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THE LEGISLATIVE AND REGULATORY HISTORY OF FOLLOW-ON BIOLOGICS

Anna Drabant*

I. Introduction

On March 23, 2010, President Obama signed the Patient Protection and Affordable Care Act (PPACA) into law.¹ Part of the PPACA, referred to as the Biologics Price Competition and Innovation Act (BPCI), amended the Public Health Service Act (PHSA). The BPCI created an abbreviated approval pathway for biologics that are biosimilar or “interchangeable” with an innovator biologic.² These similar biologics are often referred to as “follow-on biologics” (FOBs). The Food and Drug Administration (FDA) has created a focus group to determine an implementation approach to the BPCI that will be “consistent, efficient and scientifically sound”³ Since 2004, the FDA has advocated that Congress pass legislation allowing an abbreviated approval process for follow-on biologics, mirroring the abbreviated process in the Food, Drug, and Cosmetic Act (FDCA) for drugs.⁴ After years of debate and several proposed bills, the 111th Congress finally succeeded in passing legislation containing an abbreviated process for FOBs. The FDA must now determine how to draft regulations that will adequately assure safety and efficacy.⁵

Although the precise consumer savings created by allowing FOBs on the market is not known, a 2007 Congressional Budget Office report estimated that the abbreviated pathway in the FDCA for generic drugs reduced drug spending in 1994 by eight to ten billion dollars.⁶ This savings for consumers is due in part to significant savings for generic manufacturers in research and development, including fewer clinical trial requirements.⁷ One can speculate that a similar savings may result from an abbreviated pathway for FOBs.

This article will address the scientific and regulatory issues concerning FOBs, followed by a discussion on the relevant legislative and regulatory history. Then, the article will address the industry, consumer, and agency perspectives on key topics. Finally, this

article will suggest legislative and regulatory policy recommendations.

II. Background

A. Scientific and Regulatory Background of Biologics and Generics

Congress has expressly distinguished the inherent differences between traditional drug products and biologics through statutory language. Congress defined a ‘drug product’ as a product that is “intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease,” and “intended to affect the structure or any function of the body of man or other animals.”⁸ Congress defined a ‘biologic product’ as a “virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein . . . applicable to the prevention, treatment, or cure of a disease or condition of human beings.”⁹ The pharmaceutical industry generally accepts drugs as small molecule products ranging from twenty to one hundred atoms, or in the case of hormones, two hundred to three thousand atoms.¹⁰ In contrast, biologics typically have five thousand to fifty thousand atoms.¹¹ The processes by which small molecule drugs and large molecule biologics are manufactured differ greatly as well. Small molecule drugs are synthesized using chemical reactions; the proteins used in biologics have unique and complex structures that must be genetically altered through the manufacturing process.¹² Minor changes in the manufacturing process of biologics can result in significant and potentially dangerous changes between the innovator product and the FOB.¹³

The FDCA created two pathways to approve generic drugs: sections 505(j) and 505(b)(2). Under both pathways, the generic drug sponsor can rely on the FDA’s previous finding that the innovator drug was safe and effective. The generic drug sponsor is required to show either that the generic drug is chemically the same, thus bioequivalent, or sufficiently similar, as supported by non-clinical studies.¹⁴ Under this authority, the FDA has approved abbreviated FOB applications when the related to innovator biologic was originally approved under the FDCA, not the PHSA.¹⁵ These FOB approvals can only be done through the 505(b)(2) application process, because the 505(j) application requires a showing of bioequivalence, something that

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“Although not perfect, the BPCI is a valuable piece of legislation that should be saved from repeal.”

cannot be demonstrated with current scientific technology for biologics due to their large and complex nature.¹⁶ Under the 505(j) abbreviated approval process, the generic drug is deemed to be chemically and structurally identical to the innovator drug; this cannot be demonstrated for biologics.¹⁷ Thus, FOBs are biosimilar, but not chemically and structurally identical to the innovator biologic product.

B. Legislative Background

Over the past five years Congress has made over half a dozen attempts to pass legislation creating an abbreviated pathway for FOBs. After several unsuccessful attempts, the 111th Congress passed H.R. 3590, commonly known as PPACA, which included an abbreviated pathway for FOBs through the BPCI. To understand how Congress arrived at the provisions included in the BPCI, it is important to look at the various provisions that Congress debated over the past several years in previous bills.

1. Unsuccessful Legislative Attempts to Create an Abbreviated Pathway

a. 109th Congress

H.R. 6257 and S. 4016, the Access to Life-Saving Medicines Act (introduced September 29, 2006 by Congressman Waxman and Senator Schumer), created an abbreviated pathway for FOB sponsors based on similarity to an innovator biologic and required only that the FOB sponsor submit data supporting that the FOB was comparable to the innovator biologic.¹⁸ This proposed legislation also gave the Secretary of the Department of Health and Human Services (HHS) the discretion to determine interchangeability between a FOB and an innovator biologic.¹⁹

b. 110th Congress

The 110th Congress considered several bills with vastly different provisions. Support for these various bills also differed greatly depending on the provisions. For example, H.R. 1038, the Access to Life-Saving Medicine Act (introduced on February 14, 2007 by Congressman Waxman), and S. 623 (a companion bill introduced February 15, 2007 by Senator Schumer) would have amended the PHSA to allow for an abbreviated application process for FOBs where the sponsor could show that the FOB was “comparable to or interchangeable with” the innovator drug.²⁰ The bills specifically granted the FDA the authority to approve FOBs with the “same or similar active ingredient” as the innovator biologic and allowed the FDA to make a determination that the FOB and the innovator biologic are interchangeable.²¹ These bills were very similar to the bills Congressman Waxman and Senator Schumer introduced during the 109th Congress in that both sets of bills emphasized interchangeability. Unlike the majority of bills brought before Congress in recent years, these bills created only 36 months of exclusivity.²² Not surprisingly, this provision was widely supported by the generic pharmaceutical industry.

