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The Challenges of Regulating Drugs
and New Technologies

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CHAPTER TWENTY-TWO

FDA Regulation of Biosimilars

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I. INTRODUCTION

A recent development in Europe and the United States is the establishment of an abbreviated pathway to market for Biosimilars—biological products that are similar but not identical in purity, safety, and efficacy to a reference biological product. The U.S. law, the Biologics Price Competition and Innovation Act (BPCIA), was enacted in March 2010 as part of the Affordable Care Act (ACA). The objective of the BPCIA, like the Hatch-Waxman Act of 1984 before it for generic chemically synthesized drugs, was to encourage increased price competition and cost savings for biological products, while maintaining incentives for innovation.

Biological drugs are manufactured in living systems, typically using recombinant DNA technology. The resulting molecules are large, complex, and often difficult to characterize analytically. The drug substance may be heterogeneous, and its mechanism(s) of action can be poorly understood. Even seemingly minor changes to the raw materials or manufacturing process can lead to differences—sometimes
analytically undetectable—that have enormous clinical consequences. It is generally understood that it will not be scientifically possible for a biosimilar manufacturer to prove that its product is “the same as” a reference biological product. Determining instead that the product is “similar enough” to justify—as a scientific and regulatory matter—an abbreviated application that relies on approval of the earlier product is a challenging task for regulators and industry. FDA is currently implementing the BPCIA through draft guidance, public forums, and meetings with potential applicants. FDA’s decisions with respect to how biosimilarity may be shown (i.e., the content and nature of abbreviated applications)—and other related regulatory factors discussed below, such as the interchangeability standard—will have a profound impact on the number of biosimilar entrants for any particular biological product and on the evolution of market competition.

In this chapter, we consider the U.S. Food and Drug Administration’s (FDA) evolving guidelines and a number of open issues that could have important implications for development of biosimilar competition.

A. Biosimilarity

To reach the market, a biosimilar firm must demonstrate that its product is “biosimilar” to a reference product. This entails showing that (1) the candidate product is “highly similar to the reference product notwithstanding minor differences in clinical inactive components,” and (2) there are “no clinically meaningful differences” between the two, in terms of safety, purity, and potency (42 USC § 262(l)). The statute does not define these terms, leaving FDA discretion to tailor application requirements to the particular product class as well as the particular applicant and candidate product.

B. Innovation Incentives and Exclusivity Provisions

In order to maintain incentives for new biologics, the BPCIA provides biological product innovators with exclusivity periods that preclude biosimilar competition for a fixed period of time. Specifically, biosimilar applications may not be submitted until four years after
FDA licensure of the reference biological product. Also, FDA cannot approve a biosimilar application until twelve years after licensure of the reference product. An additional six months of exclusivity are available for the reference product if the innovator satisfies pediatric study requirements. The six months in question are added to both the four-year and the twelve-year periods.

The statute limits which innovative biologic license applications (BLAs) are eligible for their own four-year and twelve-year terms of exclusivity. Specifically, there are no new terms for (1) a supplemental BLA for the reference product; (2) a subsequent BLA filed by the same sponsor, manufacturer, or other related entity for a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device, or strength; or (3) a subsequent BLA filed by the same sponsor, manufacturer, or other related entity for a structural change that does not result a change in safety, purity, or potency (42 USC 262(k)(7)). Stakeholders generally assume that these “second generation” applications, while not receiving four-year and twelve-year terms of their own, will be protected under the “umbrella” of the initial application’s exclusivity terms.


The BPCIA and Hatch-Waxman Act differ significantly with respect to premarket patent litigation. Unlike the Hatch-Waxman Act, the BPCIA does not require a public listing of relevant innovator patents. Nor does it provide a thirty-month stay of biosimilar application approval when the innovator brings patent litigation. Nor does it offer 180-day exclusivity to the first firm to file an abbreviated application with a patent challenge. The BPCIA instead requires a series of complex private information exchanges between the biosimilar applicant and reference product sponsor, followed by negotiated identification of patents for litigation, and then typically two separate phases of premarket litigation (42 USC 262(l); compare 21 USC 355(j)).

