position in its final guidance, at least one stakeholder submission illustrates the practical difficulties in using data from a non-U.S.-licensed product to draw conclusions about its U.S.-licensed equivalent, which are some of the same challenges in comparing a reference product and a biosimilar (see stakeholder comments regarding EPREX®/epoetin alfa licensed by the European Commission and PROCRIT®/FDA-licensed epoetin alfa).

**Use of Trade Secrets**

Another contentious issue is the FDA’s use of innovator trade secrets as part of the biosimilars approval process. The FDA announced that it intends to publish information pertaining to innovator reference product approvals in order to facilitate biosimilar development programs and submission of 351(k) applications. As a general matter, publication would include the type of information found in the "action package" of an innovator's BLA.

In response, several stakeholders expressed concerns that BLAs and “action packages” often contain analytical, clinical and manufacturing information that qualifies as trade secrets, and that the FDA’s regulations regarding confidentiality in BLA’s dates to the 1970s. Accordingly, the FDA was requested to revise its regulations for consistency with the BPCIA and take adequate precautions to avoid disclosures of this information. Abbott Laboratories went a step further, filing a Citizen Petition with the FDA on April 2, 2012. In its Citizen Petition, Abbott requested that the FDA confirm that it would not approve a HUMIRA® biosimilar or any other biosimilar
product citing a reference product for which a BLA was submitted prior to enactment of the PPACA. The basis for making this request was that, in Abbott’s view, the FDA’s use of innovators’ trade secrets constitutes a taking under the 5th Amendment to the U.S. Constitution.

**Variance and “Carveouts” from the Innovator’s Reference Product**

The FDA expressed its views that it might approve a biosimilar that differs from its reference product in formulation, delivery device or container closure system, and fewer than all approved routes of administration – provided that any difference did not introduce a clinically meaningful difference in safety, purity, and potency. The FDA also opined that a 351(k) applicant could generally obtain approval for less than all approved reference product presentations and conditions of use as well.

The FDA received a host of comments on these related topics. Some stakeholders expressed concerns that “carveouts” might make an approved biosimilar less safe or potent or facilitate broad off-label use. Other stakeholders expressed concerns that intentionally introducing different formulations or approving fewer than all reference product delivery devices might put patients at increased and unnecessary risk.

**Unaddressed Issues**

The FDA has taken the position that it would be difficult as a scientific matter to establish that a biosimilar is interchangeable with a reference product, and therefore, it did not issue any guidance on meeting the interchangeability standard under the PHSA. Interchangeability is a key aspect of the abbreviated licensure pathway in that it allows the substitution of a biosimilar for its reference product without a physician’s intervention – which would presumably lead to lower insurance and consumer costs.

While there was general agreement from stakeholders about the importance of provisions regarding interchangeability, opinions on meeting that standard differed. At least one stakeholder indicated that interchangeability would be inappropriate for certain product classes (e.g., monoclonal antibodies), while another suggested that establishing biosimilarity and interchangeability use the same “highly similar” standard.

The FDA also refrained from addressing postmarketing considerations such as naming, labeling, pharmacovigilance, and biological “drift”. In particular, the issue of naming – that is, whether a biosimilar and a reference product should have the same or distinguishable non-proprietary name – drew numerous comments, and stakeholders on both sides cited the European Commission’s experience with EPREX® to support their respective positions on some of these issues.

**Next Steps**

Following the Supreme Court’s decision yesterday, it is expected that the FDA will focus on finalization of the Draft Guidance documents, including consideration of the important feedback from interested parties. As industry awaits the FDA’s final Guidance documents, with continued uncertainty regarding the above issues, no 351(k) applications have been filed to date.

If you have any questions concerning the issues raised in this alert, please contact the authors: Thomas A. Cawley, Jr., Ph.D., Julie Broadus Meigs, Ph.D., and Russell S. Timm, Ph.D., or any of Womble Carlyle's Intellectual Property attorneys.