H.R. 1956, the Patient Protection and Innovative Biologic Medicines Act of 2007 (introduced on April 19, 2007 by Congressman Inslee), created an abbreviated pathway for “similar” biologic products, provided two conditions were met: 1) they conformed to specific FDA guidance that was to be established following the enactment of the bill; and 2) the FDA determined the biologic was safe, pure, and potent based on non-clinical studies.²³ H.R. 1956, unlike H.R. 1038 and S. 623, would not have allowed the FDA to make a determination that a FOB was therapeutically equivalent

to the innovator biologic and thus interchangeable.²⁴ Under this bill, a FOB sponsor would not be able to submit an application to the FDA until twelve years after the date of approval of the innovator biologic.²⁵ Additionally, the FDA would not be able to approve the FOB application until fourteen years after the same date, or fifteen years if the FDA approved certain supplements to the innovator’s application.²⁶ A FOB could be approved only for the same indications as the innovator biologic.²⁷

S. 1505, the Affordable Biologics for Consumers Act of 2007 (introduced May 24, 2007 by former Senator Gregg), was very similar to H.R. 1956 in its FOB application approval requirements, indication requirements, and prohibition on a determination by the FDA that the FOB was interchangeable with or therapeutically equivalent to the innovator biologic.²⁸ However, it prohibited the FDA approval of a FOB application until sixteen years after the date of approval of the innovator biologic if the FDA approved a supplement to the innovator’s application within the first twelve years after the original date of approval.²⁹

S. 1695, the Biologics Price Competition and Innovation Act of 2007 (introduced June 26, 2007 by the late Senator Kennedy), created an abbreviated process for FOBs that are biosimilar to or interchangeable with the innovator biologic.³⁰ This bill defined an interchangeable FOB as one that: (1) is biosimilar to the innovator biologic; (2) will produce the same clinical result; and (3) can be switched or alternated with the innovator drug without any increased safety or efficacy concerns.³¹ S. 1695 also required the FDA to issue guidance on what specific criteria the agency would use to determine biosimilarity or interchangeability.³² Perhaps striking a balance between H.R. 1038 and S. 623’s thirty-six month exclusivity period and the proposed fifteen or sixteen years in H.R. 1956 and S. 1505, respectively, S. 1695 would have allowed the FDA to approve FOBs after twelve years of exclusivity.³³ The bill, however, allowed for an extended exclusivity period for biologics for rare diseases, a provision with great merit, but not often contemplated in previous bills.³⁴ To some degree, S. 1695 left reliance on the innovator’s science and experience up to the discretion of Secretary.³⁵ S. 1695 would have required the Secretary to study the agency’s efficiency in evaluating FOB applications and make a recommendation to Congress about whether the user fees for FOBs needed to be adjusted.³⁶ Additionally, S. 1695 would not allow subsequent FOBs to rely on the marketing or presence of the first FOB to show safety of efficacy.³⁷

H.R. 5629, the Pathway for Biosimilars Act (introduced March 13, 2008 by Congresswoman Eschew), also created an abbreviated pathway for FOBs that are biosimilar to or interchangeable with an innovator biologic.³⁸ H.R. 5629 left a great deal of discretion to the Secretary, requiring only that she make a determination on what the agency would consider biosimilar or interchangeable.³⁹ Unlike its many predecessors, H.R. 5629 explicitly prohibited a FOB licensure if the product contained certain agents or toxins.⁴⁰ But like S. 1695, H.R. 5629 would have allowed the FDA to approve FOB applications twelve years after the date the innovator biologic was approved.⁴¹

c. 111th Congress

H.R. 1427 and S. 726, the Promoting Innovation and Access to Life-Saving Medicine Act (introduced March 11, 2009 and March 26, 2009 by Congressman Waxman and Senator Schumer, respectively), provided an abbreviated pathway for FOB applications where the sponsor

demonstrated that the FOB was highly biosimilar or interchangeable.⁴² This legislation also required the applicant to demonstrate the safety, purity and potency of the FOB.⁴³ H.R. 1427 and S. 726 would have allowed the Secretary to make a determination of interchangeability if the same clinical results were expected from the FOB as the innovator biologic.

