U.S. Supreme Court Upholds Affordable Care Act: Significant Aspects of Affordable Care Act for Generic Pharmaceutical Companies

Clifford Katz

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On June 28, 2012, the U.S. Supreme Court upheld the Patient Protection and Affordable Care Act (Pub. L. 111-148) (Affordable Care Act). *See National Federation of Independent Business et al. v. Sebelius, Secretary of Health and Human Services, et al.*, No. 11-393. The Affordable Care Act makes the following changes in law that are of particular significance to manufacturers of generic drugs and biological products: (1) creation of an abbreviated licensure pathway for biological products shown to be biosimilar to, or interchangeable with, an FDA-licensed biological reference product, pursuant to the Biologics Price Competition and Innovation Act (BPCIA); (2) revision of the definition of Average Manufacturer Price (AMP), a price used by the Medicaid program to calculate rebates paid by generic drug companies and reimbursement amounts paid to pharmacies that dispense generic drugs; (3) increase in the amount of Medicaid rebates paid by drug manufacturers; (4) change in the calculation of Federal Upper Limits (FULs), which are prices used to reimburse providers that dispense drugs under the Medicaid program; (5) expansion of the 340B drug pricing program, which limits the cost of drugs to certain providers; (6) alleviation of the labeling roadblock for FDA approval of generic drugs when the reference brand product changes its label; and (7) reduction of the Medicare Part D coverage gap, referred to as the "donut hole". The Affordable Care Act makes additional changes in law, not discussed in this advisory, that are applicable to all drug manufacturers not discussed in this advisory, such as amendments to the False Claims Act's "public disclosure bar" and "original source" provisions.

BIOSIMILARS

Sections 7001 through 7003 of the Affordable Care Act, known as the Biologics Price Competition and Innovation Act (BPCIA), created an abbreviated licensure pathway for biological products shown to be biosimilar to, or interchangeable with, an FDA-licensed biological reference product. The BPCIA is somewhat analogous to the Hatch-Waxman Act, which established an abbreviated pathway to bring generic drugs to the market, but there are some key distinctions between the laws and the products, which will impact the ability of generic manufacturers to bring products to the market in a cost-effective manner that saves consumers money through discounted generic products.

What are "biological products"?

The Public Health Service Act (PHS Act), as amended by the BPCIA, defines "biological product" as: a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.
See 42 U.S.C. § 262(i)(1).

Generally speaking, biological products are larger and more complex in structure than the active ingredients in traditional drug products. For example, drug products may often have a molecular weight of less than 1,000 and are manufactured by chemical synthesis. By contrast, biological products generally have a molecular weight of greater than 10,000 and are made from living cells, such as a microorganism, or plant or animal cells. Because they are made from living cells, biological products present additional challenges in manufacturing with consistency.

Notably, the BPCIA amended the definition of biological product to include a "protein (except any chemically synthesized polypeptide)." In its draft Guidance, the FDA proposed to define "protein" as "any alpha amino acid polymer with a specific defined sequence that is greater than 40 amino acids in size." The FDA further proposed a definition of "chemically synthesized polypeptide" as "any alpha amino acid polymer that (1) is made entirely by chemical synthesis; and (2) is less than 100 amino acids in size." The FDA considers a chemically synthesized polypeptide to be a drug, regulated under the Food, Drug & Cosmetic Act, not a "biological product."

What does it mean to be "biosimilar" or "interchangeable"?

The PHS Act, as amended by the BPCIA, defines "biosimilar" to mean:
(A) that the biological product is ***highly similar*** to the reference product notwithstanding minor differences in clinically inactive components; and
(B) there are ***no clinically meaningful differences*** between the biological product and the reference product in terms of the safety, purity, and potency of the product.
See 42 U.S.C. § 262(i)(2) (emphasis added).

The key terms in the statutory definition – "highly similar" and "no clinically meaningful differences" – are not defined.

To be considered an "interchangeable" biological product, the applicant must show that:

(A) the biological product-
    (i) is biosimilar to the reference product; and
    (ii) can be expected to produce the same clinical result as the reference product in any given patient; and
(B) for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch.
See 42 U.S.C. § 262(k)(4).