Potential biosimilar entrants have raised concerns about the information disclosure required by the BPCIA premarket patent provisions, specifically, the obligation to provide a copy of their pending marketing applications to the reference product sponsors. This concern may prompt some companies to submit full BLAs, rather than
abbreviated applications under the new statute. This is discussed further in section V.

II. FDA REGULATORY STANDARDS

A. FDA Draft Guidance

FDA has issued a number of draft guidance documents beginning in 2012 to implement the BPCA, and several more are expected in 2014. The drafts to date indicate that the agency “intends to consider the totality of the evidence provided by a sponsor to support a demonstration of biosimilarity” (FDA Draft Guidances 2013). FDA also intends a stepwise approach, in which, for a given biosimilar application, “(t)he scope and magnitude of clinical studies will depend on the extent of residual uncertainty about the biosimilarity of the two products after conducting structural and functional characterizations and possible animal studies” (ibid.).

Eventually, FDA may permit applicants to use a “fingerprint-like analysis algorithm” to justify significant reductions in—or perhaps even omission of—preclinical and clinical testing. Fingerprinting means comparing a large number of product attributes and combinations of attributes, and in particular quantifying the similarity of the resulting patterns in two different products. Agency officials described this approach in a peer-reviewed journal article that is generally understood to represent the agency’s position (Kozlowski et al. 2011). Fingerprinting strategies also played a key role in FDA’s approval of the Sandoz abbreviated new drug application (ANDA) for enoxaparin sodium, a complex product mixture of polysaccharides that is derived from natural sources (Grabowski, Guha, and Salgado 2014b).

Advances in the fingerprinting approach could substantially lower the cost of developing and obtaining FDA approval of biosimilars. However, these advances may not be available or acceptable to regulatory authorities as sufficient for approval for a number of years, especially in the case of more complex biologics, such as monoclonal antibodies and interferons, which account for an increasing proportion of expenditures on biopharmaceuticals.

Development times and costs of FDA submissions for U.S. biosimilars could be substantially reduced for at least some biosimilars already
on the market in Europe, if the applicants can rely on the trials that supported European approval. In its draft guidance, FDA noted it will accept studies using foreign comparator products (i.e., as a practical matter, studies undertaken for approval in other jurisdictions) as supportive of FDA approval under certain circumstances, when justified scientifically and when accompanied by "bridging" data. The scientific justification may need to address issues such as whether the foreign comparator product is made in a facility inspected by a regulatory authority comparable to FDA. The scientific bridge between the products should include comparative physicochemical characterization, bioassays, and functional assays, and it may include comparative nonclinical or even clinical data (FDA Draft Guidance 2013).

Implementation of the Biosimilar User Fee Act of 2012 (BsaUFA) will also allow biosimilar applicants to streamline their development plans through early and regular meetings with FDA about the size and scope of their applications. Specifically, FDA has committed to hold various types of biosimilar product development meetings with applicants. During these meetings, FDA will provide input regarding biosimilar development programs, including with respect to the similarity of the proposed biosimilar and reference product, the need for additional studies, and the design of those studies (FDA, Biosimilar User Fee Act, 2013a).

