



THE DIFFERENCE WITH BIOLOGICS: THE SCIENTIFIC, LEGAL, AND REGULATORY CHALLENGES OF ANY FOLLOW-ON BIOLOGICS SCHEME*

I. Executive Summary

The biotechnology industry is a vital and increasingly important part of our health care system. Although relatively new, it has already provided substantial contributions to public health and has great potential for future development. At the foundation of the industry are the individual companies that risk billions of dollars in research and development without any guarantee of a return. Incentives are necessary to encourage biotechnology companies, from large established companies to small start-ups, to make these investments – and to take the significant risks – to discover, develop, and clinically test new biologics. The primary incentive provided in the U.S. system is market exclusivity for the products that are developed. This market exclusivity enables the innovator to leverage the value of the innovation, while encouraging others to invest in developing different products that will compete in the same therapeutic class as the first product.

Discussions on development of an abbreviated approval process for biological products that relate in some manner to an earlier approved biological product are underway. Various conceptual models have been proposed for such a system. Of course, any follow-on protein approval scheme must be supported by objective and defensible scientific principles that will not place the public at risk as to the safety and effectiveness of follow-on products, particularly those that are not clearly demonstrated to be safe and effective through new clinical investigations. In addition, the structure of any potential abbreviated regime must preserve the effectiveness of economic incentives for the discovery, development, and clinical testing of new biological products.

The Abbreviated New Drug Application (“ANDA”) approval process for generic drugs, established by the 1984 Hatch-Waxman Act, balanced the interests of both innovator and generic companies. The Act provides an abbreviated approval process for generic products that relies on the findings of safety and effectiveness of the innovator product. The generic version must contain the same active ingredient and be bioequivalent to the innovator product, which permits the FDA to rely on its conclusions regarding the innovator product to justify approval of a “duplicate” of that product. To mitigate the economic impact of this reliance, innovator companies can earn market exclusivity periods for their products, as well as patent term

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restoration periods for time spent obtaining regulatory approval. It is through this balance of interests that the Hatch-Waxman Act has fostered the development of both the generic and innovator industries.

The Hatch-Waxman Act also is based on sound scientific principles. The Act generally authorizes the Food and Drug Administration (“FDA”) to approve a generic version of a drug product if the generic drug contains the same active ingredient as the innovator product, is shown to be bioequivalent, and is demonstrated to be manufactured according to good manufacturing practices. If so, the generic drug is considered therapeutically equivalent to the pioneer product, and will be presumed to be safe and effective. The assumption that the generic and innovator products are the “same” drug is an essential predicate of the statutory authority that allows the FDA to rely on the innovator’s clinical proof of safety and effectiveness to support approval of the generic version of the drug product.

Some have suggested that the underlying principles of the Hatch-Waxman Act should be used to design a new and abbreviated “follow-on” biological product approval system. As discussed in this paper, the essential scientific principles and assumptions that underpin the design of the Hatch-Waxman Act and allow the FDA to conclude that a generic version of a drug product will be as safe and effective as the innovator version of the product simply do not apply to biologic products. Unlike a generic version of a small molecule drug, a follow-on protein product will not be the same as the innovator product, even if it were to share certain structural similarities to that innovator product, or be made by a similar process. In other words, it has not yet been established how a “duplicate” follow-on product that is therapeutically equivalent to an innovator product can be produced.

The distinctions also lead to substantive differences in how various types of intellectual property systems operate to provide market exclusivity for innovator biological products. For example, a follow-on product may be sufficiently similar to an innovator product for regulatory approval purposes, but sufficiently different to avoid the innovator’s patents. Similarly, unique patent issues stem from the relative newness of the techniques used to produce protein products, the importance of process technology, and the interrelationships between numerous entities associated with early stage through clinical development of a protein product. How all these issues can be resolved without fundamentally undermining the collaborative and innovative environment that has marked the development of the biotechnology industry is not clear.

II. Introduction

The United States is at the forefront of efforts to develop innovative therapeutic products using biotechnology. Indeed, one of the most promising areas of development is biological products. Biological products have already saved, extended or enhanced the quality of life for millions of patients. Additionally, they have revolutionized the treatment of diseases including cancer, heart disease, infections, arthritis, and multiple sclerosis, and offer unquantifiable potential for improving public health in the future. Importantly, the driving force behind the biotechnology revolution has been the companies that have invested in discovering, developing, testing and bringing to market new biological products.

The investment of time and money required to bring a new biologic to market is significant. As is the case with new drugs, new biologics must undergo a time-consuming and complicated process of discovery, development, clinical evaluation, manufacture, and rigorous regulatory approval. A candidate molecule for a biologic first must be discovered, tested through preclinical investigations, and identified for further development.

At this point in product development, biologics face a different path relative to small molecule drugs. Most small molecule drugs are produced via a pathway that has at least some chemical synthetic steps. Small molecule drugs are also subjected to more rigorous purification and characterization steps, which enable the production of substantially pure and objectively characterized compositions containing the active ingredient. Also, in most instances, small molecule drugs can be produced via multiple pathways, all of which end at the same known and objectively characterized composition. This capacity of a small molecule drug product to be objectively characterized as to its purity and compositional homogeneity is an essential predicate of the regulatory paradigm that governs approval of pioneer and generic small molecule drug products (*i.e.*, active ingredients that have an identical chemical structure).

By contrast, biological products are generally large complex molecules produced using living organisms.¹ The development of a reliable, consistent manufacturing process based on the use of cell cultures or other living organisms is substantially more demanding than the development and implementation of a suitable manufacturing process for small molecule drugs (*i.e.*, one based on a series of chemical synthesis and purification steps). Biotechnology production processes also, at present, are incapable of yielding compositions that are homogeneous and objectively characterized (*i.e.*, where constituents of the composition are known and verified in a process-independent manner). In other words, the identity of a biological product, and the clinical assessment of its safety and effectiveness, are inherently linked to the process by which it has been produced.

Like small molecule drugs, once a candidate biological product has been identified, it is subjected to extensive pre-clinical testing to identify toxicity. But because most biologics are expressly designed to manipulate a native human biological mechanism or cellular target, the investigations of these products can prove challenging and often present toxicity issues distinct from screening of chemical compounds. For example, a biologic may mimic a natural substance, or trigger events in the body that occur naturally in healthy individuals. The consequences of manipulating these endogenous pathways usually are not well understood, but can alter the benefit/risk profile. By contrast, toxicology screening of small molecule drugs typically focuses on identification of toxic metabolites that are produced once the active ingredient has been ingested. Those screens can be conducted on laboratory animals as surrogates for humans, as the toxicity effects are generally macroscopic and easily measurable (*e.g.*, liver failure).

If the pre-clinical testing is positive, a biological candidate, like a small molecule drug, enters clinical trials. Clinical trials for both biologics and small molecule drugs generally consist

¹ The Public Health Service Act defines biological product as a “virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, 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.” 42 U.S.C. § 262(i).

of three phases. Phase I studies involve administering the compound to a small number of healthy subjects to obtain initial data on metabolism, pharmacologic action, and side effects. Phase II studies, which may involve several hundred subjects, are directed to side effects, effectiveness, and optimal dosing. If the preliminary evidence indicates that the biological product or drug is safe and effective, then Phase III trials are conducted with up to several thousand patients. Phase III trials are intended to provide safety and effectiveness data to meet FDA's approval standards.

The investment of time and money required to bring a new biologic to market is staggering. The entire development process, from clinical trials through regulatory review takes approximately eight years and costs upwards of \$1.2 billion.² As a stark reminder of the unpredictability of the therapeutic compounds, it is estimated that less than a third of the biopharmaceuticals that enter clinical trials ever receive marketing approval.³ This type of risky development environment requires a strong market incentive.

Finding ways to overcome the challenges in developing and clinically testing new biological products, and in establishing the necessary technology infrastructure to support those efforts, have placed the United States at the forefront of this industry. The regulatory and intellectual property schemes in the United States are a significant reason for U.S. prominence in this field. Most biotechnology products that are now on the market resulted from U.S. based research and development efforts. The significant investments made by the private and public sectors in the early 1980s, coupled with measures that promoted cooperation among universities and public research institutions and start-up companies, all helped jump-start the biotechnology revolution in the United States. Those investments continued through the 1990s and laid the foundation for the basic and applied research that has made the U.S. biotechnology industry the global leader it is today. It is safe to say that the primary incentive for the private sector role in this industry was and remains the promise of market exclusivity for new products that actually reach the market, which is delivered through a combination of patent and regulatory mechanisms.

Measures that limit the duration or effectiveness of market exclusivity for innovative biotechnology products undermine the incentives needed for the private sector to invest in development, testing, and improvement of these products. Yet, in the life sciences industry, the public sector interest in managing drug costs also is an important balancing factor. Indeed, it was that desire for balance that led to the system embodied in the Hatch-Waxman Act, including the regulatory framework for the generic drug approval system. Unlike any other industry, the first (and often many) generic drugs that enter will have an assured market success in almost all cases – the innovator has developed and created the market demand for the product, which the generic will satisfy at a substantially lower development cost. This system not only delivers significant cost savings to the consumer, it also essentially eliminates the ability of the innovator

² Medical Research Law & Policy, "Cost to Develop New Biotech Products Averages \$1.2 Billion, Tufts Center Says," Vol. 5, No. 22, Page 737 (November 15, 2006) (citing a study by the Tufts Center for the Study of Drug Development (November 9, 2006). Note that the eight year figure does not include identification of the compound and preclinical testing, which also involve significant amounts of time.

³ *Id.*

to compete with the generic producer. Once generic competition has commenced, the innovator will typically move on to development and marketing of other new drug products. This is the result of the statutory design of the Hatch-Waxman Act, which permits a generic producer to rely (albeit indirectly) on the innovator's clinical data, rather than being required to conduct separate clinical investigations for the generic version of the molecule. As a result, a generic manufacturer can save hundreds of millions of dollars associated with the clinical development of a new drug product. The reduced development costs to the generic company are reflected in the market, where the innovator competes with a generic that may sell its product for as much as 80% less than the price of the innovator's drug.

In addition to authorizing a generic producer to rely on an innovator's clinical findings of safety and effectiveness, the Hatch-Waxman Act also established a patent infringement "safe harbor" period. Specifically, an innovator may not sue a party (including a generic producer) for patent infringement as long as the party is developing data reasonably related to an application that may or will be filed with the FDA. The benefits to the generic manufacturer of being permitted to conduct testing during the product's patent life, as well as to rely on the innovator's clinical data, are balanced by incentives provided to the innovator: patent restoration and non-patent exclusivity. Innovator companies receive five-years of market exclusivity for new chemical entities and three-years of market exclusivity for changes to previously approved products that are based on new clinical investigations. Innovators also can receive a patent term restoration period to compensate for lost effective patent time during the regulatory review process (*i.e.*, the period during which patent rights exist but cannot be used due to the absence of marketing approval for the innovator product). Importantly, the Hatch-Waxman Act recognizes that there would be no generic market without the products developed by the innovators, which is why that system created a system of strong set of economic incentives.

At the time that Hatch-Waxman was enacted in 1984, both the "innovator" industry and the generic industry were established, viable industries. This is very different than the industry profile that exists today that is associated with development of biological products. For example, the biotechnology industry today is populated with a large number of small start-up companies and is funded by numerous and often complex interrelationships among venture capital funds, established biological or drug manufacturers, universities and other parties. In contrast to the drug industry in 1984, there are few, if any, U.S. companies or manufacturing infrastructures dedicated to producing "copies" of existing biological products. Given that small molecule drugs are easier to manufacture and purify than biologicals, many companies in 1984 could immediately take advantage of the abbreviated approval process. In contrast, the current biologics industry is relatively nascent, and a new entry to the market faces substantial manufacturing start-up costs.

In light of the differences between biologics and small molecules, biologics are regulated separately under a different statute - the Public Health Service Act. Unlike the Hatch-Waxman Act, the Public Health Service Act does not provide an abbreviated approval scheme for follow-on products. As detailed in this paper, an analysis of the unique scientific, patient safety, regulatory, and market protection issues related to biological products indicates that the Hatch-Waxman Act would not provide an applicable paradigm for an abbreviated approval scheme for follow-on protein products. Given that any follow-on product will be different - in both an

absolute and clinically relevant sense - compared to the innovator product, the follow-on may be able to avoid the innovator's patents and market exclusivity periods. A follow-on regulatory system that is predicated on the belief that only "duplicate" products will be barred from competing with innovator products would not preserve the balance that exists under the Hatch-Waxman Act. As a result, such a scheme would jeopardize the underlying development of new products that is fundamental to the viability of biotechnology and the advancement of public health.

