Since the beginning of the 21st century, biosimilars have been hailed by many as the next major milestone in bringing affordable and potentially life-saving treatment options to patients around the world. But despite the excitement and considerable potential, biosimilars have experienced a somewhat slow start in the U.S. with only nine having the stamp of approval from the U.S. Food and Drug Administration (FDA).

Like generic drugs in the 1980s, biosimilars today face a number of regulatory, legal, scientific, and public perception obstacles to continued growth. Nevertheless, popular opinion remains that the success of biosimilars in the U.S. is imminent. Here are four areas impacting biosimilars access to keep an eye on:

1. **When Will Interchangeables Appear?**

   The U.S. follows two tiers for abbreviated approval. While biosimilars require “no clinically meaningful” difference from an already approved reference drug, interchangeable biologics require an additional standard: they are expected “to produce the same clinical result as the reference product in any given patient.” An applicant that can satisfy the interchangeable standard gets the advantage of marketing a competing product that can be automatically substituted for the reference drug at the pharmacy level without physician approval. In contrast, Europe and some other global markets treat all locally approved biosimilars as interchangeable.

   As of 2018, not a single interchangeable has been approved in the U.S. On January 17, 2017, the FDA released long-awaited draft guidance on biosimilar interchangeability designed to help sponsoring pharmaceutical companies satisfy the interchangeable standard. However, this guidance leaves much flexibility, and arguably, much ambiguity. The draft guidance emphasizes there is “no single data package that will work for all proposed interchangeable products” and urges sponsors to consider the “totality of factors” in order to identify data needed to demonstrate interchangeability. Moreover, the draft guidance asks sponsors to evaluate interchangeability through “switching studies,” during which patients would alternate between an interchangeable biosimilar and its reference product two or more times. Interested organizations quickly submitted comments on the FDA’s guidance, raising additional questions regarding interchangeability. The FDA has not yet commented on whether it will modify the 2017 draft guidance based on these comments.

   So when can we expect to see interchangeables hit the market? As of summer 2017, at least one FDA official expected interchangeable biosimilars to reach the market in less than two years. That same summer, Boehringer Ingelheim announced that it had begun the first study in the U.S. to investigate an interchangeability designation.

2. **How Will Doctors and Patients React?**

   One important element for ensuring the success of biosimilars and interchangeables is education. In the 1980s and 1990s, the generics industry faced extreme skepticism from the public. But this quickly changed, largely due to improved physician and patient education. As of last year, generic drugs account for nearly 90 percent of prescriptions in the U.S.

   Last October, FDA announced the release of new educational materials designed to educate health care professionals about biosimilar and interchangeable products. The resources included fact sheets, graphics, and webinars directed toward clinicians, as well as organizations required to share information about biosimilars to their stakeholders. The FDA further announced it will embark on additional research to identify information needed from prescribers in order to improve communication with patients about biosimilars.

   Educational goals are not, of course, limited to the U.S. In fact, the International Generic and Biosimilars Medicines Association (IGBA) launched its own educational campaign on biosimilar medicines this month.

   Will increased education help the growth of biosimilars in the U.S.? Current education is targeted toward physicians and as additional educational materials and campaigns continue to form and circulate both nationally and internationally, the adoption of biosimilars is likely to
3. What Will Congress and State Legislatures Do Next?

States have long been responsible for regulating automatic substitution laws at the pharmacy counter. Automatic substitution occurs when a more affordable generic version of a drug is dispensed instead of the costly brand product. Since the passage of the Biologics Price Competition and Innovation Act (BPCIA), state legislatures have worked to update their pharmacy laws to include interchangeable biosimilars. Today, 37 states and Puerto Rico have enacted laws aimed at regulating automatic interchangeable biosimilar substitution at the pharmacy level. At the federal level, Congress has begun addressing pricing issues regarding biosimilars, but continues to debate regulatory approval matters. Earlier this month, Congress passed a two-year budget agreement that includes important Medicare coverage provisions that will impact the biosimilars industry. These provisions added biosimilars to the Medicare Part D coverage gap discount program, permitting biosimilar manufacturers to offer discounts equivalent to those permitted to the brand biologic company. The inclusion of biosimilars in this program will not only increase patient access to more affordable alternatives to brand biologics, but will also help the federal government realize significant savings.