B. Expected Costs of Developing and Marketing Biosimilars

If FDA requires significant evidence from clinical trials to support the approval of biosimilars, biosimilar manufacturers will need to make much bigger premarket investments than do generic drug manufacturers. The investment necessary will depend on the number and size of the necessary clinical trials, the number of indications involved, and other FDA requirements. The average clinical costs to develop a new biologic entity have been estimated to be several hundred million dollars with more than a billion dollars for the complete development process (DiMasi and Grabowski 2007). Although out-of-pocket clinical development costs for biosimilars will be significantly less, they have been estimated to be up to $100 million or more (FTC 2009). By contrast, the cost of completing bioequivalence studies for a generic drug is estimated to be only $1-$5 million (FTC 2009).
The clinical data requirements are expected to vary with the complexity of the biological product and for monoclonal antibodies may well be at the upper end of the investment time and cost spectrum. These products tend to be approved for a variety of indications, sometimes in unrelated therapeutic areas with different pathophysiologies. Their mechanisms of action may be poorly understood and can differ by indication. Although the EMA has now approved one biosimilar monoclonal antibody with indication extrapolation (albeit with a commitment from the applicant to conduct an additional comparative study in the postmarket period), it remains to be seen whether FDA will be comfortable with complete indication extrapolation for these more complex products. Limiting extrapolation would increase both the cost and the time necessary to put together an application (Schneider et al. 2012). If the agency conditioned approval on verifying clinical efficacy in some or all of the extrapolated indications, this could slow market uptake and would in any case increase costs in the postmarket period.

Biosimilar manufacturers will also need to construct expensive plants or obtain long-term lease or purchase agreements with third parties that already have FDA-approved biologics manufacturing facilities if they do not already have suitable manufacturing capacity. Manufacturing processes for biologics involve numerous challenging cell culture and purification steps, and the use of living cells introduces unavoidable variability into the process. The FTC has estimated that plant investment expenditures for biosimilars will range from $250 million to $1 billion, and other more recent estimates are within this range (FTC 2009).

In sum, the total cost of entry for biosimilars in terms of clinical development expenditures and plant capacity investment is likely to be many times higher than the comparable cost for generic drug products. The high costs of entry—particularly, the substantial development and capital requirements—are likely to restrict the number and types of biosimilar entrants, at least initially (Grabowski, Guha, and Salgado 2014b). Furthermore, initial entry is likely to be limited to the biologics with the largest revenues and to companies with the capacity to pursue global investment strategies. If competition is restricted to a small number of competitors, and with most products expected to compete as therapeutic alternatives rather than equivalents (as explained in the next section, for the foreseeable future automatic
substitution is not anticipated), then competition is likely to resemble brand-to-brand differentiated product competition rather than brand-to-generic competition. Biosimilar entrants are thus expected to compete in terms of both price and quality and to engage in promotional activities.

As the science improves and in particular as analytical methodologies advance, and as FDA and its peer regulators grow more comfortable with biosimilars of the more complex biologies, biosimilars will reach the market faster, and more entrants can be expected. But it will take several years for the market to evolve in this fashion.

III. THE POSSIBILITY OF INTERCHANGEABILITY DESIGNATIONS

The BPCIA contemplates that biosimilar applicants may show their products to be not only biosimilar but also interchangeable. This contrasts with Hatch-Waxman, under which generic chemical drugs are ordinarily A-rated (therapeutically equivalent) without any additional showing needed. Interchangeability represents a higher bar than biosimilarity. In particular, FDA may deem a biosimilar interchangeable with its reference product if (1) it “can be expected to produce the same clinical result as the reference product in any given patient” and (2) “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” (42 USC § 262 (k)(4)). The first biosimilar shown to be interchangeable is entitled to a one-year exclusivity period during which no other biosimilar product may be deemed interchangeable with the same reference product.

A key regulatory issue will be the analytical and clinical evidence that FDA will require to deem a biosimilar interchangeable with its reference product, thus signaling its conclusion that substitution without physician approval (subject to state laws) is appropriate. For biosimilar products used more than once by patients (the majority of biologies), the biosimilar sponsor will essentially need to demonstrate that switching between the biosimilar and reference product poses no additional risk of reduced safety or efficacy beyond that posed by taking the reference product alone. This may require crossover trials in
which subjects switch between the products repeatedly over time. It might be difficult and expensive to recruit enough subjects to obtain statistical significance for such trials. It is also unclear what factors FDA will consider in evaluating the potential risks related to alternating or switching between the biosimilar(s) and the reference product. Finally, the agency has signaled that at least for the time being, biosimilarity and interchangeability are likely to be sequential showings, which may indicate not only the need for switching studies but also the need to evaluate postmarket data (Kozlowski et al. 2011; FDA Draft Guidance, 2013).