III. Biologics Present Many Unique Issues Compared to Small Molecule Drugs

Biological products have very different physical structures and characteristics from small molecule drugs. Generally, proteins are much larger and more complex than small molecule drugs. Each protein consists of a chain or chains of amino acid units, which may range from a few to several thousand amino acids. Illustrating the different structures, the molecular weight for protein molecules typically range from several thousand Daltons to several hundred thousand Daltons, while small molecule drugs typically weigh only several hundred Daltons.

Proteins are identified based on four different structural characteristics, all of which may affect the protein's therapeutic properties. The sequence of the amino acid chain in the polypeptide is termed the primary structure of the protein. The secondary structure of a protein refers to those intra-chain covalent bonds that form (*e.g.*, between amide groups or cysteine residues in the protein). The three-dimensional shape of the protein, which is due to folding and bending of a protein, is termed the tertiary structure of the protein, and the aggregation of multiple distinct polypeptide chains is the quaternary structure. In addition, many recombinant products are glycosylated, which means that they have an attached sugar or other complex carbohydrate molecule. The structural characteristics and glycosylation pattern are critical factors with respect to the safety and effectiveness of a biological product. Even a small variation in a characteristic, such as the substitution of a single amino acid or the alteration of a pattern of sugar residues, can dramatically alter the biological activity of the protein.

Biological products are produced by complex manufacturing processes. Importantly, biological products are manufactured from living biological materials, which are inherently variable. The characteristics of a final biological product – unlike a chemically synthesized product – will be determined by and linked to the particular steps and conditions of the manufacturing process. As explained by FDA:

Because, in many cases, there is limited ability to identify the identity of the clinically active component(s) of a complex biological product, such products are often defined by their manufacturing processes. Changes in the manufacturing process, equipment or facilities could result in changes in the biological product itself and sometimes require additional clinical studies to demonstrate the product's safety, identity, purity, and potency. Traditional drug products usually consist of pure chemical substances that are easily analyzed after manufacture. Since there is a significant difference in how biological products are made, the

production is monitored by the agency from the early stages to make sure the final product turns out as expected.⁴

The first step of the manufacturing process is to develop a transformed host cell to synthesize the protein. This is done (in general terms) by isolating the DNA sequence that codes for the target protein and inserting it into a suitable cell line. Acting as a blueprint, the exact sequence of genes and type of host cell will determine the characteristics of the resulting protein product. Next, a cell bank is established using an iterative cell screening and selection process. Due to the process, no two master cell banks are ever exactly alike. The engineered cells are then cultured on a large scale under optimal growth conditions to produce the desired protein. The physical conditions of the culture, the components of the solution, and the type of fermentation used each may significantly affect the characteristics of the final protein and the composition that is isolated from the host cell containing that protein. As the cultured cells often produce impurities with the desired protein, the mixture is purified through a series of validated steps designed to optimize purity and yield, as well as to ensure that the protein is in the desired three-dimensional form. The resulting protein mixture is then analyzed to determine if it is sufficiently free of impurities and uniform in terms of structure, character, and potency. Various analytical tools are used to examine amino acid sequence, glycosylation patterns, protein aggregation, strength, heterogeneity, and potency. It is not unusual to conduct several thousand analytical tests per single batch of product. Finally, the protein is formulated, packaged, and distributed.

Biological products also present an increased risk of unwanted immune reactions in patients.⁵ The immunogenicity risk may cause the patient to produce antibodies that inactivate the therapeutic protein, which results in safety and effectiveness concerns. For instance, the immune reaction may inactivate one of the patient's own naturally occurring proteins, resulting in severe side effects. Factors that have been shown to influence immunogenicity include amino acid sequence variation, glycosylation, impurities, aggregate formation, and formulation.⁶ Even small changes to such factors may result in immunogenicity problems, such as inactivation of the treatment, allergic or anaphylactic reactions, or a condition leading to regular blood transfusions. According to FDA, "[i]n some cases, manufacturing changes could result in changes to the biological molecule that might not be detected by standard chemical and molecular biology characterization techniques yet could profoundly alter the safety or efficacy profile."⁷

For example, a small change in the manufacturing process for Johnson & Johnson's overseas epoetin product, Eprex®, is believed to have caused a severe immunogenicity

⁴ FDA Paper: Frequently Asked Questions About Therapeutic Biological Products (2006) ("FDA Biological FAQ") (accessed at <http://www.fda.gov/cder/biologics/qa.htm>) at Question 10.

⁵ Examples of biological products that have exhibited immunogenicity issues include Factor VIII, interferon-alpha, interferon-beta, interleukin-2, erythropoietin, granulocyte macrophage colony stimulating factor, calcitonin, growth hormone, denileukin-diftox, and megakaryocyte derived growth factor. See Schellekens, H., "Bioequivalence and the Immunogenicity of Biopharmaceuticals," *Nat. Rev. Drug Discov.*, Vol. 1(6):457-62 (June 2002) at Table 1.

⁶ *Id.* at 458-60.

⁷ FDA Biological FAQ at Question 9.

response.⁸ Specifically, Johnson & Johnson replaced human serum albumin as the stabilizer in Eprex® with polysorbate 80 due to new regulations established by the European Health authorities. Subsequently, an increased number of patients taking Eprex® developed pure red cell aplasia (“PRCA”), a severe and rare form of anemia. An extensive investigation into the incident indicated that the cause of the increased rates of PRCA was most likely due to an interaction between the new stabilizer, polysorbate 80, and the uncoated rubber stoppers used in certain pre-filled Eprex® syringes. According to the investigation, the polysorbate 80 leached organic chemical compounds from the rubber stopper, and animal models confirmed that the leachates increased immunogenicity. Subsequently, Johnson & Johnson changed the syringe stoppers and instituted other measures, which returned the incidents of PRCA to baseline rates.

The Eprex® example demonstrates the potential safety issues that may result from even a minor manufacturing change. As routine analytical testing by Johnson & Johnson did not detect anything that would have predicted the increased incidence of PRCA, it also confirms that such safety issues may occur even when there are no detectable changes in the nature of the product.

IV. Biologics Historically Have Been Regulated Independently from Small Molecule Drugs

A. Biological Products are Regulated Separately Under the Public Health Service Act

As described above, biologics have unique safety, potency, and purity issues that are not raised with small molecule products. In light of those unique issues, Congress has historically regulated biologics separately from small molecules. Beginning in 1902, Congress passed the Biologics Control Act to ensure the safety of biologics.⁹ In contrast, the Federal Food, Drug, and Cosmetic Act (“FFDCA”) was passed in 1938 to establish a new approval process for drug products. Although the FFDCA broadly defines “drug” to include biological products,¹⁰ the law did not supersede the separate regulation of biologics under the Biologics Control Act. Rather, provisions from both laws are used to regulate biologics. The Biologics Control Act was incorporated into the Public Health Service Act (“PHSA”) in 1944, which is the current statutory provision governing biologics.¹¹ Consistent with the separate statutory scheme, FDA also promulgated a separate regulatory scheme for biological products.¹²

The PHSA provides that a biological product must be safe, pure, and potent. Underscoring the importance of manufacturing, the PHSA requires an applicant for a biologics product to receive a marketing license for both the product and the manufacturing facility. As

⁸ Johnson & Johnson Supplement to Citizen Petition, FDA Docket No. 2004P-0171 (July 1, 2004) at 2-4.

⁹ The Biologics Control Act was the result of a safety incident in which 13 children died after receiving an impure diphtheria antitoxin.

¹⁰ The FFDCA defines “drug” to include articles intended for the diagnosis, treatment, or prevention of disease, as well as articles intended to affect the structure or function of the body. 21 U.S.C. § 321(g).

¹¹ Underscoring the regulatory differences between biologics and small molecules, FDA did not even receive jurisdiction over biological products until as recently as 1972. Before that time, the National Institutes of Health regulated biologics.

¹² 21 C.F.R. Parts 600-680.

stated by FDA, “[b]ecause of the complexity of manufacturing and characterizing a biologic, the PHS Act emphasizes the importance of appropriate manufacturing control for products.”¹³ Until recently, FDA required separate license applications for the product and facility. These two requirements have been combined into one, so that an applicant now submits a single Biological License Application (“BLA”). In light of the unique safety issues posed by biologics, FDA phased in the single BLA scheme over many years. In particular, products defined as “well characterized” were allowed to use a BLA as early as 1996. Another segment of biologics was authorized to use a BLA in 1997, while remaining biologics were not required to use a BLA until 1999. Importantly, unlike the Hatch-Waxman scheme, the PHSA does not contain an abbreviated approval process for follow-on products.

B. Small Molecule Products are Regulated under the Hatch-Waxman Act

In contrast to biological products, small molecule drugs are regulated under the FDCA.¹⁴ The Hatch-Waxman amendments to the FDCA established the current drug approval scheme.

1. New Drug Applications and Related Market Exclusivity Periods for Innovators

Under the Hatch-Waxman Act, innovator products are approved under a New Drug Application (“NDA”). To receive marketing approval, an NDA must include data demonstrating that the new drug product is safe and effective for its intended use. The NDA must also include a list of all patents that claim the drug product and methods of using the drug. The Hatch-Waxman scheme does not permit the listing of manufacturing or process patents.¹⁵ It also does not permit the listing of patents that claim variants of the drug submitted for approval.¹⁶ After the new drug product is approved, FDA lists the product and the related patents in FDA’s publication, “Approved Drug Products with Therapeutic Equivalence Evaluations,” known as the Orange Book. The Orange Book designates the innovator product as the Reference Listed Drug (“RLD”), which is the comparator product for a generic.

¹³ FDA Biological FAQ at Question 9.

¹⁴ For historical reasons, some biologics are regulated under the FDCA. For example, human growth hormone, hyaluronidase, and calcitonin are regulated under the FDCA.

¹⁵ 21 C.F.R. § 314.53(b)(1). There is little legislative history concerning the Hatch-Waxman Act, specifically with respect to why manufacturing patents were excluded from the Act. However, it seems that manufacturing patents were excluded from the Hatch-Waxman scheme because small molecule drugs are made by chemical synthetic procedures, and it is rare that a patented process of chemical synthesis will be able to block any and all means of producing the product.

¹⁶ The patent must claim the same active ingredient that is the subject of the NDA. 21 C.F.R. § 314.53. Patents that claim a polymorph form of the same active ingredient as in the NDA may be listed only when the innovator has data to establish that the polymorph form performs the same as the NDA form, including a full description of the polymorph form, a demonstration of bioequivalence between the polymorph and NDA forms of the active ingredient, and dissolution data. *Id.* Polymorphs include chemicals with different crystalline structures, different waters of hydration, solvates, and amorphous forms.

To protect and reward the investment required to bring a new active ingredient to market, the Hatch-Waxman Act provides five years of market exclusivity for a new chemical entity (“NCE”).¹⁷ During that time, a generic may not submit an application for a generic version of the NCE.¹⁸ Additionally, companies receive three years of market exclusivity for changes to existing products that require new clinical investigations. The three-year exclusivity prevents the approval of a generic application for a product with the same change or new indication during the exclusivity period.

2. Abbreviated New Drug Applications and the Exclusivity Period for Generics

Approval to market a generic version of a drug product is provided through approval of an Abbreviated New Drug Application (“ANDA”). The Hatch-Waxman Act requires a generic product to contain the same active ingredient as the innovator product. Additionally, the generic is required to have the same conditions of use, route of administration, dosage form, strength, and, with certain exceptions, labeling as the innovator product.¹⁹ Being identical to the innovator product allows FDA to rely on the innovator’s safety and effectiveness data in determining that the generic version of the product will be safe and effective. To the extent that a generic differs from the innovator, such as by using a different excipient, it weakens the scientific basis for the abbreviated approval scheme that does not require further clinical evaluation.²⁰

Although the generic applicant does not have to provide independently generated clinical evidence of safety and effectiveness, it is required to demonstrate bioequivalence to the innovator product. In general terms, bioequivalence means that the generic product delivers the same amount of drug at the same rate as the innovator product.²¹ After showing that the generic

¹⁷ In addition to the Hatch-Waxman Act, which includes market exclusivity periods for both innovator and generic companies, several other drug regulatory schemes also utilize market exclusivity periods. For example, drugs to treat rare diseases are eligible for seven years of orphan drug market exclusivity, 21 U.S.C. §§ 360aa – 360ee, and studies regarding pediatric uses may earn six months of market exclusivity, 21 U.S.C. § 355a. Generally, the use of market exclusivity periods has been very successful. According to FDA, “the pediatric exclusivity provision has done more to generate clinical studies and useful prescribing information for the pediatric population than any other regulatory or legislative process to date.” The Pediatric Exclusivity Provision, January 2001 Status Report to Congress by FDA at 12.

