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May 15, 2003

NOTE TO JENNIE BUTLER, DOCKETS MANAGEMENT BRANCH,
FOOD AND DRUG ADMINISTRATION (HFA-305):

As we discussed earlier this week, could you please place a copy of the attached BIO petition into Docket Number 01P-0323 dated July 27, 2001. This is the docket for a citizen petition filed by Pfizer and Pharmacia. As you requested, I am sending an extra copy for you to send to your contact in the Center for Drug Evaluation and Research.

Thank you.

Sincerely yours,

Linda R. Horton

Linda R. Horton, Partner
Hogan & Hartson, LLP

01P-0323

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BIO

BIOTECHNOLOGY
INDUSTRY
ORGANIZATION

BIO Citizen Petition
(21 CFR § 10.30)

Follow-on Therapeutic Proteins

Biotechnology Industry Organization (BIO)
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April 23, 2003

BIO Citizen Petition 0521 '03 MAY 16 P3:57
(21 CFR § 10.30)
Follow-on Therapeutic Proteins:

Summary of Petition

The Biotechnology Industry Organization (BIO) hereby submits a petition to the Food and Drug Administration (FDA) under the agency's citizen petition regulation (21 CFR § 10.30). BIO, established in 1993 as a nonprofit organization, is the world's largest trade organization devoted to the advancement of biotechnology. Members include biotechnology companies, academic health institutions, and research centers. BIO represents entities of all sizes engaged in developing products and services in biomedicine, diagnostics, food, energy, agriculture and environmental applications.

The petition requests that:

(1) *FDA conduct a meaningful public participation process on the agency's policies on the issue of "follow-on approval"*1/ *of therapeutic proteins.* The BIO Citizen Petition outlines a series of steps that will help FDA and all concerned to enhance the quality of dialogue on this contentious subject. A "meaningful public participation process" is one in which FDA publishes an initial Federal Register notice in which the agency lays out its views and its legal and scientific justifications; creates a public docket for the submission of comments; holds public meetings to hear stakeholder views; and responds to comments received. Public participation would enrich FDA's decision-making in this scientifically complex field. "Good Guidance Practices" do not offer a sufficiently robust procedure for the agency to consider the complex scientific, legal and policy issues at stake.

(2) *FDA refrain from approving any application for a therapeutic protein product that does not contain a full complement of original non-clinical and clinical data and that relies on information contained in another applicant's application.* BIO's petition shows that FDA has no authority to approve follow-on versions of such products under the Public Health Service Act (covered in an Appendix) or under the Federal Food, Drug, and Cosmetic Act (FDCA).

(3) *FDA refrain from preparing, publishing, circulating or issuing any new guidance for industry, whether in draft or final form, concerning follow-on*

1/ As used here, this term refers to approval of applications that do not include a full complement of non-clinical data and human clinical data establishing the safety and effectiveness of the product. "Therapeutic protein product" encompasses polypeptide therapeutic products, including recombinant therapeutic proteins.

applications for therapeutic proteins, particularly human growth hormone or insulin, under a section of the FDCA — § 505(b)(2) — which was intended simply to codify FDA's earlier "paper NDA" policy.

(4) *FDA withdraw its 1999 Draft Guidance for Industry: Applications Covered by Section 505(b)(2).* This document violates the law by suggesting the possibility of follow-on approvals of 505(b)(2) applications for therapeutic protein products, including even recombinants. BIO is submitting a copy of its petition to the dockets for (a) this Draft Guidance (99D-4809) and (b) a pending Citizen Petition filed by Pfizer and Pharmacia in 2001 (01P-0323). BIO's Citizen Petition covers a broader range of topics than the draft guidance or the earlier petition and, therefore, is a separate proceeding.

Current science demonstrates that there can be no abbreviated approach to the approval of therapeutic proteins, whether licensed as biological products or approved as new drugs. There are significant differences between therapeutic protein products and "chemical drugs" — in size, complexity, and heterogeneity — and each manufacturer must provide its own full complement of original data. Trying to use other companies' data cannot ensure patient safety: there are just too many product differences.

Patient safety is the primary concern when discussing proposals to reduce product testing. BIO is, in particular, concerned that significant risks to patient safety would arise if biologically derived products were to be approved based on less than a full complement of original data concerning each manufacturer's product. In addition, BIO is concerned that any safety problems that could develop as a result of such approvals could undermine the confidence of physicians and patients in biologically derived products.