It is reasonable to expect that FDA will license, on the basis of relatively small applications, less complex biosimilars that have already been approved and marketed in Europe for some time, like the granulocyte colony stimulating factors (G-CSFs), such as filgrastim, and the erythropoiesis-stimulating agents (ESAs), such as epoetin alfa. These products may be approved on the basis of studies conducted with the foreign reference product, combined with bridging data, or perhaps on the basis of somewhat smaller comparative clinical trials than initially required in Europe a half-dozen years ago. Interchangeability designations will presumably come later, although earlier for these products than for the more complex products. Biosimilar versions of more complex biologics like the majority of monoclonal antibodies may well require larger applications. To date, only one (infliximab) has been approved in Europe, and the approval was very recent. Until others have been approved, and some postmarket data have accumulated, it is reasonable to expect FDA to be more cautious about application size and scope. Furthermore, FDA is likely to maintain a very high bar with respect to establishing interchangeability for these products, with correspondingly high investment costs. Perhaps eventually, scientific advances might permit a fingerprinting-type analytical characterization approach for establishing biosimilarity and even interchangeability for these products. But a purely analytical approach seems unlikely even in the medium term.

The value of an interchangeability designation may be weakened further by the fact that most state pharmacy laws must be amended to permit substitution of biosimilars (whether or not found interchangeable) for their reference products (Parker 2013). The prospects for widespread and prompt adoption of legislation enabling biosimilar substitution remain uncertain. Current state pharmacy laws typically
result in immediate substitution of therapeutically equivalent (A-rated) generic chemical drugs for their reference products. This automatic substitution, without the prescriber’s involvement, drives rapid share loss by the branded reference product. But these laws were written for chemical drugs, and the vast majority will not—as drafted—result in substitution of a biosimilar (or interchangeable biosimilar) for its reference product. While several states (such as Virginia) have enacted legislation to govern substitution of interchangeable biosimilars, one state governor vetoed such legislation, and the bills have generated controversy (particularly with respect to notifying physicians that substitution has occurred), which could slow their introduction and enactment in the rest of the country (VA. CODE ANN. §§ 54.3-408.04 (2013); Letter from California Governor Edmund G. Brown, Jr. to Members of the California State Senate (Oct. 12, 2013)). No state has considered authorizing substitution of noninterchangeable biosimilars.

There is also a question whether the decisions made by the World Health Organization (WHO) and FDA about the nonproprietary names of biologics and biosimilars could complicate substitution. Both the WHO and FDA and the United States Adopted Names (USAN) Council—in which FDA and others participate—play a role in assigning names to drugs including biological drugs. The BPCIA was silent on the issue of names, leaving this framework untouched. Consequently, since enactment, stakeholders have been discussing whether biosimilars need nonproprietary names that are distinguishable from the names of their reference products—neither the same, nor entirely different, but instead somehow distinguishable—to ensure that adverse events are appropriately attributed to the correct product. Some have suggested that identical names will facilitate either substitution or, perhaps, simply market uptake (for instance, if decision makers take the view that identical names are an additional sign of therapeutic equivalence). Others believe that the name will have no impact on payer and formulary decisions and that state pharmacy laws are likely to focus on whether FDA has designated the products as interchangeable—not whether the nonproprietary name is the same. The outcome of this debate remains uncertain (FTC 2013).

Elsewhere, one of us has considered how the decisions of various stakeholders—physicians, payers, and patients—are likely to affect biosimilar market evolution if they compete as noninterchangeable therapeutic alternatives. The rate of biosimilar penetration is expected to
vary by disease indication, patient type, and physician specialty, and to incorporate both price and nonprice considerations (Grabowski, Guha, and Salgado, 2014b). In addition, rates of biosimilar acceptance may vary according to physician-focused and patient-focused factors, such as whether the physician specialty is price sensitive or instead demonstrates brand loyalty in therapy choice; whether the biosimilar will be used long term as maintenance therapy or only once or twice (particularly if long-term clinical data are not available); whether the disease or condition is life-threatening (and the implications of therapeutic nonresponse consequently very serious); whether adverse reactions are perceived to be very serious; and whether the difference in ease-of-use or out-of-pocket cost to the patient between the reference product and biosimilar is expected to be high.