If the FDA approves the product as "interchangeable," the product "may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product." *See* 42 U.S.C. § 262(i)(3).

How do you show that a product is biosimilar?

With respect to drug products, the brand company is required to submit a New Drug Application (NDA), in which it must demonstrate the drug's "safety and effectiveness." The generic drug applicant is not required to prove the drug's safety and effectiveness with preclinical (animal) and clinical (human) data; rather it is only required generally to show that the active pharmaceutical ingredient (API) is the same as in the brand drug and that the generic drug is so formulated as to make the API equivalently bioavailable to a patient. Similarly, the brand company of a biological product submits a Biologics License Application (BLA), in which it must demonstrate that the product is "safe, pure and potent." The requirements imposed upon a biosimilar applicant, however, are much higher than those applicable to generic drug products. The application, pursuant to section 351(k) of the PHS Act, must demonstrate that the product is biosimilar based on: (a) analytical studies, (b) animal studies, and (c) a clinical study or studies. Additionally, the definition of biosimilar leaves open the possibility that the FDA will require the applicant to make a showing that the product is "safe, pure and potent". The FDA can determine, in its discretion, that certain studies or data are not necessary.

Separate and apart from the impact of applicable patents, what is the period of market exclusivity for the reference product and first interchangeable biosimilar product?

Somewhat like an Abbreviated New Drug Application (ANDA) filed for a drug containing a new chemical entity under the Hatch-Waxman Act, a 351(k) application cannot be submitted until 4 years after the reference product was licensed, nor may the later-filed application be approved before a further set period of years. However, whereas the reference drug product under the Hatch-Waxman Act receives a 5-year exclusivity period, the reference biological product enjoys 12 years of exclusivity; both laws permit a 6-month extension for pediatric exclusivity.

A biosimilar that is approved by the FDA as interchangeable is given 1-year market exclusivity, during which time the FDA will not approve additional interchangeable products. By contrast, the first-filer of an ANDA product may receive 180 days of exclusivity under the Hatch-Waxman Act.

What are the procedures for resolving patent disputes concerning biosimilar applications under the BPCIA?

Similar to the filing of an ANDA under the Hatch-Waxman Act, the filing of a 351(k) application for a biosimilar product triggers a statutory framework to resolve patent disputes, but that framework is substantially different than the framework established by the Hatch-Waxman Act. Under the Hatch-Waxman Act, brand companies are required to list all patents claimed to cover the brand drug in the Orange Book. This gives generic drug companies notice of the patents that the brand company could claim as infringed. The generic company of a biosimilar product does not have comparable advance notice. Instead, the generic company must first disclose its biosimilar application and related manufacturing process to the brand company (referred to as the "reference product sponsor"). This disclosure is the beginning of a cascade of events.

(a) Within 20 days of the date the FDA takes the 351(k) application under review: Applicant provides reference product sponsor with confidential access to the application and information concerning applicant's manufacturing process.

(b) Within 60 days: Reference product sponsor provides a list of allegedly infringed patents and specifies which patents it would license to the applicant.

(c) Within 60 days: Applicant provides reference product sponsor with a counter-list of allegedly applicable patents, along with a detailed statement for why each patent is invalid, unenforceable, or will not be infringed, or a statement that it will not market the product until the patent expires. Applicant also responds to any offer by the reference product sponsor to license any of the patents.

(d) Within 60 days: Reference product sponsor responds to applicant's non-infringement and invalidity contentions.

(e) Within 15 days: Parties negotiate the patents that will be the subject of expedited litigation or exchange lists if no agreement reached.

(f) Within 30 days: Reference product sponsor must initiate expedited litigation. If no suit is brought within this period, damages are limited to a reasonable royalty.

(g) 180 days before launch of biosimilar product: Applicant must provide notice to the reference product sponsor. Reference product sponsor may move for a preliminary injunction.

A key distinction between the Hatch-Waxman Act and the BPCIA is that the filing of the 351(k) application does not automatically stay FDA approval of the application for 30 months but the practical impact of that difference remains to be seen.

How will biosimilars affect the market?

Biosimilars are predicted to be not as heavily discounted as generic drugs. For example, the Congressional Budget Office (CBO) estimates that biosimilar products will be discounted only about 40% by the 4th year on the market. Nonetheless, the CBO estimated that the BPCIA would still reduce total expenditures on biologics in the United States by about $25 billion over the 2009-2018 period.

Automatic substitution laws and other built-in financial incentives that encourage the dispensing of generic drugs may not be applicable to biosimilars. The absence of such laws and incentives is also predicted to impact biosimilars' market penetration. Unlike generic drugs which can capture 50% or more of the market within months of launch, the CBO estimates that, by the 4th year on the market, the biosimilar product will only capture about 35% of the market.

In spite of the various additional hurdles biosimilars will face, as compared to generic drugs, there is no denying that opportunity exists for generic companies to make a profit. Annual sales of biological products are more than $40 billion in the U.S. and more than $112 billion worldwide. Biosimilars accounted for only $243 million of the U.S. market in 2010, but are expected to increase to $3.7 billion of the market by 2015.

AMP & MEDICAID REBATES

Under the Omnibus Budget Reconciliation Act of 1990 (OBRA '90), a drug manufacturer is required to enter into a Medicaid Rebate Agreement for its drugs to be covered by the Medicaid program. OBRA '90 created a price called Average Manufacturer Price (AMP), which drug manufacturers have been required to report to the Centers for Medicare & Medicaid Services (CMS) under the Rebate Agreement. CMS uses AMP to calculate Medicaid rebates. Before the Affordable Care Act, rebates for noninnovator multiple source drugs were 11% of AMP multiplied by the number of drug units dispensed under the Medicaid program. The Affordable Care Act revised the definition of AMP and

increased the rebate percentage for noninnovator multiple source drugs to 13%.

AMP Definition Replaces “Retail Pharmacy Class of Trade” with “Retail Community Pharmacy”

Prior to the enactment of the Affordable Care Act, federal law defined AMP as: “the average price paid to the manufacturer for the drug in the United States by wholesalers for drugs distributed to the retail pharmacy class of trade, after deducting customary prompt pay discounts.” 42 U.S.C. § 1396r-8(k)(1). The Medicaid Rebate Agreement further defined AMP as: “the average unit price paid to the manufacturer for the drug in the States by wholesalers for drugs distributed to the retail pharmacy class of trade…AMP includes cash discounts allowed and all other price reductions…which reduce the actual price paid…” Medicaid Rebate Agreement, § I(a).

The Affordable Care Act revised the definition of AMP by replacing the term “retail pharmacy class of trade” with “retail community pharmacy.” AMP is now defined as: “average price paid to a manufacturer for the drug by wholesalers for drugs, distributed to retail community pharmacies and retail community pharmacies that purchase drugs direct from the manufacturer.” The Affordable Care Act further defines “retail community pharmacy” to exclude certain entities as follows:

The term “retail community pharmacy” means an independent pharmacy, a chain pharmacy, a supermarket pharmacy, or a mass merchandiser pharmacy that is licensed as a pharmacy by the State and that dispenses medications to the general public at retail prices. Such term ***does not include*** a pharmacy that dispenses prescription medications to patients primarily through the mail, nursing home pharmacies, long-term care facility pharmacies, hospital pharmacies, clinics, charitable or not-for-profit pharmacies, government pharmacies, or pharmacy benefit managers.

Additional Changes to AMP Definition

The Affordable Care Act makes other changes that impact the calculation of AMP, including:

(a) The revised AMP definition explicitly excludes bona fide service fees. Bona fide service fees include: “distribution service fees, inventory management fees, product stocking allowances and fees associated with administrative services agreements and patient care programs (such as medication compliance programs and patient education programs).”

(b) The Act creates a separate definition of AMP for so-called “5i drugs,” which are inhalation, infusion, instilled, implanted, or injectable drugs that are not generally dispensed through a retail community pharmacy. AMPs for 5i drugs do not exclude “payments received from, and rebates or discounts provided to, pharmacy benefit managers, managed care organizations, health maintenance organizations, insurers, hospitals, clinics, mail order pharmacies, long term care providers, manufacturers, or any other entity that does not conduct business as a wholesaler or a retail community pharmacy.”

(c) The added definition of “wholesaler” includes manufacturers when they conduct wholesale distribution.

Early in 2012, CMS released a proposed rule implementing the new definition of AMP, as well as seeking to make other clarifications regarding the calculation of AMP. *See* 77 Fed. Reg. 5318 (Feb. 2, 2012).

FEDERAL UPPER LIMITS

The Affordable Care Act modified how Federal Upper Limits (FULs) are calculated. FULs are prices set by CMS, which are maximum payment amounts to providers, in the aggregate and exclusive of dispensing fees, for generic drugs dispensed under the Medicaid program.

Prior to the Affordable Care Act, CMS regulations provided that FULs were to be calculated based upon published prices, which include Average Wholesale Price (AWP) and Wholesale Acquisition Cost (WAC). The Deficit Reduction Act of 2005 provided for FULs to be calculated based upon 250% of AMP, but CMS never implemented this provision. In 2007, the National Association of Chain Drug Stores and the National Community Pharmacists Association obtained a preliminary injunction prohibiting CMS from implementing a new AMP Rule which provided for calculating FUL based on AMP. Subsequently, the federal Medicare Improvements for Patients and Providers Act of 2008 prohibited CMS from calculating FULs based on the AMP Rule prior to October 1, 2009. Instead, FULs would continue to be set based on the published price methodology set forth in 42 C.F.R. § 447.332 in effect on December 31, 2006.

The Affordable Care Act once again changes the law by requiring FULs to be calculated based on AMP. Specifically, the law requires that FULs be “no less than 175 percent of the weighted average (determined on the basis of utilization) of the most recently reported monthly AMPs for pharmaceutically and therapeutically equivalent multiple source drug products that are available for purchase by retail community pharmacies on a nationwide basis.” It is anticipated that this change in law will reduce the FUL amounts, which could potentially reduce reimbursement to providers of generic drugs. Other factors may play a role in whether the change in the methodology in calculating FULs impacts the overall reimbursement to providers, including, for example, whether the state Medicaid program already uses State Maximum Allowable Costs which are lower than the new FULs, or whether the state Medicaid program increases dispensing fees for generic drugs to account for the lower FULs.

340B DRUG PRICING PROGRAM

Section 340B of the Public Health Service Act limits the prices of drugs paid for by certain federally-approved entities, referred to as 340B providers. The Affordable Care Act expanded the entities eligible to become 340B providers to include: children’s hospitals, freestanding cancer hospitals, critical access hospitals, and rural referral centers.

Additionally, since the calculation of 340B prices is tied to AMP and Medicaid rebates, the changes to AMP and the rebate percentage will impact 340B prices.

FACILITATION OF APPROVAL OF GENERIC DRUGS

To obtain FDA approval for an ANDA product, the generic drug company is generally required to copy the label of the reference listed drug (*i.e.*, the brand drug). This labeling requirement gave brand companies the power to delay FDA approval of generic drugs by making labeling changes to their product. The Affordable Care Act partially alleviates this roadblock. Under the Act, if the brand company makes a change to the labeling, the FDA can approve the ANDA product if: (a) the change was approved within 60 days of the expiration of the brand drug’s patent or exclusivity period; (b) the labeling change does not include a change to the “Warnings” section; and (c) the applicant agrees to submit revised labeling within 60 days of notice from the FDA.

REDUCTION OF MEDICARE PART D “DONUT HOLE”

The Medicare Part D “donut hole” is the gap in coverage between the initial coverage limit of the

Part D plan and the point at which catastrophic coverage begins. In this gap, the beneficiary was required to pay the full cost of drugs. The Affordable Care Act provides that Medicare will pay a portion of the cost of generic drugs during the coverage gap. Presently, Medicare pays 14% of the cost of generic drugs and this contribution will increase each year until it reaches 75% in 2020.

For more information about this advisory please contact:

Clifford Katz
(212) 808-7609
ckatz@kelleydrye.com