H.R. 1548, the Pathway for Biosimilars Act (introduced March 17, 2009 by Congresswoman Eschoo), set forth similar biosimilar and interchangeability requirements as previous legislation. H.R. 1548, like H.R. 5629, prohibited an FOB approval if the FOB contained certain agents or toxins or a schedule I or II controlled substance, unless there was a determination from the Secretary that the FOB approval would not lead to any increased public health risk.⁴⁴ H.R. 1548 also prohibited the HHS Secretary from approving a FOB until twelve years after the date of approval of the innovator biologic and prohibited the FDA from evaluating a FOB application against more than one innovator product.⁴⁵

2. The BPCI in H.R. 3590 as Enacted by the 111th Congress

One goal of the 1984 Hatch-Waxman Amendments to the FDCA was to create an abbreviated pathway for generic drugs to enter the market. The BPCI was based on a very similar goal.⁴⁶ Americans spend an estimated 40.3 billion dollars a year on biologic products.⁴⁷ Although the specific reduction in prices once FOBs come onto the market is not known, the price of many small molecule drugs can be reduced by up to 80% after a generic enters the market.⁴⁸

The BPCI creates an abbreviated process for FOBs that are proven biosimilar through analytical, animal; and clinical studies that demonstrate safety, purity and potency.⁴⁹ However, the BPCI gives the Secretary the authority to determine that any of the above mentioned studies, including clinical studies, are “unnecessary.”⁵⁰ The Secretary may rely on any publicly available information when making safety, purity, and potency determinations regarding the FOB.⁵¹ Thus, it can be inferred that the FDA cannot use the innovator’s proprietary information. The BPCI also requires the Secretary to classify a FOB as interchangeable with the innovator biologic if biosimilarity is established and the FOB sponsor submits data to support that the same clinical result can be expected from the FOB as the innovator biologic.⁵² Like H.R. 1548, a FOB submitted under this abbreviated process cannot be evaluated against more than one innovator biologic.⁵³ The FDA may not approve a FOB application until twelve years after the date the innovator biologic

was approved, and a FOB sponsor may not submit an application to the FDA until four years after the same date.⁵⁴ Unlike many previous bills, the BPCI does not give an extension if the FDA approves a supplemental application to the innovator biologic.⁵⁵

C. Recent Regulatory Actions

In 2004, the Acting Commissioner of the FDA, Lester Crawford, testified before the Senate Committee on the Judiciary.⁵⁶ Crawford stated that it was a priority of the FDA to make innovative treatments more affordable.⁵⁷ He also stated that, while similarity between large biologics would be difficult to show, it was scientifically possible to show similarity for small molecule biologics.⁵⁸ Through Crawford’s testimony, the FDA stressed the public policy need to move forward with FOB legislation to allow for greater affordable access to important life-saving treatments, emphasizing a concern for seniors and others who struggle to pay for expensive biologic products.⁵⁹ The FDA also stressed the scientific limitations and proposed to hold public meetings to examine the scientific considerations involved in an abbreviated FOB pathway.⁶⁰ Crawford conceded that the agency did not believe it had the authority under the then-current legislation to move forward with an abbreviated FOB application that relies on an innovator biologic approved under the PHSA.⁶¹

Following Crawford’s testimony and the promise to examine further the scientific issues involved with approving FOBs, the FDA held three public workshops in 2004 and 2005.⁶² In response to these meetings, the FDA received several dozen comments from pharmaceutical associations and companies, consumers, and health care professionals.⁶³ More recently, in response to the 2007 and 2008 proposed legislation, the Pharmaceutical Research and Manufacturers of America (PhRMA), which represents pharmaceutical research and biotechnology companies, issued a statement commending S. 1695 as providing an environment that would sustain innovation.⁶⁴ PhRMA reiterated that the “[d]evelopment of biologics is scientifically complex, time consuming, and requires significant investment.”⁶⁵

Additionally, Janet Woodcock, Deputy Commissioner of FDA, testified before the House Committee on Energy and Commerce, Subcommittee on Health, in May of 2007.⁶⁶ In her testimony, Woodcock expressed the concern that even if a FOB is found to be safe and effective, it may not be interchangeable with the original innovator biologic.⁶⁷ Following Woodcock’s testimony, the FDA responded to a series of questions from the Subcommittee on Health in September of 2008.⁶⁸ The

“... Congress should prioritize transparency in the regulatory system and require the Secretary to issue guidance and standards.”

FDA reiterated numerous times the current scientific limitations in determining the clinical equivalence of an innovator biologic and a FOB.⁶⁹ As a result of the current scientific limitations in comparing an innovator biologic and a FOB, the FDA recommended that interchangeability be allowed only after the FOB had conducted a series of clinical studies establishing the safety and efficacy of switching between the two biologics.⁷⁰

In November of 2010, the FDA held a two-day public meeting.⁷¹ Although the FDA has not yet produced a report or made any statements about what was learned at this meeting, a few entities have submitted comments in response.⁷² The FDA has generally praised the BPCI as being in line with the FDA's policy goal of "permitting appropriate reliance on what is already known about a drug, thereby saving time and resources and avoiding unnecessary duplication of human or animal testing."⁷³

III. Perspectives on the Issues

A. Studies Required for the FOB and Reliance on Innovators' Studies

Some industry representatives assert that each FOB must be shown to be safe and effective through adequate and well-controlled clinical studies of that particular product.⁷⁴ They argue that due to the complex structure of biologics, the manufacturing process can alter the safety and efficacy of the product.⁷⁵ Further, some industry representatives argue that the FOB sponsor should not be able to rely on any studies or research from the innovator product.⁷⁶ The FDA has also expressed concern that any manufacturing changes, which would undoubtedly exist between an innovator biologic and a FOB, could significantly alter the safety, identity, purity, and potency of the product.⁷⁷ Thus, the FDA maintains that Congress should hold FOB applicants to the same high standards as innovator biologics, including requiring at least some clinical studies to show safety and efficacy.⁷⁸ The FDA contends, however, that clinical indication-specific studies may not be needed, and thus any bill should include some regulatory discretion.⁷⁹

Some have also argued that if FOB applications require extensive studies, it will take much longer and be much more expensive to develop FOBs, which in turn may discourage some potential FOB sponsors.⁸⁰ This will result in fewer price competitions for specific biologics and will result in less savings in the health care system from the abbreviated FOB process.