From a payer perspective, hospitals are expected to be most cost sensitive and receptive to initial biosimilar usage given the fact that biological products are generally subject to fixed payment bundling reimbursement schemes by Medicare and private payers. For biologics dispensed by physicians in clinics, the evaluation by pharmacy and therapeutics (P&T) committees of comparative quality and price considerations between biosimilars and their reference product will be critical in the case of deciding about other therapeutic alternatives. Interchangeability is likely to be a particularly important factor for the utilization of biosimilars in the case of self-administered biologicals dispensed by retail pharmacies, whether reimbursed through Medicare Part D or private health insurers.

In short, achieving an interchangeability designation will be associated with far greater development costs than simply obtaining approval as a biosimilar biologic. There may be diminished economic incentives for companies to pursue interchangeability, particularly if there are multiple biosimilars already in the market that have provided satisfactory outcomes for providers. The one-year exclusivity right related to interchangeability could provide only marginal economic value because it is not true market exclusivity, only the right to be identified as the only interchangeable product. More generally, the economic value associated with interchangeability will depend on the timing of approval, the competitive situation in the relevant therapeutic class, and whether a product is administered by physicians in clinics and hospitals or dispensed by retail pharmacies and self-administered by patients. This stands in marked contrast to therapeutic equivalence.
determinations in the Hatch-Waxman setting, which are automatic for the conventional generic product (upon approval and with no additional showing needed). This, in turn, leads to their rapid uptake as a result of state automatic substitution laws and corresponding economic incentives by insurers such as tiered co-payment formularies that apply in the retail pharmacy setting where most generics are dispensed.

IV. EXPECTED COSTS OF POSTMARKET ACTIVITIES AND REGULATORY COMPLIANCE

Biosimilar firms likely will need to have postmarket organizational infrastructures in place to deal with competitive and regulatory issues, at least if their products are not interchangeable. Specifically, unlike generic drug manufacturers who rely on FDA designation of therapeutic equivalence to the reference product and the operation of automatic substitution laws to drive their market share, manufacturers of biosimilars will need to invest in sales and marketing divisions to obtain market share. This would typically include a market research group and a trained sales force to call on prescribers. Biosimilar firms will also need to develop a brand strategy and promotional materials and to arrange for presentations to prescribers, payers, and formulary committees. Depending on the therapeutic category, it may also be desirable to create a patient-oriented website and direct-to-consumer promotional materials. While a firm without such an existing infrastructure can obtain these services from a contract sales organization, launching a biosimilar product on this more brand-to-brand style of commercial marketplace will require a substantial investment of upfront resources whether the work is done internally or externally.

A parallel investment will need to be made in a compliance infrastructure to ensure adherence to federal laws governing advertising and promotion. Firms will need to interact with FDA regulatory officials to ensure that advertising and promotion adhere to the approved labeling and to satisfy other legal and regulatory requirements related to promotional activity. Biosimilar firms also will need to ensure compliance with laws governing sample distribution, assuming that they choose to promote their products in this manner. Firms will also need to monitor compliance with federal and state sunshine laws, state lobbying laws that may apply to sales representatives and possibly even
medical affairs personnel, and state laws that require reporting of expenses for advertising and promotion. A biosimilar company would likely also need to establish a medical affairs group to respond to outside requests for product information, and it may want that group to commission scientific publications as well as educational and research grants, and to coordinate advisory boards and consulting arrangements with medical professionals.

Beyond this infrastructure for promotion of their products and engaging in scientific exchange about those products and the relevant disease areas, biosimilar firms will need to establish other organizational groups and systems to deal with postmarket regulatory requirements to which generic firms do not typically devote significant resources. For instance, biosimilar firms will need to establish pharmacovigilance systems in order to trace, analyze, and report adverse events. Generic companies also have adverse event reporting requirements, but their pharmacovigilance obligations are not identical to those of innovators, and in any case they do not typically receive significant numbers of adverse event reports. Additional postmarket requirements for biosimilar firms (which generic firms may not face) could include mandated risk management strategies—including patient registries or even use and distribution restrictions—as well as performance of postmarket studies regarding immunogenicity or even verification of clinical effectiveness where indications have been extrapolated.

Like other biologics, biosimilar products will likely be the subject of manufacturing process improvements and changes over time, a topic discussed at greater length in chapter 18. These will require comparability protocols—including, in some cases, clinical testing—and may also require labeling changes. Dealing with unintentional drift in the product attributes over time could also require postmarket resources that generic small molecule drug applicants do not typically need to invest. These efforts will require medical and regulatory staff within the company, although likely the same manufacturing and regulatory personnel that were required for the premarket application process.

Further, in contrast to generic products, there is no statutory requirement for biosimilar labeling to be the same as the reference product’s labeling. Although FDA policy on biosimilar labeling is presumably still under development, biosimilar firms will likely negotiate with the agency and implement decisions on any proposed labeling changes that emerge as a result of postmarket pharmacovigilance
and other postmarket developments. This too will require a medical officer and a regulatory staff to handle FDA submissions and implement approvals.

Finally, unlike generic drug companies, biosimilar companies may well face significant exposure to tort liability for failure to update their labeling to reflect emerging safety data. Generic drug companies are currently unable to make unilateral changes to their product labeling, which must be the same as the innovator's labeling. Under a recent Supreme Court case, they therefore benefit from preemption of state tort law claims for failure to warn (Pliva v. Mensing 2011:2567). In response, FDA has proposed to change the rules for generic drugs, permitting safety-related changes without prior approval, thereby eliminating preemption and exposing generic companies to tort liability (78 Fed. Reg. 67985 (Nov. 13, 2013)). Although the agency has yet to announce its approach to safety labeling changes for biosimilars, it seems likely the agency will similarly permit unilateral changes without prior approval.

V. FULL BLA AND BIO BETTERS AS STRATEGIC OPTIONS

Another factor that will affect the timing and extent of biosimilar market entry is the attractiveness, and therefore extent of use, of the full BLA option as an alternative to the biosimilar application. After passage of the BPCIA, several firms developing biosimilar-like products—including Teva—publicly stated that they might not file their applications under section 351(k) (FDA Week, 2010). They cited “drawbacks” in the biosimilar pathway, such as the need to wait for expiry of the reference product’s twelve-year exclusivity, the likely substantial data requirements, the likely lack of interchangeability designations, and the “onerous” patent litigation provisions. For these and other reasons, they may choose to submit full marketing applications under section 351(a) rather than biosimilar applications under the BPCIA. The question has been raised whether these applications might be less substantial in scope and size than would ordinarily be required for a full BLA. As a regulatory matter, it is plausible that the applications could be less substantial than would be required for a first-in-class biologic, but the question has been raised whether FDA
will (or lawfully may) permit biosimilar-like applications under the full BLA provision, which would allow those firms to avoid the burdens of the BPCIA. Some consider the August 2012 approval of Sicor’s (now Teva’s) section 351(a) application for tbo-filgrastim to illustrate the viability of this strategy. Although the application was submitted before enactment of the BPCIA, European authorities had previously approved tbo-filgrastim as biosimilar to Amgen’s Neupogen, and the U.S. BLA largely relied on the same clinical data that supported European approval.