¹⁸ A generic may submit an application after four years if the generic challenges an innovator patent. 21 U.S.C. § 355(j)(5)(F)(ii).

¹⁹ An ANDA applicant may submit a suitability petition to FDA requesting permission to change the route of administration, dosage form, and strength of an innovator product, or to substitute an active ingredient in a combination product. 21 C.F.R. § 314.93. Except as described with respect to combination products, an ANDA applicant is strictly prohibited from modifying or changing the active ingredient of the innovator product.

²⁰ An ANDA applicant must demonstrate that any changes from the innovator product do not affect safety or efficacy. *See, e.g.*, 21 C.F.R. § 314.94(a)(9) (requiring an ANDA applicant to provide information demonstrating that any differences in inactive ingredients between the ANDA product and the innovator product do not affect the safety or efficacy of the ANDA product).

²¹ Bioequivalence studies are less involved and costly than full safety and efficacy trials conducted by innovator companies.

delivers the same amount of drug as the innovator, the safety and effectiveness of the generic product may safely be inferred from the innovator's data.

As part of the ANDA, a generic must also certify as to each patent an innovator lists in the Orange Book for the RLD. There are four types of certifications: (1) a paragraph I certification asserts that there is no listed patent; (2) a paragraph II certification asserts that the listed patent has expired; (3) a paragraph III certification asserts that the generic will wait for the listed patent to expire before marketing the generic product; and (4) a paragraph IV certification asserts that the generic seeks authority to market its product immediately because the listed patent is not valid or would not be infringed by the generic product.

The filing of an ANDA containing a paragraph IV certification is defined in the patent statute as an act of patent infringement. This allows the innovator to sue the generic under the listed and certified patents. Under the statutory scheme in section 505(j) (and the comparable provisions in section 505(b)), the generic applicant must notify the innovator of a paragraph IV certification. If the innovator sues the generic applicant within 45 days of receiving the paragraph IV notice, the FDA may not approve the generic application for up to 30 months. This so-called 30-month stay is intended to provide time for the patent infringement litigation to conclude. If, during the 30-month stay, a court determines that the patent is not valid or not infringed, then FDA may grant final approval to the generic application. However, if a court were to determine that the patent is valid and infringed, then FDA may not grant final approval to the generic application until the date the patent expires. To encourage generics to challenge innovator patents, the first generic to submit a paragraph IV certification may be eligible for 180-days of market exclusivity against other generics. This "generic exclusivity" system operates by prohibiting the FDA from granting final approval to any other ANDA that is based on the same pioneer product for a period of six months. Because there is strong pressure for payors to shift to generic products as soon as they are available on the market, the first generic to market often can secure a significant economic return (*e.g.*, by pricing its product only slightly below the price of the innovator product), as well as become the "entrenched" generic provider that other generics must then compete against when the six-month exclusivity period ends.

The 30-month stay recognizes the importance of resolving patent disputes before a generic product has been approved and goes to market. As a patent provides the right to exclude the generic from the market, a generic that was approved and marketed would have to be withdrawn from the market if a court were later to determine that the generic had infringed an innovator's patent. The improper launch of an infringing generic product often will destroy the market for the innovator, leading to termination of further clinical development of the drug. In addition, withdrawing a drug product from the market is a significant event that creates confusion and potentially affects the public health. These are some of the important reasons underlying the role of the 30-month stay as a system to resolve patent disputes before any market entry of the generic drug product.

3. 505(b)(2) Applications

The FDCA also authorizes an applicant to submit an NDA "for a drug for which the investigations . . . relied upon by the applicant for approval of the application were not conducted

by or for the applicant and for which the applicant has not obtained a right of reference”²² Although seemingly simple, the 505(b)(2) provision has been very hard to implement from both scientific and regulatory standpoints.

As interpreted and implemented by FDA, “Section 505(b)(2) permits approval of applications other than those for duplicate products and permits reliance for such approvals on literature or on an Agency finding of safety and/or effectiveness for an approved drug product.”^{23, 24} Thus, FDA’s interpretation of the provision allows changes to an innovator product that are not permitted under an ANDA. To the extent that the (b)(2) product differs from the innovator product, the (b)(2) applicant must provide new clinical data.

Section 505(b)(2) applications share characteristics of both NDAs and ANDAs. Technically, 505(b)(2) applications are NDAs that require full safety and effectiveness reports. The applications do not provide an abbreviated approval process for generic drugs like the ANDA scheme. Similar to an NDA, a 505(b)(2) application must include a list of patents that cover the drug product and methods of using the product. However, similar to an ANDA, FDA allows a 505(b)(2) applicant to rely to some degree on the finding of safety and effectiveness for an innovator product. The applications must also include certifications to patents that claim the drug or methods of using the drug for which the applicant seeks approval. Section 505(b)(2) applications are also subject to the five and three-year exclusivity periods; however, they are not subject to 180-day generic drug exclusivity.

While BIO strongly disagrees with FDA’s interpretation and implementation of Section 505(b)(2) to the extent it permits reliance on a prior finding of safety and effectiveness to approve a new product that is not a duplicate of, or the same as, the innovator product, it is important to note how rarely FDA has used this authority for biologics and the difficult scientific and legal challenges FDA has encountered in attempting to utilize this pathway for the approval of even the most simple and well-characterized protein products regulated under the FFDCAs. See discussion, *infra*, at 13.²⁵

V. The Scientific Principles Underlying the Hatch-Waxman Act Do Not Support a Similar Paradigm for Biologics

The abbreviated approval scheme under the Hatch-Waxman Act is built on solid scientific principles. Specifically, once a known active ingredient has been proven to be safe and effective, there is no scientific reason to require a generic company that is using the identical active ingredient to provide new clinical data supporting safety and effectiveness of the product.

²² 21 U.S.C. § 355(b)(2).

²³ FDA Draft Guidance: Applications Covered by Section 505(b)(2), Center for Drug Evaluation and Research (CDER) (October 1999) at 2.

²⁴ As discussed in the Trade Secrets section, FDA has interpreted 505(b)(2) to mean that it may rely only on the finding of safety and effectiveness, and not any information actually contained in the innovator’s application.

²⁵ See BIO Citizen Petition, FDA Docket No. 2003P-0176 (April 23, 2003), and the related material filed with that docket.

Requiring such data could be an unnecessary use of company and FDA resources and may also raise ethical issues, by requiring the performance of unnecessary new clinical investigations. This system works because the generic product will be a duplicate of the innovator product. However, these scientific principles erode as the characteristics and clinical profile of the generic product begins to differ from the innovator product.

This is particularly true with respect to biologics, which are inherently different from each other. To know the effects of the differences, a follow-on protein product will need to have its own clinical data like an innovator. As FDA aptly stated in 1974 in the preamble to final regulations:

Unlike the regulation of human and animal drugs, all biological products are required to undergo clinical testing in order to demonstrate safety, purity, potency, and effectiveness prior to licensing, regardless whether other versions of the same product are already marketed or standards for the product have been adopted by rulemaking This is required because *all biological products are to some extent different* and thus each must be separately proved safe, pure, potent, and effective [A BLA] is under no circumstances granted by [FDA] to a second manufacturer based upon published or otherwise publicly available data and information on another manufacturer's version of the same product. . . . There is no such thing as a "me-too" biologic."²⁶

Although the science has developed since FDA made this statement, the underlying scientific principle that all biological products are unique remains true.

Accordingly, an abbreviated approval scheme for follow-on proteins cannot be modeled on the ANDA scheme because ANDAs require the generic product to have the same active ingredient as the innovator, and this requirement is an essential predicate of the ability of the FDA to approve the ANDA.²⁷ Follow-on protein products will be similar, but not the same, as the innovator product. As such, they generally cannot use an application process or format that is based on the ANDA paradigm. Even if the follow-on were to contain an active ingredient that had the same primary structure as the innovator product, the follow-on often will have a different

²⁶ Public Information Final Rule, 39 Fed. Reg. 44602, 44641 (December 24, 1974) (emphasis added).

²⁷ FDA regulations provide that the term "same as" means "identical." 21 C.F.R. § 314.92(a)(1). Despite FDA's definition, FDA approved an ANDA for a generic menotropins product that contained isoform variations from the innovator product. Relying on clinical trials and published literature, FDA concluded that any observed differences in isoforms did not have clinical significance. *See Serono Labs., Inc. v. Shalala*, 158 F.3d 1313, 1320 (D.C. Cir. 1998) ("After reviewing additional clinical data, the FDA found 'that any potential variations in . . . isoforms between the Ferring menotropins product and Pergonal appear not to be clinically significant for the product's intended uses.'"). The menotropins example underscores the need for clinical data when comparing products with different active ingredients, even products that contain only slight variations. Furthermore, as FDA relied on clinical data and published literature to assess the menotropins ANDA, it seems that the product should have been submitted under a 505(b)(2) application and not an ANDA. In fact, the ANDA product appears not to have been distributed, and was subsequently approved under a 505(b)(2) application.

safety and clinical profile.²⁸ Furthermore, there may be situations where it may not even be possible to determine whether the follow-on has the same active ingredient as the innovator.²⁹

For example, FDA has refused to approve any ANDA for the estrogen replacement drug Premarin® because the active ingredients are not fully characterized. Premarin® is comprised of several conjugated estrogens that are derived from the urine of pregnant mares. Although some of the conjugated estrogens contained in Premarin® have been identified, all of the estrogen compounds have not been fully characterized. Initially, FDA believed that all estrogens produced similar pharmacological actions, and Premarin® could be defined by its overall estrogenic potency without characterizing each estrogen. Based on its initial understanding, FDA approved several generic conjugated estrogen products. However, illustrating the risks involved in drawing conclusions based on uncharacterized drugs, FDA ultimately reversed its position. The evolving science demonstrated that each estrogen provides a distinct result. Consequently, FDA withdrew approval of the generic conjugated estrogen products in 1991. According to FDA, “because the reference listed drug Premarin is not adequately characterized at this time, the active ingredients of Premarin cannot now be definitively identified. Until the active ingredients are sufficiently defined, a synthetic generic version of Premarin cannot be approved.”³⁰

Similar to ANDAs, the 505(b)(2) pathway does not make a good model for an abbreviated approval process for follow-on proteins. Approvals under 505(b)(2) are determined on a case-by-case basis. Unlike typical generic approvals under ANDAs, there is no general standard, such as bioequivalence, that can be used to approve 505(b)(2) applications. As implemented by FDA, the 505(b)(2) provision allows a product to vary from the innovator product. The extent of the differences between the products dictates how much clinical data will be needed to assure that the product is safe and effective, an analysis that must be made for each product individually. As FDA stated with respect to 505(b)(2) applications for the biological hyaluronidase, “[t]he clinical data should be specific for the product that is proposed for marketing, as each hyaluronidase product is likely to be different in terms of origin, purity, and other CMC characteristics and therefore may be different in the potential for immunologic sensitization and immediate hypersensitivity reactions.”³¹ Having a follow-on approval scheme based on a case-by-case standard would not produce the same development cost savings as the generic scheme for small molecules.

²⁸ *Genentech, Inc. v. Bowen*, 676 F. Supp. 301, 311-12 (D.D.C. 1987) (holding that a recombinant human growth hormone (“hGH”) with the identical chemical structure as natural, pituitary-derived hGH has a superior clinical effect over the natural hGH for purposes of orphan drug exclusivity).

²⁹ FDA Memorandum from C. Rask, E. Unger, and M. Walton, Division of Clinical Trial Design and Analysis to BLA STN 103780/0 File (March 7, 2002) (“FDA Avonex Memo”) at 17 (“Analytic methodology does not provide us with a method to determine that two protein drugs such as Rebif and Avonex from two separate manufacturers are, in fact, identical.”).

³⁰ FDA Memorandum from Director, Center for Drug Evaluation and Research, to D. Sporn, Director, Office of Generic Drugs, “Approvability of a Synthetic Generic Version of Premarin” (May 5, 1997) (accessed at <http://www.fda.gov/cder/news/celetterjw.htm>) at 1.

³¹ FDA Memorandum from C. Lee, Medical Officer, Division of Pulmonary and Allergy Drug Products, to B. Harvey, Acting Director of the Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products, and

In particular, follow-on companies will likely be required to invest in and submit at least some clinical safety data to support their follow-on products. Even relatively simple and well-characterized follow-on protein products would likely need such clinical data. For example, in 2006 FDA recently approved Sandoz, Inc.'s Omnitrope® (somatropin [rDNA origin]) under section 505(b)(2).³² Sandoz's application referenced Pfizer Inc.'s product, Genotropin® (somatropin [rDNA origin]). Both products contain the active ingredient somatropin [rDNA origin]. Nevertheless, because the products were produced in different ways and therefore had potentially distinct efficacy profiles, Sandoz could not rely solely on Pfizer's somatropin product for approval, but submitted extensive original clinical data to support approval.³³ In particular, Sandoz performed four phase III clinical trials.

The Omnitrope® example demonstrates that significant clinical data should be required for approval of most, if not all, follow-on protein products. Somatropin is a relatively simple, well-characterized, and well-understood protein. It has been used as a treatment since 1958, and since 1985, FDA has approved seven recombinant somatropin products, each on the basis of independently generated clinical data. Thus, FDA has a unique level, and a substantial degree, of experience with this protein. Furthermore, somatropin, which is the only active ingredient in Omnitrope®, is relatively simple. It consists of a single non-glycosylated polypeptide that is easily purified, has a well-known and characterized primary structure and mechanism of action, and for which numerous clinically relevant bioassays are available.³⁴

The characteristics that made Omnitrope® approvable, in the view of the FDA, under the 505(b)(2) authority are not typical of the biological products regulated under the PHS Act. Those products are typically more complex and less understood than somatropin. For example, they include products that have multiple or unknown active ingredients, unknown mechanisms of action, glycosylation patterns, short clinical histories, and are not fully characterized. It is unlikely that the situation surrounding the Omnitrope® 505(b)(2) application will be encountered in other protein products. As FDA stated with respect to the approval of Omnitrope®, “nor does it mean that more complex and/or less well understood proteins . . . could be approved as follow-on products.”³⁵ In essence, the science simply does not permit an abbreviated approval scheme for follow-on proteins similar to the scheme for small molecules under the Hatch-Waxman Act.

L. Gorski, Project Manager, Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products, “Medical Officer Consultation Regarding Clinical Data Necessary to Support the Safety of Hyaluronidase Products,” (December 24, 2003) (“FDA Hyaluronidase Memo”) at 4.

³² Other biologics approved under 505(b)(2) include GlucaGen® (glucagon recombinant), Fortical® (calcitonin salmon recombinant), Hylenex™ (hyaluronidase recombinant human), and Hydase™ (hyaluronidase).

³³ Letter from S. Galson, M.D., M.P.H., Director, CDER, FDA to K. Sanzo, Esq., S. Lawton, Esq. and S. Juelsgaard, Esq. regarding Docket Nos. 2004P-0231, 2003P-0176, 2004P-0171, and 2004N-0355 (May 30, 2006) (“FDA Omnitrope Letter”) at 8.

³⁴ Id. at 7-8.

³⁵ FDA Omnitrope (somatropin [rDNA origin]) Questions and Answers (May 30, 2006) (accessed at <http://www.fda.gov/cder/drug/infopage/somatropin/qa.htm>) at Question No. 5.

VI. Follow-On Proteins Raise Significant Therapeutic Equivalence Questions

As part of the generic approval scheme under the Hatch-Waxman Act, FDA determines whether the generic product is therapeutically equivalent to the innovator product. A therapeutic equivalence rating is important because it allows the generic to be substituted freely for the innovator product. At its base, the Hatch-Waxman Act is intended to provide a line of identical products that can be interchanged without any clinical concerns.

FDA considers products to be therapeutically equivalent only when the products are pharmaceutical equivalents and can be expected to have the same clinical and safety profile. Pharmaceutical equivalents have the same active ingredient, dosage form, route of administration, and strength. FDA has underscored the fact that the “*concept of therapeutic equivalence . . . applies only to drug products containing the same active ingredient(s) and does not encompass a comparison of different therapeutic agents used for the same condition (e.g., propoxyphene hydrochloride vs. pentazocine hydrochloride for the treatment of pain).*”³⁶ Products that do not have identical active ingredients are not therapeutic equivalents. Rather, FDA considers such products pharmaceutical alternatives.

Unlike small molecules, an abbreviated approval scheme for follow-on proteins will likely require the follow-on product to be similar, but not the same, as the innovator. In some situations, it may not even be possible to determine whether or not a follow-on product has the same active ingredient.³⁷ A follow-on product that does not have the same active ingredient as the innovator can not be therapeutically equivalent to the innovator and thus may not be substituted for the innovator. In a discussion regarding why similarly labeled conjugated estrogen products are not interchangeable, FDA underscored the fact that the legal and scientific test for a generic product is “not whether the generic product would result in the same clinical effects as the innovator, but rather *whether the active ingredients in the generic product are the same.*”³⁸

Furthermore, even if a follow-on product could be demonstrated to have the same active ingredient as an innovator, it may nonetheless have a different safety and effectiveness profile.³⁹ In that situation, the only way to definitively establish that the follow-on product has the same clinical effect and safety profile as the innovator product would be through clinical testing.

³⁶ FDA’s Approved Drug Products with Therapeutic Equivalence Evaluations, Preface Section 1.2, Therapeutic Equivalence-Related Terms, 27th Ed. (2007) at vi (emphasis in the original).

³⁷ FDA Avonex Memo at 17 (“Analytic methodology does not provide us with a method to determine that two protein drugs such as Rebif and Avonex from two separate manufacturers are, in fact, identical.”).

³⁸ FDA Backgrounder on Conjugated Estrogens (July 7, 2005) (emphasis in the original) (accessed at <http://www.fda.gov/cder/news/cebackground.htm>).

³⁹ *Genentech, Inc. v. Bowen*, 676 F. Supp. 301, 311-12 (D.D.C. 1987) (holding that a recombinant human growth hormone (“hGH”) with the identical chemical structure as natural, pituitary-derived hGH has a superior clinical effect over the natural hGH for purposes of orphan drug exclusivity).

FDA's therapeutic equivalence determination is based on strong scientific principles that ensure the integrity of the public health. According to FDA, "[t]he public expects that drugs that are rated as therapeutically equivalent will provide the same amounts of the same active ingredients as the reference listed drug The Agency stands firmly behind the quality of its generic drugs program. Decisions on bioequivalence of generic drugs must remain supported by strong and current science."⁴⁰

However, the same scientific principles that allow therapeutic equivalence determinations for small molecule products have not been established for follow-on protein products. Biologics are more complex and variable than small molecule drugs, and follow-on products probably will not have the same active ingredients as the innovator product. Thus, any type of therapeutic equivalence evaluation of biological products will involve novel and complicated scientific issues that are not applicable to small molecule drugs. The unique therapeutic equivalence issues raised by biological products are cutting-edge, and regulatory agencies have acknowledged that they have not determined how interchangeability can be established for follow-on proteins. As FDA recently explained:

With small molecular products, there is a long history to support the use of various scientific approaches to establishing "bioequivalence" between products with the same active ingredient(s) produced by different manufacturers. We know now that these "bioequivalent" products can indeed be expected to behave in a pharmacologically interchangeable manner when used in patient care.

With protein products, as of today, the FDA has not determined how interchangeability can be established for complex proteins.

Different large protein products, with similar molecular composition may behave differently in people and substitution of one for another may result in serious health outcomes, e.g., generation of a pathologic immune response.⁴¹

For example, FDA was unable to determine that Sandoz's Omnitrope® (somatropin rDNA origin) is therapeutically equivalent to Pfizer's Genotropin® (somatropin [rDNA origin]). Although somatropin is a simple and well-characterized compound, FDA did not determine therapeutic equivalence. As a result, FDA provided Omnitrope® with a BX therapeutic equivalence evaluation code, which means that there was insufficient data to determine therapeutic equivalence.

VII. Application of Market Exclusivity Periods to Biological Products Raises Novel Issues

The differences between a follow-on protein product and the innovator product also create novel issues with respect to the application of market exclusivity periods. The Hatch-

⁴⁰ FDA Backgrounder on Conjugated Estrogens.

⁴¹ U.S. FDA Considerations: Discussion by National Regulatory Authorities with World Health Organization (WHO) On Possible International Non-proprietary Name (INN) Policies for Biosimilars (September 1, 2006) (accessed at <http://www.fda.gov/cder/news/biosimilars.htm>).

Waxman Act provides innovators with either a five- or three-year market exclusivity period. During this time, a generic may not rely on the innovator's data or receive approval. In addition to market exclusivity, the Hatch-Waxman scheme conditions the final approval of a generic application on the resolution of certain patent issues.

A. Five-Year Exclusivity

An innovator company that develops a new chemical entity is entitled to five years of market exclusivity. Specifically, FDA's regulations provide that "no person may submit a 505(b)(2) application or abbreviated new drug application under section 505(j) of the act for a drug product that contains *the same active moiety* as in the new chemical entity for a period of 5 years from the date of approval of the first approved new drug application"⁴² As stated in the regulation, new chemical entity exclusivity applies against generic products that contain the same active moiety as the innovator. To determine whether a follow-on product contains the same active moiety as the innovator product, FDA analyzes such characteristics as the molecule's amino acid sequence and covalently bonded structure.

The five-year exclusivity provision was developed with respect to small molecule drugs, which are generally easy to analyze and characterize, and in respect of which one can define a universe of "related" molecules (*e.g.*, via reference to the "active moiety" of the original product). However, most biological products are not easily characterized and are not susceptible to an analogous structure. To the extent that follow-on protein products can be characterized, such products will likely contain inherent differences from the innovator product. Determining whether two biological products contain the same active moiety for exclusivity purposes raises unique and difficult issues.

For example, FDA considered these types of issues with respect to the active ingredient hyaluronidase. Hyaluronidase is a protein enzyme used to increase the absorption of other drugs and to treat hypodermoclysis. As with many biologics, hyaluronidase has never been fully characterized with respect to the chemical structure of the pharmacologically active enzymes or to impurities. Hyaluronidase is obtained from several different mammalian sources, including bovine and ovine testicles. Additionally, the USP contains a monograph test for hyaluronidase that groups all mammalian sourced hyaluronidase together.

However, there are differences between the various products. The ovine form of hyaluronidase differs in amino acid sequence, protein structure, carbohydrate analysis, and enzyme function from the bovine hyaluronidase. There are even differences between hyaluronidase sourced from different tissues from the same species, as well as between batches. Accordingly, FDA stated that "each hyaluronidase product is likely to be different in terms of origin, purity, and other CMC characteristics and therefore may be different in the potential for immunologic sensitization and immediate hypersensitivity reactions."⁴³

⁴² 21 C.F.R. § 314.108(b)(2) (emphasis added). The regulation further provides that an application may be submitted after four years if the application contains a paragraph IV certification. *Id.*

⁴³ FDA Hyaluronidase Memo at 4.

Although a biologic, FDA has traditionally regulated hyaluronidase as a drug product. Hyaluronidase products have been marketed for more than 50 years. There are millions of uses per year. There are also numerous approved NDAs for hyaluronidase products, and the earliest application received approval in 1950. Based on FDA's extensive experience with the drug, ISTA Pharm. and Amphastar submitted 505(b)(2) applications for mammalian testicular hyaluronidase products. FDA approved both applications, but was faced with the unique issue of how to implement market exclusivity. Although hyaluronidase had been previously approved, FDA recognized that the specific structure had not been fully characterized and each form of hyaluronidase is different. As stated by FDA:

To make an exclusivity determination for ISTA's Vitrase, the Agency had to resolve a novel regulatory question that arose in an unusual factual context. The general question raised is what exclusivity to grant a drug product if the Agency does not have sufficient information to determine whether the drug contains a previously approved active moiety.

...

The hyaluronidase in these products is not fully characterized (and thus the Agency does not know whether these products, in fact, contain any previously approved active moieties).⁴⁴

FDA originally interpreted the statute to provide ISTA with three-year market exclusivity for Vitrase®. However, FDA subsequently changed its position and concluded that both ISTA and Amphastar deserved five-year exclusivity. According to FDA, "[t]he Act and the Agency's regulations are silent as to which marketing exclusivity is appropriate if a product has not been sufficiently characterized to allow the Agency to determine whether any active moiety the product contains has been previously approved"⁴⁵ In light of the statute's silence, FDA made a policy decision that a product is a new chemical entity eligible for five-year exclusivity when FDA cannot determine whether the product contains a previously approved active moiety.

The fact that FDA awarded new chemical entity exclusivity to both hyaluronidase products, even though hyaluronidase has been marketed for over 50 years, illustrates the complexities involved in making exclusivity determinations with respect to biological products. Furthermore, FDA's hyaluronidase exclusivity decision appears to be so narrow as to make the exclusivity for each product effectively meaningless. Although each product received exclusivity, neither was able to use the exclusivity to block marketing of the other product, as FDA considers each product to be a different product.

Another example illustrating the difficulties involved in determining whether two biological products are the same for exclusivity purposes arose in the orphan drug context. The Orphan Drug Act of 1983 (which is not part of the Hatch-Waxman Act) provides incentives for

⁴⁴ Letter from S. Galson, Director, CDER, to M. Garrett, Vice President, ISTA Pharm., Inc., FDA Docket No. 2005P-0134 (October 25, 2005) at 2.

⁴⁵ *Id.* at 8.

companies to research and develop drugs for rare diseases, *e.g.*, diseases that affect less than 200,000 people.⁴⁶ In particular, the Orphan Drug Act provides tax credits and a seven-year market exclusivity period for orphan drugs. The market exclusivity period blocks the approval of other applications for the same drug for the same indication.⁴⁷

The term “same drug” is defined broadly for orphan drug purposes to prevent companies from easily circumventing the exclusivity. According to FDA’s regulations, large molecule drugs that contain the same principal molecular structural features are considered the same drug.⁴⁸ Importantly, this definition of “same drug” is a policy decision, intended only for defining the scope of orphan drug market exclusivity. It does not provide guidance with respect to the scientific issues underlying approval standards, such as whether a product may safely rely on another product’s data and whether two products are therapeutically equivalent.

To the contrary, the orphan drug scheme recognizes that seemingly similar biological products may, in fact, be different and have very different safety and effectiveness profiles. Specifically, a product that is considered the same as another product with exclusivity may avoid the exclusivity by demonstrating that it has a different and clinically superior profile compared to the product with exclusivity.⁴⁹ For example, FDA had awarded an interferon beta-1a product, Avonex®, orphan drug exclusivity. Despite the exclusivity, FDA granted approval to another interferon beta-1a product, Rebif®. Although Avonex® and Rebif® are both interferon beta-1a products, FDA concluded that Rebif® was different than Avonex®. According to FDA:

[A]n important reality about proteins - some very small modifications in these large molecules have no effect on the activities, whereas other minor modifications have large effects, potentially resulting in substantial benefits to patients. Similarly, differences in how the active moiety is formulated or administered could make no clinical difference or a very large one.

...

Analytic methodology does not provide us with a method to determine that two protein drugs such as Rebif and Avonex from two separate manufacturers are, in fact, identical. The demonstrated clinical superiority of Rebif over Avonex might result from chemical differences in the active molecule, physical differences such as microaggregation, differences in impurities, differences in formulation, differences in route, differences in the injection schedule, differences in the amount of protein given, or any combination of the above.⁵⁰

⁴⁶ 21 U.S.C. §§ 360aa – 360ee.

⁴⁷ 21 C.F.R. § 316.31.

⁴⁸ 21 C.F.R. § 316.3(b)(13)(ii).

⁴⁹ 21 C.F.R. § 316(b)(13).

⁵⁰ FDA Avonex Memo at 17.

Although FDA could not analytically determine whether Avonex® and Rebif® were the same, FDA relied on clinical results to conclude that Rebif® was clinically superior to Avonex®.⁵¹ Similar to the hyaluronidase example, this interferon beta-1a example demonstrates the unique issues involved in making exclusivity determinations with respect to biologics. In particular, it is not always possible to characterize a biological product. Thus, determining the scope of exclusivity and whether a product deserves, or is subject to, exclusivity is a complex and potentially arbitrary decision.

On a broader level, these instances of FDA interpretation of the “sameness” of a protein product create a significant challenge to delivering to an innovator biological developer any degree of effective regulatory-based market exclusivity. Under the logic of the current regulatory exclusivity system for new drugs, the reliance of the generic upon the clinical proof of safety and effectiveness of the innovator product justifies the deferral of the date of market approval for the generic product. Allowing immediate market entry of the generic provides an unjustified and unfair commercial advantage for the generic producer; namely, that it can launch a product with a known and defined market and achieve significant profits for sales of that generic version at a substantially lower price than the pioneer developer. Shortening the period of innovator status for the drug product shrinks the economic return that can be achieved for the product.

In the biologic setting, every follow-on product will have to be subjected to some degree of clinical investigation to ensure safety and effectiveness. The scientific legitimacy of this reliance model is inextricably linked to FDA’s scientific assumptions that are grounded upon its review of the clinical or other data associated with the pioneer biological product. At the same time, for any viable follow-on system to be justifiable economically, the FDA will have to reduce the overall burden on the follow-on producer with regard to the breadth and cost of clinical investigations (relative to what is faced by the innovator biological product). In other words, the conceptual model of an abbreviated pathway for biologics assumes that the economic cost of delivering the follow-on product to market will be less than that of the pioneer because the FDA is using (directly or indirectly) the proof of safety or effectiveness from the pioneer product approval.

As noted above, the market exclusivity delivered by the regulatory approval process, to be effective, must not result in a diminishment of the effective exclusivity period for the innovator biologic product. This risk exists if a follow-on product is approved for entry as a substitute for the pioneer product yet is based, to some degree, on the proof of safety or effectiveness of the pioneer product. Substitutability of the product will lead to a significant price erosion, which, if it occurs during the regulatory exclusivity period, will seriously erode the economic incentives for the pioneer product. In other words, effective market exclusivity can be realized only if the FDA defers approval of any follow-on product that relies to any degree on the clinical data provided to the FDA in support of approval of the pioneer biologic.

⁵¹ Cf., *Genentech, Inc. v. Bowen*, 676 F. Supp. 301, 311-12 (D.D.C. 1987) (holding that a recombinant human growth hormone (“hGH”) with the identical chemical structure as natural, pituitary-derived hGH is a different drug than the natural hGH for purposes of orphan drug exclusivity).

For example, the follow-on may provide enough information about its active moiety to rely on the innovator's data, but not enough to be blocked by the innovator's exclusivity. In fact, such a situation occurred with hyaluronidase. FDA considered each product to be a member of the same general class of hyaluronidase products, which allowed the products to rely on FDA's previous safety and effectiveness determinations regarding hyaluronidase. However, for exclusivity purposes, FDA treated each product as a new chemical entity. As such, each product received its own exclusivity and was not blocked by the other product.

B. Three-Year Exclusivity

The Hatch-Waxman Act also provides three years of market exclusivity to certain applications involving old chemical entities. Under the Act, three years of market exclusivity is awarded to an application for a product containing an active moiety that had been previously approved when the application contains new clinical studies that are essential to approval.⁵² Three-year exclusivity is typically awarded for new indications, new formulations, and other label changes the approval of which requires and is based on reports of new clinical investigations. During the three-year exclusivity period, FDA may not approve a generic application for the change or condition of approval that received exclusivity.

Similar to five-year exclusivity, the application of three-year exclusivity to biological products raises unique and complicated issues. For example, a biologic with the same formulation as a previously approved product may perform differently due to manufacturing or other inherent differences. Would such a product, which contains a previously approved active moiety, be eligible for three-year exclusivity based on its different performance? Generally, if a new formulation requires additional clinical evidence to be approved, the additional exclusivity should be provided. Furthermore, would a biological product that is seemingly similar to another product that received three-year exclusivity be able to avoid the other product's exclusivity by performing differently (*e.g.*, clinically superior as with orphan drug exclusivity)?

As noted earlier, the manufacturing process is extremely important to approvability of biological products. Although most manufacturing processes are kept confidential as trade secrets, would important manufacturing processes that are publicly available be eligible for exclusivity? Furthermore, as with five-year exclusivity, the application of three-year exclusivity to biologics may be difficult because it is not always possible to characterize the scope of the exclusivity. Would a hyaluronidase product (described above) that received three-year exclusivity for a new indication block another hyaluronidase product from receiving approval for the new indication?

C. Patent Linkage

As was the case in the Hatch-Waxman Act, it will be important to consider patent exclusivity, along with market exclusivity provided through the regulatory approval mechanism, as an integral part of the follow-on biologic approval framework. The Hatch-Waxman Act provides for the early resolution of patent issues when the generic application is filed.

⁵² 21 C.F.R. § 314.108(b)(4) and (5).

Specifically, a generic applicant must provide a certification for each patent listed by the innovator company in FDA's Orange Book. The filing of an ANDA with a so-called "Paragraph IV" certification asserting that the listed patent is invalid or not infringed is a technical act of patent infringement, and establishes jurisdiction for the innovator to sue the generic. If the innovator sues for patent infringement within 45 days of receiving notice of the Paragraph IV certification, then FDA may not approve the ANDA for up to 30-months. Final approval can be granted before this point if the court issues a judgment in patent litigation adverse to the patent owner (*i.e.*, finding the listed patent invalid or not infringed). The 30-month stay provides time for resolution of the patent litigation before a generic product receives approval and goes to market.

Identifying and resolving patent issues before a generic receives approval and goes to market provides several benefits. In particular, the early enforcement of patent rights provides certainty for an innovator company and protects the innovator's investment. Moreover, many generic companies are hesitant to launch a product "at risk" while there are outstanding and unresolved patent infringement questions. Addressing patent issues when a generic application is filed allows the FDA's substantive review of the application and the patent litigation to proceed in parallel. For those companies that do not want to launch "at risk," this provides for an earlier market entry than if the litigation commenced after approval.

The early resolution of patent issues also prevents consumer confusion. If patent issues were not part of the approval framework, then an innovator company generally could not sue a generic manufacturer until after the generic drug was placed on the market. If the patent owner were to prevail, it could secure a permanent injunction against the generic producer, and require that the generic product be withdrawn from the market. Such a withdrawal of a product from the market creates the potential for confusion, as consumers may be unsure as to why the product was withdrawn, and could result in safety and effectiveness concerns if patients must then switch from product to product.

Addressing patent issues as part of the approval process allows the FDA to prioritize its resources. Recently, the FDA implemented a policy in which certain generic applications receive an expedited review when there are no blocking patents. This move reflects the FDA's appreciation not only that patent issues are important matters to resolve prior to approval of a generic product, but also that an appropriate amount of time should be allocated to permit resolution of these patent conflicts.

VIII. The European Approach to Approval of Similar Biological Products

The European Medicines Agency ("EMA"), the European equivalent to the FDA, recently implemented an approval scheme for similar biological products. Consistent with the issues discussed in this paper, the EMA recognized that the traditional approach to generic drugs is not applicable to biological products. According to the EMA, "[d]ue to the complexity of biological/biotechnology-derived products the generic approach is scientifically not appropriate for these products."⁵³ In particular, the EMA noted that biological products are

⁵³ Guideline on Similar Biological Medicinal Products, EMA Committee For Medicinal Products for Human Use (October 30, 2005) ("EMA Guideline on Similar Biological Products") at 4.

difficult to characterize, complex, and may be significantly altered by seemingly minor manufacturing changes.

Europe adopted a case-by-case approach based on the comparability of similar biological products. A similar biological product must be similar in molecular and biological terms with respect to the reference product.⁵⁴ For example, only an interferon alfa-2a, not an interferon alfa-2b, could be compared with an interferon alfa-2a reference product. Furthermore, the EMEA indicated that the similar biological scheme will likely apply only to highly purified products that can be thoroughly characterized, and will not be applicable to those products that are difficult to characterize and have little clinical and regulatory experience.⁵⁵ In particular, whether a product is acceptable as a similar biological depends on the state of the art of the analytical procedures, the manufacturing processes, and the clinical and regulatory experiences.

The EMEA recognized that there may be safety and effectiveness differences between seemingly similar products. Accordingly, the EMEA has taken a case-by-case approach to similar biological products. “Any differences between the similar biological medicinal product and the reference medicinal product will have to be justified by appropriate studies on a case-by-case basis.”⁵⁶ The EMEA has indicated that this will typically require clinical trials demonstrating clinical comparability.⁵⁷ Additionally, safety data will be needed because, as the EMEA noted, a similar biological product may have a different safety profile than the reference product even if the effectiveness is comparable. As explained by the EMEA:

It should be recognized that, by definition, similar biological medicinal products are not generic medicinal products, since it could be expected that there may be subtle differences between similar biological medicinal products from different manufacturers or compared with reference products, which may not be fully apparent until greater experience in their use has been established.⁵⁸

Additionally, Europe provides ten years of market exclusivity for innovator drugs and biologicals against generics, hybrids, and similar biological products.⁵⁹ The ten-year period may be extended for an additional year, for a total of 11 years of market exclusivity, with respect to certain new indications.

⁵⁴ *Id.* at 5.

⁵⁵ *Id.* at 4.

⁵⁶ *Id.* at 5.

⁵⁷ Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues, EMEA Committee For Medicinal Products for Human Use (February 22, 2006) at 5-6.

⁵⁸ EMEA Guideline on Similar Biological Products at 4.

⁵⁹ Article 14(11) of Regulation (EC) No. 726/2004; and *see also* “What is the Period of Protection for My Medicinal Product?” EMEA (2006) (accessed at <http://www.emea.eu.int/hums/human/presub/q35.htm>).

Similar to the U.S., Europe recently approved Omnitrope® as a similar biological product. Omnitrope® is a simple and well-characterized product. The overall viability of the EMEA’s scheme with respect to a broader range of biological products will not become evident for a substantial number of years.

IX. Any Abbreviated Approval Scheme for Follow-on Proteins May Not Rely on Trade Secrets of the Innovator Company

Any follow-on protein approval scheme is likely to raise unique issues with respect to the unlawful use of trade secret information relative to the FDA review of small molecule products under the Hatch-Waxman Act. Under current law, when reviewing another party’s biological license application, the FDA is not allowed to rely on an earlier licensee’s manufacturing and related information or, for that matter, the reports of clinical investigations in that earlier license. This information, however, plays a critically important role in the review of a biological product license application – indeed, the FDA reliance on the manufacturing information is integral to the decision to approve the product. Manufacturing information, however, is protected as trade secret information and is distinct from the reports of clinical investigations submitted with the biological product.

Unlike small molecules, biologics are particularly sensitive to manufacturing process issues. Chemistry, manufacturing, and controls (“CMC”) information plays a far more significant role in the approval process, and is extremely important to ensuring that a biological product is safe, pure, and effective.⁶⁰ Such information includes product specifications, analytical testing procedures, recipes, equipment, purification and fermentation processes, and other related information. To a large degree, these manufacturing process are critical elements for defining the resulting biological product. This CMC information plays an important role in allowing an innovator to make even minor changes to its manufacturing process (*e.g.*, by providing a reference point against which changes can be assessed and quantified).⁶¹ For comparable reasons, this information would be likely to play an important role in assessing whether information regarding a new biological product (*e.g.*, a follow-on product) could be considered relevant to comparable information associated with the original or innovator product.

According to FDA’s regulations, “[a] trade secret may consist of any commercially valuable plan, formula, process, or device that is used for the making, preparing, compounding, or processing of trade commodities and that can be said to be the end product of either innovation or substantial effort.”⁶² Manufacturing and other CMC information clearly fall within

⁶⁰ For example, until recently, FDA required biological manufacturing establishments to receive a separate license.

⁶¹ *See, e.g.*, ICH Guidance Document: Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process (June 2005).

⁶² 21 C.F.R. § 20.61(a).

the definition of trade secret information.^{63, 64} As the District Court for the District of Columbia recently stated, “[p]laintiff does not challenge the redaction of trade secret information such as *chemistry, manufacturing and control information* from the requested documents under exemption 4 [FOIA trade secrets], in light of the definition of ‘trade secret’ that this circuit and the FDA have adopted.”⁶⁵

FDA may not disclose trade secret information under Federal law. Specifically, the FFDCFA prohibits “[t]he using by any person to his own advantage, or revealing . . . any information . . . concerning any method or process which is a trade secret”⁶⁶ Underscoring the importance of maintaining the confidentiality of trade secret information, the FFDCFA further provides that a person who discloses such information is subject to criminal penalties.⁶⁷ Similarly, the Freedom of Information Act (“FOIA”) prohibits the disclosure of trade secret information.⁶⁸ According to FDA’s regulations, “trade secret or confidential commercial or financial information are not available for public disclosure.”⁶⁹

Furthermore, the FDA’s unauthorized use of trade secret information submitted by a BLA applicant may be an unconstitutional taking of property in violation of the Fifth and Fourteenth Amendments to the U.S. Constitution.⁷⁰ The Constitution prohibits the taking of private property for public use without just compensation and due process. The U.S. Supreme Court has indicated that the following factors should be considered to determine whether there is an unconstitutional taking of property: (1) the character of the government action; (2) the

⁶³ 21 C.F.R. §§ 601.51(f)(1) and 314.430(g)(1) (stating that drug and biological manufacturing methods or processes, including quality control procedures are protected trade secrets).

⁶⁴ Letter from V. Zonana, HHS, to R. Theis (August 20, 1996) (attached as Exhibit 2 to Genentech, Inc.’s Citizen Petition, FDA Docket No. 2004P-0171) at 3, stating:

I have determined to continue to withhold the data and information in the Avonex file that constitutes trade secret or confidential commercial information within the meaning of Exemption 4 of the FOIA. 5 U.S.C. 552(b)(4). Such information includes manufacturing methods or processes, production data, comparability data, and safety and effectiveness data. 21 C.F.R. 20.61; 601.51. The Food, Drug, and Cosmetic Act, 21 U.S.C. 331(j) and the Trade Secrets Act, 18 U.S.C. 1905, prohibit FDA from publicly releasing such information.

⁶⁵ *Public Citizen v. Food and Drug Administration*, 997 F. Supp. 56, 62 n.2 (D.D.C. 1998) (emphasis added), *rev’d on other grounds*, 185 F.3d 898 (D.C. Cir. 1999); *see also Bowen v. U.S. Food and Drug Administration*, 925 F.2d 1225, 1227-28 (9th Cir. 1991) (trade secrets includes “manufacturing formulas and processes, as well as quality control . . . measures”).

⁶⁶ 21 U.S.C. § 331(j); *see also* Trade Secrets Act, 18 U.S.C. § 1905.

⁶⁷ *Id.* § 333(a).

⁶⁸ 5 U.S.C. § 552(b)(4).

⁶⁹ 21 C.F.R. § 20.61(c).

⁷⁰ *See* Genentech, Inc., FDA Citizen Petition, Docket No. 2004P-0171 (April 8, 2004) at 24-26, and related comments filed with that docket.

economic impact of the government action; and (3) the government's interference with reasonable investment-backed expectations.⁷¹

The primary issue that would affect whether FDA's unauthorized use of previously submitted trade secret information is an unconstitutional taking would be whether there was a reasonable investment-backed expectation with respect to the information.⁷² In light of FDA's longstanding restrictions regarding trade secrets and the fact that FDA has never used trade secret information to approve a follow-on biologic under the PHSA, companies that have already submitted trade secret information as part of existing biologics applications seem to have a reasonable investment-backed expectation that FDA will not use that information to approve another biological product. Any follow-on protein scheme that retroactively violates that expectation raises important constitutional issues.

It is unclear whether FDA would be able to avoid relying on trade secret information contained in an innovator's application when evaluating follow-on protein products. That information often may be critical to determining the safety, potency, and purity of a follow-on product. Additionally, FDA may be reluctant to ignore the trade secret information when it would further the public health, such as when use of the information would obviate the need for duplicate clinical studies. As stated aptly by the District Court for the District of Columbia:

Apparently, what primarily separates competitors in the recombinant DNA human growth hormone market is manufacturing 'know how.' A detailed description of Lilly's manufacturing process would cut to the heart of virtually any valuable innovation that Lilly may have developed. *Further, the Court agrees that once seen it would be very difficult for Genentech's scientists to 'unlearn' the secrets revealed.*⁷³

Recently faced with a similar situation, FDA appears to have initially relied on trade secret data contained in an innovator's application. Specifically, Dr. Reddy's Labs., Inc. ("DRL"), submitted a 505(b)(2) application for an amlodipine maleate product that relied on Pfizer Inc.'s application for an amlodipine besylate product. Although Pfizer's product was the besylate salt, Pfizer's application contained additional data regarding the maleate salt. FDA approved DRL's application based on Pfizer's application.

While FDA takes the position that it can rely upon the Agency's finding of safety and effectiveness for an innovator drug, here it went beyond just relying upon the finding of safety and effectiveness for Pfizer's amlodipine besylate product. It seems that FDA relied on the trade secret data concerning the maleate salt contained in Pfizer's application. Pfizer submitted a Citizen Petition to FDA questioning FDA's use of "non-public, proprietary data in Pfizer's New

⁷¹ *Penn Cen. Transp. Co. v. New York City*, 438 U.S. 104, 124 (1978); *PruneYard Shopping Center v. Robins*, 447 U.S. 74, 83 (1980).

⁷² See *Ruckelshaus v. Monsanto Co.*, 467 U.S. 986, 1006 (1984).

⁷³ *Genentech, Inc. v. Bowen*, 1987 U.S. Dist. LEXIS 16914 at *5 (D.D.C. April, 21, 1987) (emphasis added).

Drug Application.”⁷⁴ In response, FDA stayed approval of DRL’s maleate product due to issues surrounding the source of data FDA used to approve DRL’s product. As FDA stated in the administrative stay of action notice, “the effective date of the approval of NDA 21-435, is hereby stayed until FDA has reevaluated the application . . . based on data from appropriate sources.”⁷⁵

The amlodipine example illustrates the difficulties involved in protecting trade secret information contained in an innovator’s application. Trade secret information is critical to protein products, and any abbreviated approval scheme must provide strong protections for trade secret information contained in an innovator’s application. Having strong trade secret protection is particularly important because it is often difficult to determine whether trade secrets have been, in fact, misappropriated or used without authorization. Additionally, strong trade secret protection would likely minimize challenges regarding FDA’s basis for approval, similar to the amlodipine petition. Ultimately, the fact that trade secret information may not be used to support the approval of a follow-on protein product raises significant issues regarding the scientific and administrative viability of such an approval scheme for all but the most simple and well-understood biologics.

X. Patent Issues

A follow-on protein scheme also raises important and unique patent issues not presented for small molecules drug products under the Hatch-Waxman Act.

In general terms, patent protection is available for both biological products and small molecule drugs under the U.S. patent system. Obtaining patent coverage for a biotechnology product that is not fully characterized, however, can prove difficult. Additionally, broader patent coverage of variants of a novel compound is often more difficult to obtain for biological products than for products that are chemically synthesized. Biotechnology is considered an unpredictable field because it is often not known how even a minor change may affect the structure, behavior, and biological activity of a protein. Patent coverage often is limited to the compounds that are known and adequately described in the patent disclosure. Short of making and describing every possible variant in a patent application, there is no certainty that an innovator can obtain adequate patent protection covering variant proteins.

Currently, innovators are also protected by the fact that a variant follow-on product is required to conduct its own clinical trials and develop its own data. However, allowing a follow-on to rely on the innovator’s data would leave the innovator protected primarily by its patent coverage. As described in detail below, a follow-on product that varies from the innovator product may avoid the innovator’s patent protection. A scheme that allows the follow-on to benefit from the innovator’s data, but that does not provide adequate protection to the innovator’s investment, would seriously disrupt the balance achieved by the Hatch-Waxman Act.

⁷⁴ K. Sanzo, Esq. and J. Chasnow, Esq., on behalf of Pfizer Inc., FDA Citizen Petition, Docket No. 02P-0447 (October 11, 2002) at 1.

⁷⁵ FDA Administrative Stay of Action Re: NDA 21-435 (February 4, 2004).

A. Background on Patents

The U.S. Constitution provides the basis for the patent system, and its important incentive for scientific innovation and development.⁷⁶ Patent exclusivity rewards the risk and investment involved in developing a new product by prohibiting another person from using the invention for a specified period of time.⁷⁷ In return, the inventor must disclose the invention and related information to the public, which allows immediate use of the information about the invention, and actual use of the patented technology once the patent expires.

To obtain a patent, an invention must be novel, non-obvious, and useful.⁷⁸ Additionally, the patent laws require a patent applicant to provide a detailed written description of the invention sufficient to enable another person to make and use the invention.⁷⁹ As described below, the practical challenges associated with describing biological products often operate through the written description and enablement requirements to limit the scope of patent protection available for these types of biotechnology inventions.

Ultimately, the property right protected by a patent is defined by the claims of the patent. A patent typically contains many claims of varying scope. For example, a patent directed to a class of novel compounds that provide a therapeutic effect may have narrow claims covering specific chemical compounds and broad claims covering the genus of compounds. Additionally, there may be claims directed to methods of using the compounds to treat a particular condition, as well as claims to the method of manufacturing the compounds. Claims are asserted and analyzed on an individual basis. Thus, a broader claim directed to a genus of compounds may be invalid, while a narrow claim directed to a specific compound may be valid.

As biologics involve products made from living organisms, the potential subject matter of biotech patents is more diverse and complicated than small molecule drugs, which are chemically synthesized. Patents covering biotechnology inventions may include claims directed to DNA and RNA sequences, polypeptide sequences, cell lines, monoclonal antibodies and other proteins, fermentation and purification processes, and methods of diagnosis. Furthermore, there may not be very much contextual knowledge surrounding a biotechnology discovery. For example, a biological product may not be fully characterized. Similarly, the significance of a discovery, such as the overexpression of a certain protein, may not be fully understood. The

⁷⁶ U.S. Const. Art. I, Section 8 (“Congress shall have Power . . . *To promote the Progress of Science* and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries.”) (emphasis added).

⁷⁷ Generally, the term of a patent is 20 years from the earliest effective filing date. 35 U.S.C. § 154. However, patents filed before June 8, 1995 may have a term of 17 years from the issue date of the patent if that term is longer than the 20 year term.

⁷⁸ 35 U.S.C. §§ 101-03.

⁷⁹ 35 U.S.C. § 112 (“The specification [of the patent] shall contain a *written description* of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to *enable* any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.”) (Emphasis added.)

underlying subject matter and relative unknowns for biologicals create unique patent issues that must be considered for any follow-on protein scheme.

B. Strict Written Description and Enablement for Biotech

More so than for small molecule products, patents covering biological inventions are limited by written description and enablement issues. This results in patent claims with a narrower scope, which, in turn, creates the possibility that a biological product may be “similar” enough to justify approval under an abbreviated regulatory process, yet “different” enough to avoid the innovator’s patent. As explained by one commentator, “under the heightened written description requirement, the patent law will not protect an inventor that claims a gene and its corresponding protein from competitors that generate slight variations in the nucleotide sequence of the gene, which result in a structurally different but still biologically equivalent protein.”⁸⁰

1. Written Description

The written description requirement helps to define the scope of the invention and ensures that the inventor actually possessed the invention when the application was filed. It also functions to ensure that the patented invention is effectively conveyed to the public. To satisfy the written description requirement, a patent applicant generally must describe the invention in sufficient detail so that a person skilled in the art can reasonably determine that the inventor possessed the invention.⁸¹

As biotechnology is an emerging and unpredictable field, the Patent and Trademark Office subjects biotechnology patent applications to a rigorous application of the written description requirement, which, in turn, often limits the scope of patent rights granted for such inventions.⁸² Generally, biotechnology patents are limited to subject matter that is precisely defined by structure, formula, chemical name, physical properties, or functional characteristics when coupled with a known correlation to a structure.⁸³ Thus, it may be difficult to obtain claims that cover variant sequences or related subject matter that could be utilized by a follow-on product.

⁸⁰ Sampson, M., “The Evolution of the Enablement and Written Description Requirements Under 35 U.S.C. 112 in the Area of Biotechnology,” 15 Berkeley Tech. L.J. 1233, 1262 (2000).

⁸¹ Manual of Patent Examining Procedure (“MPEP”) § 2163 (August 2006).

⁸² See United States Patent and Trademark Office; Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1, “Written Description” Requirement, 66 Fed. Reg. 1099, 1106 (January 5, 2001) (“Written Description Guideline”) (“In most technologies which are mature, and wherein the knowledge and level of skill in the art is high, a written description question should not be raised for original claims even if the specification [of the patent application] discloses only a method of making the invention and the function of the invention. *In contrast, for inventions in emerging and unpredictable technologies, or for inventions characterized by factors not reasonably predictable which are known to one of ordinary skill in the art, more evidence is required to show possession.*”) (Footnote omitted.) (Emphasis added.)

⁸³ *Fiers v. Revel*, 984 F.2d 1164 (Fed. Cir. 1993); Written Description Guideline, 66 Fed. Reg. at 1106.

For example, the Federal Circuit has held that a cDNA requires a specificity that is typically achieved by recitation of the sequence of nucleotides that make up the DNA.^{84, 85} The court also discussed how biotechnology patents may be limited as compared with small molecule patents. Specifically, the Federal Circuit stated:

In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass Accordingly, such a formula is normally an adequate description of the claimed genus. In claims to genetic material, however, a generic statement such as ‘vertebrate insulin cDNA’ or ‘mammalian insulin cDNA,’ without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.⁸⁶

As indicated by the Federal Circuit, biotechnology products may have limited patent protection due to the inability to adequately describe the full scope of the invention. In particular, the written description requirement restricts patents to subject matter that is possessed by the applicant. To the extent a biological product involves relative unknowns, the patent coverage surrounding the product will be limited.

2. Enablement

Similar to the written description requirement, the enablement provision requires a patent applicant to describe the invention in such detail as to enable another person to make and use the invention without undue experimentation.⁸⁷ Also similar to the written description requirement, the enablement provision has been strictly applied to biotechnology patents to exclude coverage for potential follow-on products.

For example, in *Amgen, Inc. v. Chugai Pharm. Co.*, the Federal Circuit invalidated several claims directed to various DNA sequences related to erythropoietin (“EPO”).⁸⁸ EPO is a protein consisting of 165 amino acids that simulates the production of red blood cells. Amgen owned a patent with generic claims directed to DNA sequences for polypeptides with an amino acid sequence “sufficiently duplicative” of EPO to possess the property of increasing production of red blood cells.⁸⁹ Noting the complexities of the EPO gene and the numerous potential

⁸⁴ *The Regents of the Univ. of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1568-69 (Fed. Cir. 1997) (holding that a description of rat insulin cDNA is not a description of the broad classes of vertebrate or mammalian insulin cDNA).

⁸⁵ *Genentech, Inc. v. The Wellcome Foundation Ltd.*, 29 F.3d 1555, 1565 (Fed. Cir. 1994) (“It would also give rise to a problem with the description requirement because the specification does not even remotely describe all the DNA sequences that encode the proteins within the scope of the functional definition.”).

⁸⁶ *The Regents of the University of California*, 119 F.3d at 1568.

⁸⁷ MPEP § 2164.

⁸⁸ *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200 (Fed. Cir. 1991).

⁸⁹ *Id.* at 1204.

analog, the court held the claim invalid for lack of enablement.⁹⁰ As stated by the court, “[i]t is not sufficient, having made the gene and a handful of analogs whose activity has not been clearly ascertained, to claim all possible genetic sequences that have EPO-like activity.”⁹¹

Importantly, the language rejected in Amgen’s patent seems to be exactly the type of language that a follow-on approval scheme would adopt. Amgen attempted to cover products with sufficiently duplicative structures to possess the primary biological property of EPO. Although the patent coverage was denied, it seems that those could be exactly the types of follow-on products that would be allowed to rely on EPO data under an abbreviated scheme.

C. Specific Hatch-Waxman Patent Issues Presented by Biological Products

1. Manufacturing Patents

Small molecules are made by chemical synthetic procedures. It is rare that a patented process of chemical synthesis will be able to block any and all means of producing the product. As such, the Hatch-Waxman Act does not require an innovator to list manufacturing and process patents, and a generic is not required to certify against those patents. Although manufacturing patents may be asserted after a generic is approved, the Hatch-Waxman scheme is not designed to resolve those types of disputes.⁹²

However, unlike small molecules, manufacturing is an essential part of a biological product’s identity. Manufacturing may include specific cell lines, fermentation procedures, and purification processes, all of which have the potential to affect the performance of the final product significantly.⁹³ In essence, manufacturing and process patents are as important as product and use patents with respect to biologics. Thus, it is important that any follow-on biologics approval process take into account the specific manufacturing processes to be used by a follow-on applicant, and provide an opportunity for patent issues to be resolved before a follow-on product is approved. Otherwise, the manufacturing issues may create a second phase of

⁹⁰ *Id.* at 1213-14 (“The district court found that over 3,600 different EPO analogs can be made by substituting at only a single amino acid position, and over a million different analogs can be made by substituting three amino acids.”)

⁹¹ *Id.* at 1214; *see also In re Fisher*, 427 F.2d 833 (CCPA 1970) (rejecting claims to a polypeptide having at least 24 amino acids when the patent application disclosed only a 39 amino acid product); and *Genentech, Inc. v. The Wellcome Foundation Ltd.*, 29 F.3d 1555, 1564 (Fed. Cir. 1994) (“[A]n infinite number of permutations of natural t-PA are covered by these other definitions Thus, we are unwilling to say that the specification satisfies the enablement requirement”).

⁹² Of course, it may be possible in certain situations to assert a manufacturing patent before a generic is approved under a declaratory judgment action.

⁹³ *Genentech, Inc. v. Bowen*, 1987 U.S. Dist. LEXIS 16914 at *5 (D.D.C. April, 21, 1987) (“Apparently, what primarily separates competitors in the recombinant DNA human growth hormone market is manufacturing ‘know how.’ A detailed description of Lilly’s manufacturing process would cut to the heart of virtually any valuable innovation that Lilly may have developed.”).

patent litigation after the generic is approved and on the market, which would unduly burden the court system and may require the generic to be withdrawn from the market if the patents are held valid and infringed.

2. Variant Patents

Additionally, the patent scheme under the Hatch-Waxman Act involves only patents that “claim the drug for which the applicant submitted the application” and methods of using the drug.⁹⁴ With respect to drug substance patents, FDA’s regulations provide that the innovator must list patents that claim the same active ingredient that is the subject of the innovator’s NDA.⁹⁵ Patents directed to polymorphs of the active ingredient, such as different crystalline structures, waters of hydration, solvates, and amorphous forms, may be listed as long as the innovator has supporting data to show that the polymorph performs the same as the form of the active ingredient in the NDA.⁹⁶

Thus, an innovator may not list patents that cover different active ingredients, even if the differences are minor, and may list patents that cover different forms of the active ingredient only with supporting data. This patent scheme works for small molecule drugs under the Hatch-Waxman Act because the generic is required to have the same active ingredient as the innovator.⁹⁷

However, follow-on proteins will not be required to have the same active ingredient as the innovator. An abbreviated follow-on protein scheme will likely require follow-on products to be similar to, but not the same as, the innovator product. Thus, the scheme under the Hatch-Waxman Act is too narrow to be applied, *mutatis mutandis*, to follow-on protein products. The scope of the drug substance patents included in any follow-on protein scheme should be consistent with the scope of the products that will be authorized to rely on the innovator’s data. For example, if a follow-on protein may be “similar” to an innovator, then an innovator should be able to assert patents that cover “similar” products. Otherwise, a follow-on would be able to rely on the innovator’s data, but avoid the innovator’s patents.

⁹⁴ 21 U.S.C. § 355(b)(1).

⁹⁵ 21 C.F.R. § 314.53(b)(1).

⁹⁶ 21 C.F.R. § 314.53(b)(2) (providing that the test data must include: (1) a full description of the polymorph, (2) a demonstration that the polymorph form is bioequivalent to the NDA form, (3) comparative dissolution testing, and (4) batch records and a list of manufacturing components for the polymorph).

⁹⁷ Although seemingly simple, the question of what types of patents are included under the Hatch-Waxman Act has resulted in numerous disputes and litigation. In fact, the complexity of the issue caused FDA to issue new regulations regarding patent listing in 2003. As FDA stated, “[t]hese disputes sometimes resulted in judicial decisions that are inconsistent with our regulatory policies or our interpretation of our own regulations.” Applications for FDA Approval to Market a New Drug: Patent Submission and Listing Requirements and Application of 30-Month Stays on Approval of Abbreviated New Drug Applications Certifying That a Patent Claiming a Drug Is Invalid or Will Not Be Infringed; Final Rule; 68 Fed. Reg. 36676, 36677 (June 18, 2003).

D. Pending Changes To the Patent System Would Limit Biotech Patent Protection

Furthermore, the U.S. Patent and Trademark Office (“PTO”) has proposed reforms to the current patent examination system that may significantly limit the protection available for biotechnology inventions.⁹⁸ In particular, the PTO has proposed to limit the number of “continuing applications.” Under the PTO’s proposed rule, an applicant generally would be allowed to file only one continuing application. In contrast, it is not unusual for a biotechnology applicant to currently file numerous, *e.g.*, two or more, continuing applications.

A continuing application claims priority to an earlier parent application with the same subject matter, and thus receives the benefits of the parent’s filing date. The continuation practice allows an applicant to refine the patent claims in light of the examiner’s evidence and arguments, so that the ultimate scope of the patent is complete with respect to the invention. Furthermore, an applicant may update its patent application to better define a particular invention as additional data regarding the invention becomes available. Although new matter does not receive the earlier filing date, continuing applications generally allow for the protection of different aspects of the same invention without having the earlier application cited as prior art.

As the patent law encourages an inventive entity to file a patent application early, patent applications for biotech inventions may be filed before the full scope of the invention is known. In particular, it takes many years to bring a biologic to market, during which time the compound and its methods of use may be modified in response to clinical trial data. Thus, the continuation practice is important to obtaining a full range of patent coverage for biotechnology inventions, particularly with respect to potential follow-on compounds. The proposed rule is a dramatic departure from current practice, and has the potential to significantly affect the scope of patent coverage for biological products. Any follow-on protein scheme must be considered in light of these proposed changes.⁹⁹

XI. The Patent Term Restoration Scheme May Prove to be Too Narrow for Follow-On Proteins

A new biological product that undergoes a regulatory review period is eligible for patent term restoration.¹⁰⁰ The period of restoration is intended to compensate the innovator for loss of “effective” patent term due to the time needed to complete the regulatory review of the product. The patent laws encourage an inventor to file a patent application as early as possible, which may occur many years before the product receives marketing approval. As the term of a patent generally runs from the filing date, a significant portion of the patent term may be lost during the regulatory review period for the product. Thus, the statute provides that a patent that claims the approved product or a method of manufacturing the product may be extended for up to five years based on the length of the product’s regulatory review period.

⁹⁸ Changes To Practice for Continuing Applications, Requests for Continued Examination Practice, and Applications Containing Patentably Indistinct Claims; Notice of Proposed Rule Making; 71 Fed. Reg. 48 (January 3, 2006).

⁹⁹ See Hogarth, M.A., “Biotech Firms See Big Danger in Patent Regulations Changes, Pittsburgh Business Times,” October 13, 2006 (accessed at <http://www.bizjournals.com/pittsburgh/stories/2006/10/16/focus4.html>).

¹⁰⁰ 35 U.S.C. § 156.

Importantly, the statute limits the scope of rights granted in a patent term restoration to a product's active ingredient.¹⁰¹ Due to the nature of protein products, a follow-on product will not have the same active ingredient as the innovator. Rather, the active ingredient in a follow-on product will likely be considered similar to the innovator. Some follow-on products may be highly similar to the innovator, while other may be less similar. Based on the similarities between the products, the follow-on may be permitted to rely on the safety and effectiveness data of the innovator. However, the differences between the products may allow the follow-on to circumvent the innovator's patent term extension. Such a scenario would severely undercut the purpose of patent term restoration.

This issue was recently highlighted in a case involving the small molecule drug, amlodipine.¹⁰² In that case, Dr. Reddy's Labs., Ltd. ("DRL") developed a generic product that was similar to Pfizer Inc.'s innovator product. Specifically, DRL changed the salt of Pfizer's amlodipine besylate product to maleate. DRL also attempted to rely on the data contained in Pfizer's amlodipine besylate application. Pfizer received a patent term extension for the patent directed to amlodipine and its salts, including the besylate and maleate salts. DRL argued that the patent term extension was limited to the approved product, amlodipine besylate, and did not cover DRL's maleate product. Based on the differences between the products, the district court agreed with DRL that Pfizer's patent term extension did not cover DRL's amlodipine maleate.¹⁰³ The Federal Circuit, however, reversed on appeal. According to the Federal Circuit, the statute specifically provides that patent restoration applies to any salt or ester of the active ingredient, which would cover both amlodipine besylate and maleate.¹⁰⁴

The DRL case demonstrates the issues that arise when applying the patent term restoration statute to different products, as will be likely with follow-on protein products. Unlike follow-on proteins, however, the DRL case involved a relatively simple set of facts. The products contained a small molecule active ingredient with a clear and identifiable difference, *i.e.*, the different salt. Furthermore, the situation involving different salts is specifically addressed in the statute. Despite the deceptive simplicity, the DRL case was litigated and the district court decision was ultimately reversed by the Federal Circuit. In contrast, biological products will routinely present far more complex issues. The differences between a follow-on protein and an innovator product may be more subtle than simply a different salt, and such differences may not even be quantifiable. Applying the current patent term restoration scheme to such a diverse group of products may be particularly difficult.¹⁰⁵ Ultimately, the fact that the

¹⁰¹ *Id.* § 156(f)(2) (defining the term "drug product" to mean the active ingredient of a new drug, antibiotic, or biological product).

¹⁰² *Pfizer Inc. v. Dr. Reddy's Labs., Ltd.*, 2002 Extra LEXIS 610, No 02-02829 (D.N.J. Dec. 17, 2002), *rev'd*, *Pfizer Inc. v. Dr. Reddy's Labs., Ltd.*, 359 F.3d 1361 (Fed. Cir. 2004).

¹⁰³ *Pfizer*, 359 F.3d at 1365.

¹⁰⁴ *Id.* at 1366.

¹⁰⁵ Potential patent term extension issues include: (1) determining whether a follow-on product that differs from the innovator product, or is not even characterized, should be subject to the innovator's patent term extension, and (2) determining whether a follow-on product that does not show any analytical differences between the innovator, but demonstrates a clinical difference, should be subject to the innovator's patent term extension.

extension is limited to the active ingredient will likely allow follow-on protein products, which will be similar but not the same as innovator products, to unfairly circumvent the innovator's patent term extension.

XII. Conclusion

In summary, biological products are an integral part of today's health care system and represent an immeasurable potential for the future of the public health. At the core of the biotechnology industry are the companies that invest billions of dollars to develop and market innovative biological products. These companies do not have reference products to copy or a set of pre-approved clinical data upon which to rely. They must conduct basic research to identify potential new candidate products, perform extensive amounts of applied research, perform the necessary clinical trials, demonstrate safety and effectiveness, clear the approval process, and develop a market vis-à-vis other companies with similar products. Drug discovery is an inherently risky venture. In fact, many companies exhaust their financial resources before even bringing a single product to market. To ensure the survival of biotechnology companies and the future of the industry, the investment made by these companies must be protected.

Recognizing the importance of finding a balance between the competing interests of the generic and innovator industries, the Hatch-Waxman Act established a complex abbreviated approval scheme for generic small molecule products. Under the Hatch-Waxman Act, innovator companies received five- or three-year market exclusivity periods for their innovations. Additionally, they received a patent term restoration period to compensate for patent time lost while the product was undergoing regulatory review and could not be marketed. In return, generic companies received an abbreviated approval scheme and a means for obtaining 180-days of market exclusivity against other generics for being the first to challenge an innovator patent.

Importantly, the Hatch-Waxman scheme is premised on the scientific principle that the generic product is a duplicate of the innovator product. In particular, an ANDA product must have the same active ingredient as the innovator product. Small molecules are chemically synthesized and determining whether two products have the same active ingredient is relatively simple. Basically, the structure of a compound equals its function, and two compounds with the same structure can be safely presumed to have the same function. A product that differs from an innovator undermines this basic principle and may not simply rely on the innovator's data. Rather, the differences must be shown not to affect safety and effectiveness.

Although the overarching goals of the Hatch-Waxman Act may apply to biological products, the specific mechanisms are not easily applied due to the differences between small molecules and biologicals. In contrast to small molecules, proteins are large and complex compounds comprised of chains of amino acids. The sequence of the amino acids and the three-dimensional shape of the chains all may affect the therapeutic profile of the protein. Additionally, unlike small molecules, proteins are manufactured by complex processes that involve the growth and fermentation of living cells, and purification of the resulting product. As with any living thing, there are inherent differences between manufacturing processes for biological products. Furthermore, due to their nature, proteins have the potential to cause strong immunogenicity reactions in patients. Small changes in a protein's physical characteristics or

manufacturing process may have a significant effect on the protein's safety and effectiveness profile.

As described above, a follow-on protein will virtually always be different from the innovator product. Thus, the scientific basis underlying the Hatch-Waxman Act (*i.e.*, that the generic is a duplicate) is not applicable to follow-on proteins. The differences between products mean that a follow-on product will not simply be able to rely on the prior FDA finding of safety and effectiveness. Rather, at a minimum, the follow-on must prove that the differences do not affect safety and effectiveness, which will likely require substantial clinical data. In many instances, it will not even be possible to analyze a follow-on product and innovator product because many biological products are not fully characterized. Furthermore, the differences between follow-on and innovator products raise unique and challenging issues with respect to substitution. Currently, products must have the same active ingredient to be considered therapeutically equivalent. FDA's therapeutic equivalence standard is based on strong scientific principles and a long history of clinical experience. However, the standard is not applicable to biologics because follow-on and innovator products generally will not have the same active ingredients.

Biologicals also raise unique and challenging issues with respect to market exclusivity and patent protection. The market exclusivity periods under the Hatch-Waxman Act generally apply to small molecule drugs, which are easily characterized. Determining the scope of exclusivity and whether another products falls within that exclusivity is relatively easy for small molecule products. However, proteins are not easily defined and it may not be possible to determine the scope of exclusivity and whether another product is subject to the exclusivity. Furthermore, biological products that are seemingly similar to innovator products may actually have different clinical profiles. Would such products be entitled to their own exclusivity or be able to avoid another product's exclusivity?

Additionally, patent protection for biotechnology products is limited to what can be defined and enabled in the patent application. This is typically based on the innovator's approved product, and variants of the product may not have patent protection. Thus, a follow-on product that varies from the innovator product may not infringe the innovator's patent. A critical issue with respect to both patent and market exclusivity is that a follow-on protein product may be sufficiently similar to an innovator product to rely on the Agency's prior approval, but sufficiently different to circumvent the innovator's exclusivity. Allowing a follow-on product to benefit from the innovator's data but avoid the innovator's market and patent protection would render such protection meaningless and be contrary to the balance achieved under the Hatch-Waxman Act. Accordingly, any statutory pathway for the approval of follow-on biologics must contain an appropriate mix of patent-based and market/data-based exclusivity to ensure effective market protection to incentivize investment and innovation. Furthermore, the early identification and resolution of patent issues should be considered as an integral part of the overall follow-on approval framework.

The issues discussed in this paper are critical to any potential follow-on protein scheme. They impact the underlying scientific basis for abbreviated approval, as well as the market incentives that will continue to encourage innovator companies while allowing potential follow-

on products. Due to the differences between biologics and small molecules, biological products pose significant challenges that are not raised with small molecules under the Hatch-Waxman Act. As a telling sign, complex issues relating to the implementation of the Hatch-Waxman Act continue to be worked through today, over 20 years after the Act was enacted. The unique and complex issues presented by biological products must be subject to a thorough examination to ensure the safety of the public health and the future of the biotechnology industry.