Immunogenicity is how a particular biologic stimulates one's immune system.⁸¹ The FDA has recently stated

that current science will not allow it to determine the immunogenicity of complex proteins based on the innovator biologic's immunogenicity, and thus, clinical studies will be needed to establish the immunogenicity of the FOB.⁸² In 2008, the FDA specifically told Congress that any legislation creating an abbreviated FOB process *must* mandate such clinical studies, but perhaps give the FDA the discretion to determine the extent of clinical studies required.⁸³

While many assert that the current science cannot support safety, purity, potency findings without product-specific clinical studies, other associations assert the science and technology to establish that two complex biologic products are equivalent not only does exist, but has for years.⁸⁴

FDA practice to date, with regard to biologics approved through the 505(b)(2) abbreviated pathway when the innovator application was made as drug under the FDCA rather than a biologic under the BLA, has always been to require clinical studies.⁸⁵ Further, to date, the FDA has not been willing to make determinations of interchangeability.⁸⁶

B. Interchangeability

Unlike small molecule drugs, where chemical testing can show that the generic is chemically equivalent to the innovator and thus therapeutically equivalent to the innovator drug, biologics cannot be deemed chemically the same due to their complexity and the manufacturing process, nor would such be sufficient to warrant a finding of therapeutic equivalence.

Even as recently as 2008, the FDA has asserted that the technology to determine if a FOB is the same as an innovator biologic does not exist, or at least not with sufficient reliability.⁸⁷ The FDA contends that even if a FOB can show biosimilarity, there are still significant scientific challenges to showing interchangeability and, as such, the FDA has serious safety concerns about any determinations of interchangeability.⁸⁸ Switching between biologic products has also been shown having serious negative impacts on efficacy, as well as raising patient safety concerns.⁸⁹ These safety concerns are paramount to any benefits that patients might derive from switching from an innovator biologic to a FOB. The FDA has long advocated that a patient should only be switched from an innovator biologic to a FOB upon the express advice of the patient's physician as an alternative treatment, and that allowing pharmacists to switch the two biologic products could result in serious safety concerns or even death.⁹⁰

Some industry representatives further assert that a FOB sponsor must conduct "adequate comparative

“While getting more cost-effective medications to patients in need should always be a high priority of HHS, patient safety should be paramount.”

clinical trials to establish that its product acts the same as, rather than similar to, the innovator product” before the pharmacist should be allowed to substitute the FOB for the innovator product.⁹¹ Others also assert that a pharmacist should only be allowed to substitute the innovator product with the FOB if the treating physician agrees to it.⁹² Currently, the FDA defines therapeutic equivalence as products that are safe and effective, “contain identical amounts of the same active drug ingredient in the same dosage form and route of administration, and . . . meet . . . applicable standards of strength, quality, purity, and identity,” and are bioequivalent.⁹³

To establish interchangeability, the FDA has asserted that the FOB would need to show that repeated switches between the FOB and the innovator biologic would not negatively affect safety and efficacy.⁹⁴ Given the current state of science, it is highly unlikely that an FOB sponsor could establish this without extensive clinical studies.⁹⁵ Absent of which, the FDA believes a switch between biologics should only happen when a physician has determined that another biologic would be the appropriate treatment option.⁹⁶ The FDA asserts that any bill passed by Congress should require clinical studies before the Secretary can consider making a determination of interchangeability.⁹⁷

C. Traceability

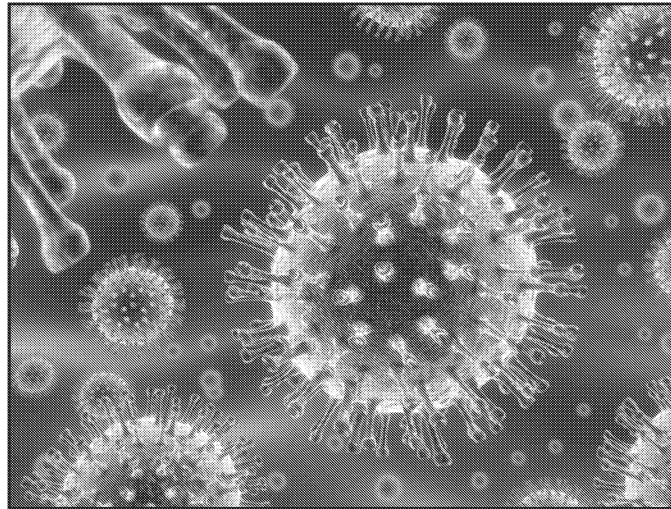
To allow for quick and efficient recalls in case of an adverse event, some industry representatives call for FOBs to be clearly identifiable and traceable.⁹⁸ This seems unnecessary, as it will be easy to determine which drug a patient was taking from his/her prescription records. Where there is threat to public health, the FDA will work with the manufacturer to get the product off the market.⁹⁹ Although the FDA has not voiced support for the same degree of traceability as some industry representatives, the FDA has asserted that FOB products must have distinguishable, non-proprietary names to avoid any confusion and safety hazards.