Even more notable, however, were biosimilar provisions that were not included in the bill. Since 2016, Congress has debated the Creating and Restoring Equal Access to Equivalent Samples (CREATEs) Act. The legislation would ease the ability for biosimilar applicants to access the critical reference samples they need to demonstrate biosimilarity to and speed the development of biosimilars in the U.S. CREATEs incorporates a number of concepts proposed in 2014 and 2015 under the Fair Access for Safe and Timely (FAST) Generics Act and seeks to expedite approval of generic drugs and biosimilars. Although the bill enjoys bipartisan support from both ends of the political spectrum and has been scored as nearly $4 billion dollars in savings over 10 years, Congress declined to incorporate the legislation into the new budget agreement, leaving the future of CREATEs uncertain.

4. What Will Biosimilars Litigation Look Like in the Coming Year?

Much like the Hatch-Waxman Act set up a patent dispute system for generic drugs, the BPCIA established a dispute “resolution” scheme for biosimilar patent litigation. A unique aspect of the BPCIA patent scheme is colloquially termed the “patent dance” and sets up a series of disclosures that are made between the owner of patents associated with the reference biologic, and the biosimilar applicant. As of 2014, however, biosimilar applicants began opting out of this dance entirely, arguing that this portion to the statute was optional. Last year, the U.S. Supreme Court agreed in Amgen v. Sandoz. The Supreme Court held that when a biosimilar applicant opts out of the patent dance, the only federal remedy for the patent owner is to bring an immediate declaratory judgment action to enforce the patents. In December 2017, the Federal Circuit followed up on the Supreme Court ruling and held that state laws are preempted by BPCIA.

Moving forward, biosimilar applicants may continue to opt out of the patent dance, giving them more control over how patent disputes are addressed. A biosimilar applicant may now choose whether to disclose its application early on, forcing the reference product sponsor to either bring suit early or face limited remedies; or the biosimilar applicant may choose to not disclose its application and instead consider challenging the patents at the U.S. Patent and Trademark Office (USPTO), where it faces a lower burden of proof for invalidity.

What Will Happen With IPRs?

Although the USPTO proceedings known as inter partes review (IPR) have become a prominent pathway for challenging patents outside of the federal court system in the past few years, they currently face uncertainty. The most fundamental question is whether IPRs will continue to exist as an alternative for challenging biosimilar or other patents. The Supreme Court is expected to hand down a decision any day in Oil States Energy Services, LLC v. Greene’s Energy Group, LLC, which will decide whether the IPR process is unconstitutional. If the Supreme Court upholds the current system, IPRs will continue to be a strategic consideration that every biosimilar applicant must consider during the product selection process. If IPRs are held unconstitutional, we may see a renewed return to the patent dance in order to expedite resolution of patent disputes.

Will Antitrust Disputes Heat Up?

Finally, keep an eye out for antitrust disputes. Reverse payment patent settlements, also known as “pay-for-delay” agreements, have been a hotly contested antitrust matter in the realm of generic drugs arising from the Hatch-Waxman Act. In short, reverse payment settlements occur when a brand-name pharmaceutical company pays a generic pharmaceutical company to delay market entrance of a generic drug as part of the patent lawsuit settlement. In a 2013 landmark antitrust decision in FTC v. Actavis, the Supreme Court held that reverse payment settlements must be analyzed under a rule-of-reason framework. Since this ruling, the number of reverse payment settlements has decreased due to the uncertainty of how the rule will be applied, and the Supreme Court has not provided additional guidance on the matter.

The added complexity of biosimilars is likely to place a thumb on the scale of protecting reverse payment settlements under the existing antitrust framework. For example, biologics typically will hold a larger market value than a small molecule drug, and the acceptable settlement values under antitrust law may increase. In September 2017, AbbVie and Amgen settled a patent dispute over AbbVie’s proposed biosimilar for adalimumab (Humira). As the first publicized biosimilar patent settlement, this settlement marks the potential revival of the antitrust debates surrounding reverse payments. The details of this Humira settlement remain unknown, but moving forward there may be additional attention from the Federal Trade Commission and the courts, which may result in additional guidance for appropriate settlements.

In addition, the pricing activities by the reference sponsors themselves are likely to be scrutinized by payers and competitors alike. Courts are already being asked to consider whether the pricing structures and volume discounts provided by reference sponsors go beyond...
traditional competition and constitute improper monopolization.

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