Whether these firms will file their applications or seek approval under section 351(a) will affect when—if at all—biosimilars of certain reference products enter the market. On the one hand, a firm that uses the full BLA pathway will likely seek to differentiate its product (and may permissibly do so). Indeed, that firm will not be constrained by the requirements of biosimilarity, so its product could incorporate deliberate differences from, or improvements to, the reference product (a so-called biobetter strategy). On the other hand, a firm that wishes to extrapolate indications or obtain an interchangeability designation will need to file its application under section 351(k). Even where interchangeability is of uncertain value, for complex biologics with multiple indications (such as the monoclonal antibodies), the cost savings from extrapolation may drive firms to the BPCIA.

Another factor that might affect sponsors’ willingness to choose the section 351(k) pathway is whether the innovator has introduced a next-generation product that will divert sales from the first-generation biosimilar. The innovative process in biopharmaceuticals is dynamic in character, with the development of improved formulations, dosing, delivery methods that provide better clinical outcomes, and convenience/quality of life advantages for patients. As seen from the experience in Europe, the introduction of longer-lasting, next-generation PEGylated versions of Neupogen (filgrastim) and Procrit (epoetin alfa) significantly extended the duration of treatment and provided cost savings elsewhere in the health-care system and quality of life benefits for patients. From an economic perspective, these next-generation products captured a large share of the overall market in their respective therapeutic classes (ESAs and G-CSFs) in many European countries (Grabowski, Guha, and Salgado 2014a). This in turn constrained the potential market for the first-generation products that are currently subject to biosimilar competition.
Complicating the decision for innovator firms considering a second-generation strategy is the significant discretion afforded to FDA with respect to exclusivity for these products. As noted, the law contains a provision that precludes a separate twelve-year exclusivity period for subsequent BLAs—filed by the same sponsor or manufacturer, a licensor, or a related entity—that involves a “modification to the structure” of an approved biologic that does not result in a “change in safety, purity, or potency” (42 USC 262(k)(7)(C)(ii)(II)). FDA must therefore decide whether each particular next-generation product (e.g., a pegylated version of the original molecule) is entitled to its own twelve-year exclusivity period as opposed to falling under the umbrella of the first-generation product’s exclusivity. A very high bar for manufacturers to obtain a twelve-year exclusivity period for next-generation products could have an adverse effect on investment incentives in the research and development of these products, at least in instances where the patent protection for these products is uncertain or narrow in scope. Given the importance of these decisions to innovators, FDA may well face litigation as it fleshes out its policy on biologics exclusivity. To the extent FDA’s decisions turn on matters of science (what constitutes a “modification to the structure,” for example, and what constitutes a “change” in safety), the courts are likely to defer to the agency. The area of exclusivity policy will be particularly important to watch, given its likely effect on innovative research and development incentives.

VI. CONCLUSION

The primary objective of the BPCIA, like the Hatch-Waxman Act before it, is to encourage increased price competition and consumer cost savings while maintaining a favorable environment for innovation. Although FDA has approved no applications to date, more than four years after enactment, it is clear that the premarket process for biosimilars entails the submission of data from multiple comparative clinical trials as well as overall a significantly greater investment of time and resources than are required of generic firms. Given this fact, as well as the likelihood that most biosimilars will not (for now) be rated as interchangeable with their reference products, one can expect fewer entrants and a pattern of biosimilar competition that is more
likely to resemble branded competition than generic competition for the foreseeable future. Over a longer time frame, scientific advances could reduce the regulatory costs of developing biosimilars and allow demonstration of interchangeability through analytical characterization (e.g., “fingerprinting” structural analysis).

For the immediate future, a number of thorny regulatory issues remain to be sorted out, including permissible extrapolation of safety and effectiveness from one indication (demonstrated in clinical trials) to other indications (not tested), naming requirements, and the use of bridging studies to justify use of global marketing dossiers. These and related issues may need to be resolved on a class-by-class basis. It may take several years for this process to complete, during which time analytical science will improve and important new medical treatments will become available. FDA regulatory actions and decisions, as well as those of associated health care providers and payers, will need to evolve continually to take advantage of the opportunities of the BPCIA while ensuring that patients are protected and continued innovation is encouraged.

REFERENCES

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