Recent FDA statements indicate that the agency is actively considering its policies with regard to therapeutic proteins that have been approved as new drugs without offering the public the opportunity to participate meaningfully in the debate on this most significant change. Such FDA action would constitute a substantial shift away from long-standing law and agency positions and would profoundly alter the established regulatory framework for therapeutic proteins, create risks to the public, and produce regulatory inconsistencies. The confusion and uncertainty associated with this unstable regulatory environment impedes investment decision-making in the vital biotechnology sector.

In all the press reports, nowhere is there any indication that any meaningful public participation would precede FDA's adoption of such drastic changes in long-standing laws and policies. BIO is seeking to have FDA open up its decision-making process so that the public has a chance to be heard before decisions

are made — thereafter, decisions should be made only after a thorough, public consideration of the scientific, legal and policy issues involved.

Most important, the notion that FDA should excuse new market entrants from conducting the normal battery of tests on biologically-derived medicines — many of which are injected directly into patients — creates an unacceptable risk of harm to the nation's patients.

BIO Citizen Petition

(21 CFR § 10.30)

Follow-on Therapeutic Proteins

OUTLINE OF PETITION

APRIL 23, 2003

BY HAND DELIVERY

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: *Citizen Petition under 21 CFR § 10.30: Follow-on Therapeutic Proteins*

Dear Sir or Madam:

The Biotechnology Industry Organization (BIO) submits this petition to the Food and Drug Administration (FDA) under 21 CFR § 10.30.

A. ACTION REQUESTED

(1) BIO petitions FDA to conduct a meaningful public participation process on the agency's policies concerning new drug applications (NDAs) under § 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA)(505(b)(2) applications), and specifically, the quantity and quality of data and information needed for such approvals. By "meaningful public participation process," BIO means publication of an initial Federal Register notice in which FDA lays out its views and the legal and scientific justification therefore; creates a public docket for the submission of comments (including submissions on legal and scientific issues); holds public meetings to hear stakeholder views; and issues a notice at the close of the proceeding in which the agency responds to written and oral comments received. Public participation through such a process would enrich FDA's decision-making in this scientifically complex field. As is discussed in this petition, "Good Guidance Practices" do not offer a sufficiently robust procedure for the agency to consider the complex scientific, legal and policy issues at stake. The BIO Citizen Petition outlines a series of steps that will help FDA and all concerned to enhance the quality of dialogue on these issues.

(2) BIO requests that FDA refrain from approving, under any statute it administers, any application for a therapeutic protein product that does not contain a full complement of original non-clinical and clinical data and that relies on any data or information contained in another applicant's application.2/

2/ Approval of applications that do not include a full complement of non-clinical data and human clinical data establishing the safety and effectiveness of the product are referred to as

BIO believes that, considering the substantial scientific, legal, and policy reasons laid out in this petition, FDA must refrain from any follow-on approvals of any therapeutic protein products and, indeed, any consideration of such approvals, under not only the Public Health Service Act (PHSA) but also the FDCA, as the public has not had the opportunity to participate meaningfully in the agency's decision-making on its change of course in this area.

(3) BIO further requests that FDA refrain from preparing, publishing, circulating, or issuing any new guidance for industry, whether in draft or final form, concerning follow-on applications filed under § 505(b)(2) seeking approval of therapeutic proteins, particularly human growth hormone or insulin.

(4) Finally, BIO requests that FDA withdraw the document, "Draft Guidance for Industry: Applications Covered by Section 505(b)(2) (October 1999)" (1999 Draft Guidance).3/ This document includes provisions that are at odds with the statute and long-standing agency interpretations of the FDCA forbidding reliance without permission by a 505(b)(2) applicant upon another sponsor's data,4/ and requiring a full complement of data in applications for therapeutic protein products, especially recombinant versions. Also, the 1999 Draft Guidance lacks adequate explanation of how FDA believes the document comports with the law and agency interpretations. Therefore, the Draft Guidance did not put the public on notice of issues deserving comment, as required by law. For this reason and others, the Draft Guidance does not meet the standards of the Data Quality Act of 2001.5/

BIO, established in 1993 as a nonprofit organization, is the world's largest trade organization devoted to the advancement of biotechnology. Members include biotechnology companies, academic health institutions, and research centers. BIO represents entities of all sizes engaged in developing products and

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"follow-on approvals." "Therapeutic protein product" encompasses polypeptide therapeutic products, including recombinant versions of therapeutic protein products.

3/ FDA, Draft Guidance for Industry: Applications Covered by Section 505(b)(2) (October 1999) (1999 Draft Guidance) (available at www.fda.gov/cder/guidance/2853dft.htm).

4/ Citizen Petition of Pfizer and Pharmacia (July 27, 2001) (Docket No. 01P-0323). This petition from BIO incorporates by reference, rather than repeating in their entirety, the arguments made in the Pfizer-Pharmacia petition, as well as comments from Amgen (Dec. 17, 2001), Abbott (July 10, 2002), Bristol-Myers Squibb (July 15, 2002), and Pfizer and Pharmacia (April 7, 2002).

5/ *See* section C.8 of this Citizen Petition.

services in biomedicine, diagnostics, food, energy, agriculture and environmental applications. It therefore is uniquely qualified to present this citizen petition.

B. BACKGROUND

1. BIO Is Concerned About Patient Safety, The Impact Of FDA Policies On Innovation, Adherence To Legal Requirements, And Public Participation In Agency Decisions.

For the past two years, BIO members have devoted significant attention to the issue of follow-on biologics. On December 4, 2002, the BIO Board of Directors adopted the following position:

> Biotechnology products include complex substances that are produced using living organisms for therapeutic use. While most biotechnology products are licensed as "biological products" under the Public Health Service Act, some are approved as "new drugs" under the Federal Food, Drug and Cosmetic Act. After careful analysis of the science, BIO takes the following position regarding approval standards for follow-on biotechnology products in cases in which statutory marketing protections such as patents and orphan drug exclusivity are no longer available for the approved pioneer product:
>
> Approval of follow-on biotechnology products must be based on the same rigorous standards applied by the FDA for the approval of pioneer biotechnology products. Patients should not have to accept greater risks or uncertainties in using a follow-on product than when they use an innovator's product.
>
> Currently, the science does not exist to provide an alternative to a full complement of data, including clinical evidence, to demonstrate safety and effectiveness for biotechnology products. As FDA has frequently acknowledged, biotechnology products can be difficult to fully characterize. Also, due to differences in the composition of a biotechnology product or differences in how the product is manufactured, different versions of the same biotechnology product produced by different companies will inevitably differ in certain respects from the innovator product. Experience shows that even small product differences can result in significant safety or efficacy differences. Therefore, in the current state of scientific knowledge and technique, a clinical trial remains a fundamental principle for evaluating the safety and effectiveness of a biotechnology product.

Patient safety is the primary concern when discussing proposals to reduce product testing. Significant risks to patient safety could be the direct result of decisions by FDA to approve biologically derived products based upon less than a full complement of original data about each marketed product. As discussed in

section C.6. of this petition, current science demonstrates that there can be no incomplete or abbreviated approach to the approval of therapeutic proteins, whether regulated as biological products under the PHSA or, for historical reasons, as new drugs under § 505 of the FDCA. Due to significant differences between therapeutic protein products and other drugs — in size, complexity, and heterogeneity, among other attributes — each manufacturer of such a product, and particularly any recombinant version of a product, must provide its own full complement of original non-clinical and clinical data to ensure patient safety.

In addition, BIO is concerned that any safety problems that could develop as a result of such approvals could undermine the confidence of physicians and patients in biologically derived products. The innovative biotechnological industry also is concerned about the potential economic impact of FDA decisions allowing reliance on data developed by pioneer sponsors. Innovative sponsors have reasonable investment-based expectations predicated on existing law and on long-standing agency laws and policies that require each sponsor to develop and submit its own data for each product for which approval is sought — except in the carefully delineated circumstances permitting abbreviated new drug applications (ANDAs) in which applicants for truly generic products must demonstrate "sameness" and satisfy other requirements. Established law, practice, and policies provide that data each sponsor develops, and which is provided to FDA in its application, may not be disclosed to or relied on by other manufacturers, without the authorization of the applicant. Changes to such long-standing policy would undermine investor confidence and interrupt the flow of investment into bioscience innovation upon which patients depend.

Recent indications that FDA might change its established requirements with regard to full data requirements for therapeutic proteins, subject to the new drug approval provisions, including polypeptide therapeutic agents, are a particular concern to BIO and its members.6/ The agency actions that are apparently contemplated would constitute a substantial shift away from long-standing agency positions and would profoundly alter the established regulatory framework for therapeutic proteins in which a full complement of original data, including clinical evidence, has long been regarded as scientifically and legally essential. Further, it would create a precedent that simply cannot be coherently reconciled with the present science-based approval process under the PHSA. The confusion and uncertainty associated with this unstable regulatory environment is impeding decision-making and threatening investments in the biotechnology sector. Yet, nowhere in the press is any indication that FDA will allow the public the

6/ *See* note 14 and accompanying text.

chance to have any say in whether the agency should make such drastic changes in long-standing requirements.

For the biotechnology marketplace to function in a way that serves society, and for the investment community to continue to put capital into bioscience discovery, there is need to reduce uncertainty about the future direction of core governmental policies that profoundly affect the value of biopharmaceutical innovations. Among these are the criteria for, and contents of, various applications; the extent to which such governmental requirements protect the public by assuring adequate testing and corresponding product safety and effectiveness; and the extent to which competitors are not only to be excused from requirements that innovators were required to meet but also, through FDA's reliance on innovators' data, to use others' work without just compensation.

Although a public participation process cannot alone give FDA authority that it lacks under its statutory framework,7/ the process requested by this petition will give FDA the opportunity to set forth its position on this critical issue in a manner that permits interested persons to participate directly and meaningfully in the formulation of policies that directly affect their interests. BIO believes that such a process should lead to an FDA conclusion that the agency lacks authority *both* to approve follow-on versions of therapeutic proteins under the FDCA (just as it lacks such authority under the PHSA, as discussed in the Appendix) *and* that the agency lacks authority to rely on one sponsor's data in support of another's application (except with consent or in the context of a drug eligible for the ANDA provisions of the FDCA, which require that any drug subject to an ANDA meet specific statutory criteria for approval, including "sameness"). BIO's members are aware that their convictions are not shared by all and believes that both FDA and interested persons would benefit from a meaningful public process on the scientific, legal, and policy issues that are at stake.

7/ "[N]o matter how important, conspicuous, and controversial the issue . . . an administrative agency's power to regulate in the public interest must always be grounded in a valid grant of authority from Congress." *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 161 (2000) (internal quotation omitted). *See also Aid Assoc. for Lutherans v. United States Postal Service*, 321 F.3d 1166 (D.C.Cir. 2003) (invalidating Postal Service regulations that exceeded the agency's delegated authority under the statute); *Atlantic City Electric Co. v. FERC*, 295 F.3d. 1, 8 (D.C. Cir. 2002) (holding invalid a FERC order for lack of statutory authority and noting, "As a federal agency, FERC is a 'creature of statute,' having 'no constitutional or common law existence or authority, but *only* those authorities conferred upon it by Congress.'") (quoting *Michigan v. EPA*, 268 F.3d 1075, 1081 (D.C. Cir. 2001)); *Health Ins. Assoc. of America, Inc. v. Shalala*, 23 F.3d 412 (D.C. Cir. 1994) (holding agency regulation invalid because it went beyond Secretary's statutory authority).

2. For Historical Reasons, Some Therapeutic Proteins Are Regulated As New Drugs Rather Than As Biologics.

The vast majority of therapeutic protein pharmaceuticals are licensed under the PHSA as biological products and have been assigned to FDA's Center for Biologics Evaluation and Research (CBER).8/ For historical reasons, however, certain therapeutic proteins that meet the definition of biological products have been regulated as drugs, only, under the FDCA, and not also as biologics.9/ Among these are insulin and hormone products.10/ Importantly, the decisions to regulate these and other therapeutic protein products under the FDCA were not based on any identifiable physical or chemical differences between these and similar therapeutic proteins approved under the PHSA. There was no express intent to establish a regulatory process distinct from the agency's general framework for approving biologically derived therapeutic proteins.

As recombinant versions of these products were developed, FDA regulated them, like their predecessors, under the new drug provisions of the FDCA and in FDA's Center for Drug Evaluation and Research (CDER). For example, due to the historical regulation under the FDCA of early versions of insulin products, newer recombinant insulin products have been approved as new drugs, rather than as biologics.11/ Specifically, FDA authorized marketing of insulin products for the treatment of diabetes (*e.g.*, Iletin® (insulin beef/pork), Humulin® (insulin recombinant)); human growth hormone (hGH) to treat growth deficiency problems (*e.g.*, Asellacrin® (somatropin), Protropin® (hGH recombinant));12/ hormone

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8/ *See* notes 13 and 19 on FDA's planned CBER-CDER reorganization.

9/ *See* 21 CFR § 600.3(h)(5)(ii). In 1972, the biologics program was moved to FDA from the National Institutes of Health, 70 years after the enactment of the biologics statute and 66 years after the enactment of the Food and Drugs Act.

10/ Presumably FDA's approval of an NDA for the hormone product, Premarin®, first introduced in 1942, led the agency thereafter to regulate all hormone products as new drugs, even though some now are manufactured using recombinant techniques. The recombinant products, like the original versions of these products, meet the biological product definition.

11/ Most recombinant protein pharmaceuticals approved by FDA have been licensed by CBER under the PHSA. Of 46 recombinant protein products approved between 1980 and 2002, 32 were approved by CBER and 14 by CDER. