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Division of Dockets Management
U.S. Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Scientific Considerations Related to Developing Follow On Protein Products
FDA Docket No. 2004N-0355

The Novartis Group of companies ("Novartis") submit these comments regarding Follow-On Protein Products (FOPPs) in response to the Agency's request for comments following the Public Workshop convened on September 14-15, 2004. At that public meeting, Novartis was pleased to have had the opportunity to present testimony briefly addressing some of these issues (subsequently submitted to this docket and docketed as TS1 by the Agency on September 30, 2004).

The Novartis Group is a world leader in the research and development of products to protect and improve health and well-being. The Group's success as a global leader of the innovator biopharmaceutical industry is demonstrated by the approval and launch of eleven (11) new molecular entities over the last four years by its US affiliate, Novartis Pharmaceutical Corporation – more than any other US company. Companies in the Novartis Group have demonstrated expertise in the development and production of recombinant proteins derived from microbial and mammalian cell culture systems. These affiliates have been producing recombinant proteins in state-of-the-art facilities for over twenty years (which coincides with almost the entire history of the biotechnology industry). These products have been marketed by companies in the Novartis Group and other well-known and respected pharmaceutical firms. Based upon our collective experience and expertise, we are uniquely positioned to address the questions that the Agency raised in soliciting comments.

Executive Summary

Novartis supports a broad public process on how to develop the most appropriate science-based, regulatory pathway for Follow-On Protein Products. The pathway must require high regulatory standards that will be consistently applied to all manufacturers, both innovator and follow-on, to assure that the justified confidence of patients in biotechnology-based medicines is maintained. The innovator's intellectual property must be legitimately protected. While analytical technology has advanced immensely since the first biotechnology medicines were created, Novartis believes that the generic drug model is not appropriate for PHS Act biologics. A sponsor must provide an appropriately extensive and sound set of data at all relevant levels; i.e., chemical, preclinical, clinical studies (including immunological) will need to form part of any submission for a Follow-On Protein Product.

Introduction

Like the Agency and our industry colleagues, Novartis believes that rigorous, scientifically-justified standards are essential for subsequent versions of off-patent biologics, so called Follow-On Protein Products (FOPPs). The development of these standards by a fair and transparent process, as initiated in the1990s by the Agency, will ensure the efficient and appropriate development, evaluation, and manufacture of FOPPs. Novartis supports this ongoing public process whereby the Agency is continuing to consider all thoughtful suggestions, but we also expect the existing regulatory pathways will continue to be utilized appropriately and in a timely manner to the full extent allowed by the law.

In 1984, when the Hatch-Waxman amendments spawned the modern generic drug industry, the biotechnology sector was in its infancy - the first FDA approved biotechnology medicine was Eli Lilly's recombinant insulin, Humulin®, approved in 1982 – significantly, a drug approval that occurred two years prior to the enactment of Hatch-Waxman. Twenty years later, over one hundred innovative protein-based products produced through recombinant DNA technology treat a wide range of diseases and conditions. They represent approximately 12% of the value of the prescription market in the US. Ongoing research and development in the biotechnology sector holds the promise of further advances that were unimaginable even a few years ago, and approximately one-third of the medicines in development are now biotechnology-based. The development, testing, and commercial scale manufacturing of these innovator biological products involve costly processes that are typically lengthy, scientifically complex, and that are carefully regulated by the Food and Drug Administration ("FDA") and other health authorities around the world.

While it is to be expected that defined regulatory standards will initially apply to those well-characterized products (so-called specified biotechnology and specified synthetic biological products) whose identity, purity, potency, and quality can be determined and controlled utilizing present technologies, they may subsequently apply to others, such as vaccines and blood products, whose complexity currently makes them less suitable for the analytical assessments that presently can be undertaken for well-characterized proteins. This may change as analytical science continues to develop. It is important to recognize at the outset the distinct and complex attributes of proteins through appropriate categorization. Among therapeutic recombinant protein products, there are different orders or levels of complexity that allow products to fall into natural groups which can usefully be applied for regulatory purposes, and for which guidance may usefully be developed. The approval process that ultimately is applied to any particular follow-on protein product will proceed by necessity on a product-by-product basis, just as it does today for innovator products, but regulatory requirements can define more general criteria that all sponsors must achieve.

Traditionally, biologics have been described by the phrase "the product is the process". This concept was based on the requirements of the Public Health Service Act of 1902[1] and in the subsequent revision of that Act in 1944. In that Act, biological products were defined as a "virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood components or derivative, or allergenic product". The active ingredient of almost all of the extant biological agents had not been identified at that time, much less characterized, and a consistent manufacturing process was absolutely critical to ensure the ability to "prevent, treat, or cure diseases" with these agents. This same concept was applied to the early recombinant DNA-based products at the time that the FDA Bureau of Biologics (precursor to

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[1] Pub. L. No. 57-244, 32 Stat. 728 (1902).

the Center for Biologics Evaluation and Research) was established in the early 1970s. It was considered that the products were inextricably linked to the raw materials used, the processes (patented processes and trade secret) through which they were produced, as well as the facilities and personnel used to make them. This historical situation was in large part due to the limited number and relatively unsophisticated nature of analytical methodologies that were available to manufacturers and regulators alike in evaluating biologics at the time that the first recombinant protein drugs were under development, as well as the complexity of the products themselves when compared to traditional small molecule drugs. This thinking has evolved concomitant with the development of the science.

The relatively primitive scientific tools which innovators could utilize left a large gap in the scientific knowledge in terms of characterizing and defining these early molecules, their properties, and the intermediates and related molecules arising during their production. Thus, during the early years of the biotech revolution, it was essential that a biologic shown to be safe and effective clinically was produced continually using the same methods with the same raw materials, in the same facilities, and using identical, often trade secret and site-specific, validated assays. For a subsequent manufacturer to make the same product was considered impossible because the later entrant necessarily did not have the means to ensure that every raw material, every assay, and every aspect of manufacturing was identical.

More recently, however, the development of much more sophisticated analytical tools and methodologies has made it possible to vastly increase the degree of characterization possible to substantiate the structure and composition of biological products. A full understanding of their mechanisms of action is now often possible, and a variety of assays can measure key attributes both during manufacture and with the final product. Advanced analytical tools can differentiate differences of a single Dalton molecular weight, and can detect and quantify post-translational modifications that could not have been discovered even a decade ago. Indeed, innovator manufacturers routinely use Comparability Protocols to assure “sameness”, as authorized and approved by FDA, to change their manufacturing processes without complete preclinical and clinical trials.[2] This is because, depending upon the product under consideration, contemporary technologies permit a direct analysis of key features critical to safety and efficacy. Innovator companies correctly claim that it is their access to the full historical database that enables them to determine the most appropriate assays to use, as well assessing the results of said assays in an expeditious manner. Nonetheless, advanced analytical technology is widely available to any interested party, and, if rigorously applied by others, can equally be applied by them to establish and evaluate the key features related to safety and efficacy. Any sponsor’s file must be complete, and each sponsor must be able to assure a consistent and high quality product through the application of the same analytical approaches

Consequently, it does not necessarily matter if the processes by which a given biologic was created remain confidential and exclusive to a single manufacturer because new technologies can enable a subsequent version to be developed, compared to an earlier product, and differences identified. This analytical capability is not limited to those products for which details regarding the underlying molecule and the processes utilized to produce the finished product have entered the public domain through patents and scientific publications. By definition, the original product is on the market, and therefore samples are available for valid comparisons by subsequent manufacturers developing a follow-on candidate. Once

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[2] *Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-Derived Products* (April 1996).

the analytical profiles of the original product and follow-on are established, an appropriate clinical program can be designed and initiated to compare the clinical effectiveness and safety of the two protein drugs, including an assessment of immunogenicity.

As a result of these scientific advances, it is increasingly possible to produce and reproduce biopharmaceutical products with the same measurable properties as those of the innovator. Contemporary and evolving technologies are rapidly removing the historical barriers which, until now, have precluded robust and meaningful comparisons between an innovator and a follow-on product. Today, many, but perhaps not yet all, off-patent recombinant therapeutic proteins can be compared chemically, biologically, and functionally. Hence, as the patents on the first generation of biotechnology products begin to expire, it is now appropriate to discuss follow-on protein products and their role in the future portfolio of medicines.

Not surprisingly, the drugs that were first produced by recombinant biotechnology were smaller and simpler than many of those that have been produced subsequently. Furthermore, a great deal is known about the mechanism of action of the first recombinant protein drugs. Thus, the first off-patent products are the most amenable to manufacturing and characterization. Nonetheless, the traditional generic drug model of approval based on chemical characterization and limited human pharmacokinetic studies does not apply to protein drugs currently outside the scope of that model, i.e., not regulated under the Federal Food, Drug, and Cosmetic Act (FD&C Act). Because a follow-on protein product's activity, as well as the safety of the patient receiving it, requires an accurate duplication of the innovator product's active ingredient as well as an appropriate formulation to ensure safety and efficacy, existing metrics for generic drugs – such as bioequivalence testing of blood levels in healthy volunteers – represent an inapplicable paradigm for biologics regulated under the Public Health Service Act (PHS Act). The situation for PHS Act biologics contrasts with that which currently is in place for FD&C Act drugs, most of which have relatively simple structures that can be completely and definitively characterized. While, for chemical drugs, routine bioequivalence testing is a pivotal element of the approval process for generic products, this will be insufficient for Follow-On Protein Products under the PHS Act. Consequently, Novartis does not support the approval of PHS Act biologics utilizing a traditional generic drug model like 505(j).

Development and approval of PHS Act Follow-On Protein Products is a natural step in the evolution of the biotechnology sector. Nonetheless, it is essential to define a science-based regulatory paradigm that reflects both an understanding of the intricacies of recombinant DNA technology, the subsequent and on-going development in the technology since the innovators' products were approved, plus integrate an appreciation of the fine points of the human body's response to proteins. In all these respects, the regulatory pathway for Follow-on Protein Products needs to be flexible to accommodate and encourage the inclusion of state-of-the-art scientific developments, and it cannot be bound by what was known when the innovator product was developed.

A limited number of protein drugs were approved under the FD&C Act, and subsequent sponsors could use at least one of the same generic approval pathways that are used for chemical drugs. Novartis believes that, irrespective of the pathway, the scientific and medical standards should be rigorous and comprehensive to ensure that the follow-on protein drug is effective and does not compromise patient safety in any manner.

Creation of a new regulatory pathway for Follow-On Protein Products, beyond those few biotechnology products currently regulated as FD&C Act drugs, requires Congress to enact legislation. Such legislation will authorize FDA to design and implement a pathway

which balances the technological progress that enables subsequent sponsors to make Follow-On Protein Products with the need to maintain viable economic incentives for continued R&D in this critical sector. Legislation also should concurrently reduce regulatory burden to enable innovators to more easily gain approval for and subsequently improve first-generation products.

The Role Of Comparative Studies Between Different Manufacturers' Products

A subsequent sponsor will manufacture a follow-on protein product according to processes they themselves develop through the application of modern techniques. The follow-on sponsor will utilize the information that is available in the public domain on the innovator's process where this is possible without infringing legitimate intellectual property rights and where it makes sense scientifically. As such, the technology used to make a follow-on protein product may or may not be the same as that used to create the innovator product. This will not be known with any degree of certainty by the follow-on sponsor (nor by the sponsor of the original product). The manufacturing process must be developed throughout the entire production chain as would be the case for an innovator product, and a comparison between the innovator and follow-on protein product must be conducted – first in the laboratory and then by preclinical (animal) and clinical (human) testing.

By definition, a follow-on protein product will depend on the same physiological mechanism(s) for its activity and be used to treat the same disease(s) and condition(s) as the innovator product against which the comparison is being made. However, it is possible that the subsequent manufacturer may only address a subset of the indications of the innovator, and may or may not subsequently also propose others. Clinical studies would be performed to provide final confirmation that the efficacy and safety profile of the follow-on product – especially with regard to its ability to cause severe hypersensitivity, including allergic and potentially life-threatening anaphylactic reactions, in patients – is unchanged from that of the innovator product. In addition, like foreign proteins and innovator products, follow-on protein products may induce neutralizing antibodies that can impact the safety and efficacy of the product. This potential must be carefully considered during the development and subsequent clinical use of follow-on protein products.

It is important to note that the only comparisons that can be made are between the final marketed product of the innovator with the subsequent sponsor's own, as-yet unapproved product. In process materials are not available to any sponsor other than of their own manufacture, and, as such, samples from different products cannot be compared to each other in the same validated assay system. Even the comparisons of final products can only be done by the subsequent sponsor, which uniquely has access to its own final product and can compare it to commercially available innovator samples. The innovator can neither do the studies nor dispute the data, as the innovator does not have access to the proprietary information of the second sponsor or to that other sponsor's as-yet unapproved product.

Thus, it is critical that fair and consistent regulatory requirements are established and implemented by FDA and other health authorities, with the considered input of all industry viewpoints and those of other interested stakeholders – as FDA has sought during this public process. These standards must apply to <u>all</u> biologic products, both innovative and follow-on, and as submitted by <u>all</u> manufacturers, both brand-name and generic.

A Rational Approach to the Development of Follow-on Protein Products

Given the paradigm that the same standards should be applied to all protein drugs, it is then appropriate to discuss the scientific and regulatory requirements needed to ensure that follow-on protein products are made to the same standards as innovator products, and that those standards are appropriate, while acknowledging that the scientific pathways to arrive at those standards will be differ in certain aspects between the original and the follow-on products. As set forth below, Novartis proposes a hierarchical, rational, scientific approach. First, a rigorous physiochemical and bioassay analysis will confirm that the identity and purity of a follow-on protein product's active drug substance and finished product are the same, and that the latter matches the innovator product. The results of this comparison will provide an efficient screen during development, and the results then can be confirmed through rigorous preclinical and clinical testing once it is demonstrated that indistinguishable material can be synthesized and formulated.

1. Analytics

Advances in analytical science now permit in-depth, reproducible chemical structural analyses and enable the direct comparison of the structure and composition of a follow-on product with an innovator product. This crucial and continuing progress in the technology vastly reduces dependence on a single proprietary manufacturing process to determine whether two products are the same. Interestingly, the analysis of both the innovator and follow-on products done for the purposes of comparison will be to a depth and detail substantially beyond that ever done for those biologic products already on the market. Indeed, today's microanalytical technology can be expected to identify differences in the structures of both naturally occurring molecules – and in the innovator's marketed, first-generation material – which will reveal the presence of molecular variants that have never before been identified in the first-generation, marketed product. The distribution of such variants, the microheterogeneity profile, must be compared for the innovator and follow-on products to ensure that any variation is understood.

This major progress in analytical science has been paralleled by improved instrumentation, increased automation of new and existing technologies, improved sensitivity through miniaturization (and the associated need for smaller samples), with the net result of enhanced accuracy and reproducibility of results. In addition, advances in methods development have improved analytical strategies and test protocols, notably by use of recently developed computer hardware and software. These combine to give analytical tools with enhanced selectivity and separation power which allow earlier decisions and therefore more efficient research and development of candidate follow-on molecules.

Despite the complexity of a given analytical method, each of the analytical techniques plays a relatively straightforward and fundamental role in the creation and manufacture of biopharmaceuticals. They can variously facilitate the comparison of different samples from whatever source, intra-manufacturer or inter-manufacturer, and be used to determine the relative quantitative and qualitative difference, if any, between them. That comparison can be achieved without specific reference to the method of manufacture of the innovator product, i.e., based solely upon full characterization of the innovator and follow-on products using a simple hierarchical process of analysis. Not all available methods will be used for every protein, but specific methods will be selected depending on the properties of the protein under investigation. The methodology employed by the follow-on company need not be the same as that used by the innovator. In fact, a follow-on manufacturer will likely use the most sophisticated methodology available, whereas an innovator may retain the less

advanced methodology with which the protein drug was first approved. Thus, assertions made by some that a follow-on sponsor must duplicate the analytical methodology of the innovator are not true, nor in many cases would this be desirable.

Therefore, it is not useful or necessary to rigidly constrain which techniques must be used for which purposes. However, it is appropriate to require a certain level of assurance of consistency and characterization of all manufactured biologic products, and it is up to the sponsor to use any and all available technologies to achieve this assurance. One wants to stimulate continued development of more and better analytical approaches, and the best way to do this is to have a regulatory mechanism that rewards their creative and efficient use. Thus, there can be no strict rules for application of these state-of-the art techniques. Instead, the use of analytical methods must proceed on a protein-specific basis. Each molecule must be evaluated separately, and the requisite analytical techniques will depend on the molecule and its degree of complexity.

There is, however, one across-the-board observation that applies today that was not true at the time when many target follow-on protein products originally were developed and approved by FDA. Namely, modern analytical techniques now make it possible to utilize a laboratory-based demonstration of comparability to connect a follow-on product to much of the published preclinical and clinical data previously generated with the innovator product such that the published finding of safety and efficacy of the innovator that was established in the clinic can be applied to the follow-on product. While formal comparability protocols were developed to enable reduced regulatory burdens on innovators changing their manufacturing processes, it is fair to say that comparability is in and of itself a comparable exercise for the way we now need to think about regulating follow-on protein products. Not all aspects of comparability protocols will apply, but many will be highly relevant.

The availability of modern analytical techniques removes the limitation of arcane legacy manufacturing systems, and justifies a significant reduction in the scope of the development program, thereby accelerating market entry of a follow-on product, and updated regulations for innovator products. Although it is essential to preserve the same basic, highly-controlled technologies in manufacturing the product, modern bioprocessing and downstream processing technologies that have been devised – sometimes long after the original approval of the innovator product – can be employed where appropriate to obtain an unaltered, state-of-the-art drug substance, which is not tied to a legacy manufacturing process and that meets today's stringent quality standards.

2. Bioassays

Once the sponsor of a follow-on protein product develops an acceptable drug product from a defined drug substance, the next step is to show that it has the same biological functions as the original innovator product. Again, a hierarchy of tests can be pursued, much as occurs with the development of an innovator product, in which the attributes of the molecule and its formulation are measured *in vitro* and *in vivo* in a series of experiments with defined acceptance criteria. The quality-related comparability established through analytical testing needs to be evaluated through *in vitro* (cell or tissue culture) bioassays for those products for which the pharmacokinetic and pharmacodynamic profile is well defined. This step is necessary to confirm the link between that profile and the molecule's physicochemical properties. Further, in vivo bioassays will model the time the protein circulates in the body prior to its clearance, and its efficiency in activating the relevant receptor(s).

For proteins with post-translational modifications, such as glycosylation, those alterations can influence a variety of parameters that impact the pharmacokinetic and pharmacodynamic profile. For example, glycans can impact pharmacokinetics by affecting the size of the protein, and therefore renal clearance, or by changing the receptor binding kinetics, both target and hepatic binding. Glycosylation also can affect receptor activation and thereby impact the pharmacodynamic profile. Accordingly *in vitro* bioassays do not cover all functional aspects of the product because they do not capture the time the protein circulates in the body. That can only be seen in an *in vivo* (animal) bioassay, which provides an accurate model of both receptor activation and pharmacokinetics. Alternatively, animal or human PK data can be combined with *in vitro* bioassay (or animal or human PD) data to yield the same information. The bioassay that is chosen for a particular protein should mimic the pathological condition and/or pharmacodynamic events occurring during treatment of patients as closely as possible.

For many molecules, the preferred approach will include an appropriate combination of *in vitro* and *in vivo* assays that demonstrate the absence of any difference in results for the innovator and follow-on products. However, as with the analytical testing, it will be necessary to include case-by-case considerations.

3. Preclinical Testing

If the results obtained from physicochemical characterization and biological assays demonstrate that the follow-on protein product is comparable with the innovator, a defined preclinical program can be initiated to confirm those results in a limited number of animals treated for a limited period of time. This testing provides legitimate assurance in advance of clinical testing that production of the active substance and finished product formulation has not overlooked anything that might inadvertently harm the patient. This testing also ensures that the excipients in the follow-on product, and their quality, will be acceptable and comparable to those in the innovator product.

The innovator already has demonstrated what the molecule *per se* does to the body by defining the key preclinical parameters of the molecule for the approval of the innovator product. In the setting of follow-on protein products, it is necessary to ensure that there is nothing else in the formulation that could cause some adverse effect in patients. This includes manufacturing contaminants that may have co-purified with the active ingredient, including those related to the active ingredient (aggregates, degradates, and structurally related molecules), and those derived from the process. Nonetheless, it is reasonable and appropriate to proceed with a limited acute or subchronic toxicology study and a study of the effect at the injection site (local tolerance study) in animals in which the product is pharmacologically active. If the results of the pre-clinical safety assessment demonstrate that the safety of the follow-on and innovator products is the same, those results will provide an added level of assurance of safety as the protein moves into clinical testing in patients. All animal studies should be comparative in nature, including both an inactive/negative (carrier) and an active/positive (innovator) control. Studies may focus on single-dose or sub-chronic toxicity (depending on the product's intended use), pharmacokinetic and pharmacodynamic parameters, immunogenicity, and/or local tolerance depending on the characteristics of the product. Pharmacodynamic and toxicokinetic parameters should be determined at suitable points.

4. Clinical Studies

In a phase I clinical study, the first trial of a follow-on protein product in humans, the pharmacokinetic, pharmacodynamic, and safety properties of the follow-on product will be

compared to those of the innovator product. Comparable results in these studies will demonstrate that the follow-on product performs in the same way in humans as the innovator product and has a similar safety profile. Because the dosing parameters of the molecule were established with the innovator product, and comparability of the follow-on product and the innovator product has been demonstrated at the analytical and preclinical levels and in a clinical phase I trial, the follow-on product sponsor can conduct subsequent efficacy studies using the same dosing regimen(s) as the innovator product .

The clinical program for the follow-on product will include a concise phase III clinical study. The scope of the phase III program and its acceptance criteria would need to be determined on a protein-specific basis. The goals of this study will be the confirmation of comparable efficacy and safety and, as such, the study usually will be a direct comparison in a double-blinded study of innovator versus follow-on products. This will be especially important for evaluating immunogenicity where is it not clear that results from different studies such as those reported in the scientific literature and not conducted concurrently can be compared due to differences in the assays. While many foreign proteins induce antibodies, the key question is whether these have any clinical significance. The assurance that the follow-on protein product does not induce neutralizing antibodies can be confirmed only by appropriate studies in humans.

Considered in light of the publicly available data on the innovator product (including published literature on its modes of action in various indications), the demonstration of comparability between the innovator and follow-on products on all levels (physicochemical, bioactivity, pharmacokinetic/pharmacodynamic, preclinical, and clinical) will provide confidence that the follow-on product will perform equivalently in all indications in which the innovator product has been tested and approved by FDA. Thus, in addition to pharmaceutical equivalence and bioequivalence required for small molecule drugs, comparable safety and efficacy of the follow-on and innovator protein product will have been shown through a well-designed, adequately powered clinical study program.

Establishing Regulatory Requirements Under A New Statutory Pathway

As the regulatory paradigm for therapeutic proteins evolves, it will be essential for industry and FDA alike to remain open to scientific breakthroughs that facilitate comprehensive and rigorous assessments of biologics – regardless of whether they are innovator or follow-on products. That approach should be applied to all recombinant therapeutic proteins – those regulated as drugs under the FD&C Act and those regulated as biologicals under the PHS Act.

Today, FDA possesses the full, requisite authority under the FD&C Act to approve follow-on drug products utilizing the longstanding 505(b)(2) NDA process. That pathway provides a viable mechanism for the registration of a comparable drug product by relying in part on the publicly known data, while facilitating submission of the additional information necessary to fully evaluate any differences between the follow-on product and the innovator and therefore its safety and efficacy. See FDA Consolidated Response (Oct. 14, 2003) (FDA Docket Nos. 2001P-O323, 2002P-O447, and 2003P-O408). Despite assertions to the contrary by some, an NDA under Section 505(b)(2) does not utilize or otherwise rely upon the underlying data in the innovator's NDA, and FDA has consistently limited its 505(b)(2) regulations to reliance on the public finding of safety and efficacy. Novartis agrees that reference to data itself in the innovator's file is inappropriate, but agrees with the Agency that the reference to the already published finding of safety and efficacy is appropriate, just has been the case for small molecule drugs under FD&C Act since 1984. Since the FD&C Act makes no distinction between drugs and biologics, the interpretation should at least be

consistent and therefore with a right of reference for both (which is the Novartis position), or for neither. The well-established 505(b)(2) process should proceed with respect to therapeutic proteins regulated as FD&C Act drugs (such as insulin and human growth hormone). The scientific rationale for approval of these products will be enhanced by application of the rigorous, science-based regulatory approach outlined here.

No parallel mechanism for biological license applications ("BLAs") has been enacted by Congress under the PHS Act. Leading policymakers such as Senator Orrin Hatch have highlighted the absence of an approval process for off-patent follow-on protein product under that statute. According to Senator Hatch, "pressure will grow on Congress and the Food and Drug Administration to find new ways to bring new biotechnology products to the public when the patents expire." For this reason, Senator Hatch has encouraged his colleagues "to create a fast-track FDA approval system for off-patent biological products" that observes "the principle of balance contained in the original 1984" Hatch-Waxman amendments. That balance depends upon strong intellectual property protection, which is the lifeblood of innovation and drives the discovery of new drugs to prevent or treat diseases. Indeed, the invention of new patent-protected medicines is essential to medical progress. At the same time, patent life is finite. Competition should proceed in the interest of patient access to alternative medicines where medically appropriate as patents expire. In managing their businesses, the Novartis Group of companies are committed to maintaining this balance, which reflects a balance similar to that which Senator Hatch struck in the 1984 Hatch-Waxman law.

Reaching a consensus on the scientific principles that should be adhered to in an updated statutory framework is the first in a series of steps that must be accomplished if a new regulatory pathway is to be created. Under the leadership of former-FDA Commissioner Mark B. McClellan, FDA has been working towards that objective by taking a very deliberate, step-wise approach to ensure scientific rigor and protection of the public health in drafting a regulatory Guidance document on follow-on protein products. Although now deferred, it ultimately will be released for public comment by the scientific and medical community, patient advocates, industry, and the public at large. As the Agency authorized by Congress in 1972 to regulate development and approval of biologics, FDA is uniquely positioned to tackle these fundamental technical questions and establish an appropriate scientific framework. The delayed but hopefully rapidly forthcoming draft Guidance is a logical and appropriate next step in the process initiated by Dr. McClellan, which we support.

Conclusion

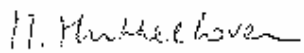
Novartis believes the open and objective scientific debate facilitated by FDA's public processes will ensure a broader and better informed understanding of the rigorous scientific principles and technological methods applicable to follow-on protein products. We support science-based regulations that incorporate the advanced analytical techniques now available. The preclinical and clinical development criteria developed must continue to assure patient safety achieved through science-based regulation. Implementation of a follow-on protein product pathway utilizing state-of-the-art science will enhance patient access to safe and effective follow-on protein products, expand the field of competing treatments and manufacturers, and stimulate further R&D and manufacturing investments leading to the next generations of new and improved innovative therapies.

It is important to continue to stimulate a broad medical policy debate surrounding the statutory framework that would be necessary in order to modernize the regulatory paradigm for these products. However, such a debate must not go on indefinitely and be used as a delaying tactic such that FDA is unable to acknowledge nor patients realize the great advances in scientific progress that have been made since the first biotechnology medicine was approved over two decades ago. Scientific progress will always be iterative, and we must create a regulatory model that similarly stimulates creativity rather than stalling or discouraging progress in the development of new manufacturing capabilities for biotech medicines.

The Novartis Group of companies appreciates this additional opportunity to contribute to this critically important scientific debate. We look forward to continuing to play a constructive role in the development of a scientifically-based strategy to define the technical elements of a new regulatory framework such as that outlined above, with specific emphasis on the rigorous, science-based requirements for analytical, preclinical, and clinical testing necessary to support successful submissions. To create a regulatory pathway for PHS Act biologics is timely and appropriate, and to ensure that all FD&C Act biologics are approved according to consistent regulatory standards in the meantime is both fair and reasonable. Over the ensuing months, Novartis will continue working with the Agency, companies in industry and their trade associations, professional and patient groups, and other stakeholders to shape innovative solutions for the biopharmaceutical industry that maintain necessary R&D incentives for innovators while enhancing patients' access to medicines.

Should there be any questions, or if any additional information is required in connection with this submission, please contact the undersigned at (862) 778-6035.

Respectfully submitted,



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