D. Post-Marketing Studies

Different industry representatives, the FDA, and consumer representatives have expressed wide-spread support for post-market studies. The FDA posits that the best model for post-market studies will give the agency the authority to determine the extent of the post-market requirements based on the information contained, or lacking, in the application.¹⁰⁰

Some questions, however, still remain as to the FDA’s ability to oversee effectively post-market studies. In 2006, after several high-profile drug safety cases and Congressional hearings, Senator Grassley and Congressman Barton requested that the Government Accountability Office (GAO) review the FDA’s postmarket decision-making process.¹⁰¹ The 2006 GAO report generally found that the “FDA lacks a clear and effective process for making decisions about, and providing management oversight of, postmarket drug safety issues.”¹⁰² The 2006 report attributed these findings to a lack

of resources and authority, and ultimately recommended that Congress expand the FDA’s authority to require drug sponsors to conduct postmarket studies when the FDA determines additional data is needed.¹⁰³ The report concluded that, while the FDA has the authority to withdraw the approval of a drug on the market for safety concerns, the FDA rarely exercises such authority. Finally, the report observed that the ten drugs withdrawn from the market between 2000 and 2006 were all withdrawn voluntarily.¹⁰⁴



This low withdrawal rate can be attributed to FDA’s efforts to work with sponsors to change their labeling or take other measures to remedy the safety concern.¹⁰⁵ Although noting that the FDA often relies on voluntary postmarket commitments (PMCs) from sponsors, the 2006 report relied on a Tufts Center report to conclude that such PMCs are not consistently completed.¹⁰⁶ Even though it seems clear that the FDA has the authority to withdraw approval, the 2006 report cited administrative penalties as the leverage the FDA often uses to get compliance with PMCs, often unsuccessfully.¹⁰⁷ The 2006 report

also cited a PMC study completion rate of 17% in the 1980s and 24% between 1991 and 2003.¹⁰⁸ Following this report, Congress passed the Food and Drug Administration Amendments Act of 2007 (FDAAA), which further expanded the FDA’s authority to require postmarketing studies under certain circumstances.¹⁰⁹ The FDAAA also gave the FDA additional means of funding.¹¹⁰

In 2009, at the request of Senator Grassley, the GAO again looked into the FDA’s oversight of postmarketing requirements and commitments (PMRs and PMCs), specifically those related to accelerated approval applications.¹¹¹ The 2009 report concluded that the “FDA has not been routinely monitoring the status of postmarketing studies, primarily because oversight of these studies is not considered a priority. Regarding its enforcement of postmarketing study requirements, we found FDA has not fully utilized its available enforcement tools, even when sponsors have failed to complete required studies.”¹¹² This conclusion was based on statements by both the HHS Office of Inspector General and an HHS contractor that PMC and PMR studies are not as high a priority as reviewing new drug applications.¹¹³ The 2009 report also found FDA’s enforcement action lacking based on a review of twelve sponsors of drugs approved through the accelerated process that were late in submitting their PMC/PMR status reports. The GAO found that FDA only sent an administrative action letter to one of those twelve sponsors.¹¹⁴ Additionally, the 2009 report found that, while thirty-six of ninety selected applications with PMCs or PMRs had not fulfilled the study requirements, including several approved more than ten years ago, none were withdrawn from the market.¹¹⁵ The 2009 report also criticized the FDA for not creating guidelines under which it would withdraw an accelerated approval drug from the market upon failure to complete the PMC or PMR.¹¹⁶ In response to the 2009 report, the FDA conceded that its oversight of postmarketing studies had been inadequate,

which it attributed to insufficient staffing, deficient IT resources, and competing priorities.¹¹⁷ The FDA proposed to address such inadequacies through improved tracking by its contractor and a new database.¹¹⁸

Later in 2009, the GAO released another report on FDA's efforts to oversee postmarketing studies.¹¹⁹ This report concluded that since the 2006 report, the FDA had taken initiatives to increase staff and implement tracking systems focused on postmarket safety; however, since the expansion of the FDA's authority under FDAAA, the FDA's postmarket workload has also increased significantly.¹²⁰ Therefore, it is still unclear if these additional efforts the FDA has taken will allow for a more effective oversight of postmarket studies.¹²¹ Under the current regulations drug sponsors have clear obligations to complete PMCs/PMRs; however, sponsors may be able to successfully argue to the FDA that they should be released from the PMC because the study is either no longer feasible or no longer would provide useful information.

Some industry representatives have called for heightened postmarket requirements for both innovator biologics and FOB products.¹²² A case study of Omnitrope, a biologic approved by the FDA through the 505(b)(2) abbreviated pathway based on Genotropin's existence, further reveals the need for postmarket studies.¹²³ After Omnitrope was approved for the markets in the United States and Europe, two adverse events occurred in children overseas. Because these adverse events occurred overseas, and thus beyond FDA's scope, the FDA does not have as complete reports as it normally would and thus refused to make conclusions based on these adverse events.¹²⁴ Quite possibly, if there had been more stringent postmarket requirements, at the very least, these two adverse events could have been detected sooner and perhaps even avoided.

E. Exclusivity Period

The FTC has stated a twelve-to-fourteen year exclusivity period is too long and projects that many innovators will continue to dominate the market even after an FOB enters the market.¹²⁵ Some economists, however, have estimated that an innovator company will need 12.9 to 16.2 years of market exclusivity before it will be able to break even.¹²⁶ Yet others assert that we do not have enough information to know that the frequently discussed twelve year period will be sufficient to protect innovators' interest, and suggest a more flexible rule to preserve these interests.¹²⁷

There is a serious concern that, without a sufficient exclusivity period, innovators' profits, or even ability to break even will be less certain, resulting in innovators not being able to ascertain financing and, in turn, resulting in a fewer innovative biologics, which unquestionably help thousands of Americans every day. In the drug market, once a generic enters the market, the innovators' profits drop drastically.¹²⁸ The research and development risks associated with biologics are not isolated to innovators. Some have speculated that the uncertainties in development and high costs may deter many potential FOB manufacturers.¹²⁹

The FDA recognizes the need for a period of market and/or data exclusivity that would allow innovation to continue.¹³⁰ If Congress had not created additional exclusivity protections beyond the current patent protections for innovators, the FDA is concerned that innovation would suffer.¹³¹

IV. Policy Recommendations and Conclusion

Almost a decade of political discourse has given light to the many possibilities in creating and regulating an abbreviated pathway for FOBs. With the new composition of the 112th Congress, a repeal of the PPACA or parts of it is not out of the realm of possibilities. Although not perfect, the BPCI is a valuable piece of legislation that should be saved from repeal. Congress, however, might be well advised to readdress some provisions of past bills and amend the BPCI.

A new amendment would include a provision, such as that in S. 1695, which would extend the exclusivity period for biologics intended for treat rare forms of diseases. Federal agencies and the public have voiced serious concerns about a short exclusivity period stifling innovation, and about how long an innovator biologic needs exclusivity to make a profit, which in turn encourages further research and development. Unquestionably, estimates vary drastically on the required length of an exclusivity period because different biologic products take different amounts of time and money to develop. Biologic products will be used by a smaller population and thus manufacturers will have a much harder time recouping expenses and would benefit greatly from a longer exclusivity period. Such a provision also would allow for a continued incentive for such research and development, while allowing FOBs for more widely used biologic products onto the market in an expeditious manner.

Congress should also amend the BPCI to require the Secretary to issue guidance to inform the industry and public on how the FDA will make FOB application determinations. Although the Secretary could issue guidance on her own accord, Congress should prioritize transparency in the regulatory system and require the Secretary to issue guidance and standards.¹³²

Another important amendment to the BPCI would be one that limits the FDA's authority to designate FOBs and biologics as interchangeable. The BPCI gives the Secretary full discretion to designate FOBs and biologics as interchangeable without clinical studies. The FDA has repeatedly asserted that the current state of scientific technology does not allow one to establish the safety and efficacy of interchanging biologic products, and that clinical trials are still needed to ensure the public health. Although the current language of the BPCI may make the regulatory and legislative processes easier down the road when the scientific technology has developed far beyond what it is capable of today, Congress should not have delegated to the Secretary to do something that, as even the Secretary concedes, cannot be done today.¹³³ Congress should amend the BPCI to strike this provision and readdress the legislation when Congress itself can establish that the scientific technology exists.

At a minimum, the Secretary should make it clear through guidance and policy statements that it will not waive the clinical studies requirement in the BPCI until there is substantial scientific evidence that safe and effective interchangeability can be established through non-clinical means. While getting more cost-effective medications to patients in need should always be a high priority of HHS, patient safety should be paramount. Without an interchangeability determination, the FOBs will still be available to the patients who need them, but only through the qualified expertise and case-by-case analysis of that patient's own medical doctor. Absent clear, widely supported scientific evidence to establish the safety and efficacy of interchanging an innovator biologic and an FOB, the decision to switch

the patient's medications should be left in the able hands of the medical profession.

Overall, the BPCI was a much needed piece of legislation and expansion of the FDA's authority. After nearly a decade of debating various proposals, the BPCI seems to strike a fairly good balance between the innovator and the generic industries.

¹ Sheryl Gay Stolberg & Robert Pear, *Obama Signs Health Care Overhaul Into Law*, N.Y. TIMES, Mar. 23, 2010, at A1.

² Patient Protection and Affordable Care Act, H.R. 3590, Pub. L. No. 111-48, § 7002 (amending the Public Health Service Act § 351).

³ FDA Guidance: Implementation of the Biologics Price Competition and Innovation Act of 2009 (June 23, 2010), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm215089.htm> [hereinafter FDA Guidance – BPCI Implementation].

⁴ See Testimony of Lester Crawford, Acting Commissioner of Food and Drugs before the Senate Committee on the Judiciary (June 23, 2004), available at <http://www.fda.gov/NewsEvents/Testimony/ucm113745.htm> [hereinafter FDA Testimony 2004]; see also Food Drug and Cosmetic Act § 505, 21 U.S.C. § 355 (2007).

⁵ See FDA Guidance – BPCI Implementation, *supra* note 3 (explaining that FDA is planning its approach to implementing the statute through public meetings, which will allow the agency to receive comments from the public, especially stakeholders, experts, innovators, and patients).

⁶ Judith A. Johnson, Cong. Research Serv., RL34045, FDA Regulation of Follow-On Biologics 2 (June 18, 2007) [hereinafter CRS Report 2007].

⁷ *Id.*

⁸ Food, Drug and Cosmetic Act § 201(g)(1), 21 U.S.C. § 321(g)(1) (2007).

⁹ Public Health Service Act § 351, 42 U.S.C. § 262 (1995).

¹⁰ Genentech: Biosimilars or Follow-on Biologics Background, <http://www.gene.com/gene/about/views/followon-biologics.html> (last visited Nov. 11, 2010).

¹¹ *Id.*

¹² See *id.* (explaining how two biologics can be chemically similar, but structurally different analogizing it to a raw egg and a cooked egg, both of which are chemically the same, but structurally different); Bio: Biotechnology Industry Organization, Why is Patient Safety A Concern in the Biosimilars Debate?, <http://www.bio.org/healthcare/followonbkg/PatientSafety.asp> (last visited Nov. 11, 2010).

¹³ *Id.*

¹⁴ CRS Report 2007, *supra* note 6, at 5.

¹⁵ See *id.* (noting that the FDA approved Omnitrope, a follow on human growth hormone under its authority under the FDCA).

¹⁶ See Letter from Frank M. Torti, Principal Deputy Comm'r, FDA, to Hon. Frank Pallone, Chairman, U.S. H.R. Comm. Energy and Commerce, Subcomm. Health (Sept. 18, 2008) at 7, available at <http://www.fdalawyersblog.com/congressional-documents.html> (noting that the FDA has been approving insulin, which is a protein, under the FDCA for over 60 years), [hereinafter FDA Letter to Congress].

¹⁷ Food, Drug and Cosmetic Act § 505(j).

¹⁸ H.R. 6257; S. 4016, 109th Cong. (2006).

¹⁹ *Id.*

²⁰ CRS Report 2007, *supra* note 6, at 11.

²¹ *Id.*

²² *Id.*

²³ *Id.* at 11-12.

²⁴ See *id.*

²⁵ *Id.*

²⁶ *Id.*

²⁷ See *id.* at 14.

²⁸ *Id.*

²⁹ See *id.* at 16.

³⁰ See generally S. 1695, 110th Cong. (2007).

³¹ See *id.* § 2(K)(4).

³² See *id.* § 2(K)(5), (8).

³³ See *id.* § 2(K)(7).

³⁴ See *id.* § 2(i).

³⁵ See Cong. Research Serv., Summary of S. 1695 (Nov. 19, 2008).

³⁶ See *id.*

³⁷ See *id.*

³⁸ See H.R. 5629, 110th Cong. (2008).

³⁹ See *id.* § 101(K)(3)(A).

⁴⁰ See *id.* § 101(K)(5)(D).

⁴¹ See *id.* § 101(K)(7).

⁴² See H.R. 1427; S. 726, 111th Cong. (2009).

⁴³ See *id.* § 3(K).

⁴⁴ See H.R. 1548, 111th Cong. § 101(K)(5)(D) (2009).

⁴⁵ See *id.* § 101(k)(7).

⁴⁶ See FDA Guidance – BPCI Implementation, *supra* note 3.

⁴⁷ See FTC Press Release – FTC Releases Report on Follow-on Biologic Drug Competition (June 10, 2009), <http://www.ftc.gov/opa/2009/06/biologics.shtm> [hereinafter FTC Press Release] (explaining that the annual treatment cost for Herceptin, a biologic used to treat breast cancer, costs \$48,000); Richard G. Frank, *Regulation of Follow-on Biologics*, 357 N. Engl. J. Med. 841, 841-43 (2007) (showing how biologics are becoming more fundamental to treatment options).

⁴⁸ See *id.*

⁴⁹ See Patient Protection and Affordable Care Act, Pub. L. No. 111-148 (2010) (H.R. 3590 § 7002 (k)(2)(A) (2010) (enacted)).

⁵⁰ See *id.*

⁵¹ See *id.*

⁵² See *id.* § 7002(k)(4).

⁵³ See *id.* § 7002(k)(5)(A).

⁵⁴ See *id.* § 7002(k)(7).

⁵⁵ See *id.*

⁵⁶ FDA Testimony 2004, *supra* note 4.

⁵⁷ *Id.*

⁵⁸ *Id.*

⁵⁹ *Id.*

⁶⁰ *Id.*

⁶¹ See *id.* But see CRS Report 2007, *supra* note 6, at 2 (explaining that the Generic Pharmaceutical Association (GPhA) has long advocated that the FDA approve FOBs under its current authority).

⁶² FDA, *Follow-on Protein Products: Regulatory and Scientific Issues Related to Developing*, <http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/ucm085854.htm> (last updated June 22, 2010).

⁶³ *Infra* Part III.

⁶⁴ PhRMA Statement on Follow-On Biologics Legislation (June 27, 2008), http://www.phrma.org/news_room/press_releases/phrma_issues_statement_on_follow-on_biologics_legislation.

⁶⁵ See *id.*

⁶⁶ CRS Report 2007, *supra* note 6, at 9-10.

⁶⁷ See *id.*

⁶⁸ FDA letter to Congress, *supra* note 16.

⁶⁹ See *id.*

⁷⁰ *Id.* at 9.

⁷¹ FDA, Biologics Price Competition and Innovation Act of 2009 Summary, available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm215031.htm>.

⁷² Approval Pathway for Biosimilar and Interchangeable Biological Products; Public Hearing; Request for Comments, 75 Fed. Reg. 61497 (Oct. 5, 2010) (Comment period closed December 31, 2010).

⁷³ FDA Guidance – BPCI Implementation, *supra* note 3.

⁷⁴ Genentech: Biosimilars or Follow-on Biologics, *supra* note 9.

⁷⁵ *Id.*

⁷⁶ See *id.* (arguing that an FOB application should have to show, through clinical studies, that the product is safe and effective for every indication it seeks to get approved, including each indication the innovator product was approved for).

⁷⁷ FDA letter to Congress, *supra* note 16, at 2.

⁷⁸ *Id.* at 5.

⁷⁹ *Id.* at 2, 5.

⁸⁰ See Frank, *supra* note 11, at 841-43 (speculating that the more complicated the biologic is the less competition it will have from FOBs).

⁸¹ FDA letter to Congress, *supra* note 16, at 1.

⁸² *Id.* at 2.

⁸³ *Id.*

⁸⁴ GPhA Comments to FDA on Generic Biopharmaceuticals (March 16, 2005), <http://www.gphaonline.org/resources/2005/03/15/comments-fda-generic-biopharmaceuticals> (last visited February 12, 2011) (conceding that additional case-by-case testing may be needed).

⁸⁵ FDA Letter to Congress, *supra* note 16, at 5.

⁸⁶ *Id.* at 9.

⁸⁷ *Id.* at 4.

⁸⁸ *Id.*

⁸⁹ *Id.*

⁹⁰ *Id.*

⁹¹ Genentech: Biosimilars or Follow-on Biologics, *supra* note 9.

⁹² *Id.*

⁹³ See FDA, CTR. FOR DRUG EVALUATION & RESEARCH, *Orange Book Preface, 30th Edition* (last updated Feb. 22, 2010), available at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079068.htm>.

⁹⁴ FDA letter to Congress, *supra* note 16, at 9.

⁹⁵ *Id.*

⁹⁶ *Id.*

⁹⁷ See *id.* at 9.

⁹⁸ Genentech: Biosimilars or Follow-on Biologics, *supra* note 10.

⁹⁹ See FDA, *Guidance for Industry: Product Recalls, Including Removals and Corrections* (Nov. 3, 2003), <http://www.fda.gov/Safety/Recalls/IndustryGuidance/ucm129259.htm> (noting that manufacturer cooperation is vital to recalling potentially harmful products in a timely manner).

¹⁰⁰ FDA letter to Congress, *supra* note 16, at 3.

¹⁰¹ U.S. GOV'T ACCOUNTABILITY OFFICE, GAO-06-402, DRUG SAFETY: IMPROVEMENT NEEDED IN FDA'S POSTMARKET DECISION-MAKING AND OVERSIGHT PROCESS 1, 3 (2006).

¹⁰² *Id.* at 5.

¹⁰³ *Id.* at 5-6.

¹⁰⁴ *Id.* at 10.

¹⁰⁵ See *id.*

¹⁰⁶ *Id.* at 28.

¹⁰⁷ *Id.*

¹⁰⁸ *Id.*

¹⁰⁹ U.S. GOV'T ACCOUNTABILITY OFFICE, GAO-10-68, REPORT TO THE RANKING MEMBER, COMMITTEE ON FINANCE, U.S. SENATE: DRUG SAFETY: FDA HAS BEGUN EFFORTS TO ENHANCE POSTMARKET SAFETY, BUT ADDITIONAL ACTIONS ARE NEEDED 1 (Nov. 2009) [hereinafter GAO REPORT Nov. 2009].

¹¹⁰ *Id.* at 12-15.

¹¹¹ See U.S. GOV'T ACCOUNTABILITY OFFICE, GAO-09-866, NEW DRUG APPROVAL: FDA NEEDS TO ENHANCE ITS OVERSIGHT OF DRUGS APPROVED ON THE BASIS OF SURROGATE ENDPOINTS 1 (2009).

¹¹² *Id.* at 29.

¹¹³ *Id.* at 29-30.

¹¹⁴ *Id.* at 32.

¹¹⁵ *Id.* at 33.

¹¹⁶ *Id.* at 36.

¹¹⁷ *Id.* at 40.

¹¹⁸ *Id.*

¹¹⁹ See GAO REPORT Nov. 2009, *supra* note 109.

¹²⁰ *Id.* at 19-20, 31.

¹²¹ *Id.* at 40-41.

¹²² *Why is Patient Safety A Concern in the Biosimilars Debate?*, BIOTECH. INDUS. ORG., <http://www.bio.org/healthcare/followinbjg/PatientSafety.asp> (last visited Feb. 4, 2011).

¹²³ FDA Letter to Congress, *supra* note 16, at 5-6.

¹²⁴ *Id.*

¹²⁵ FEDERAL TRADE COMM'N, FTC RELEASES REPORT ON "FOLLOW-ON BIOLOGIC DRUG COMPETITION" (June 10, 2009), available at <http://www.ftc.gov/opa/2009/06/biologics.shtm> (last modified June 10, 2009).

¹²⁶ Arie M. Michelsohn, "Follow-On" Biologics: What Will It Take?, 5 SCI. TECH. LAW. (Fall 2008).

¹²⁷ See Frank, *supra* note 11, at 841-43.

¹²⁸ See *id.* (stating that the manufacturer of Prozac lost more than 70% of its profits within the first two months of generics coming onto the market).

¹²⁹ See *id.* (speculating that if very few FOBs are developed due to these uncertainties there will not be enough competition to drive prices down to the same extent as what we have seen in the generic drug market).

¹³⁰ FDA Letter to Congress, *supra* note 16, at 12.

¹³¹ See *id.* at 13 (noting that not all biologics will qualify for a patent, and even for the biologics that are patented, the cost of litigating patent disputes would be high).

¹³² See Biologics Price Competition and Innovation Act of 2007, S. 1695, 110th Cong. (2008) (requiring the Secretary to issue guidance).

¹³³ See FDA Letter to Congress, *supra* note 16, at 7.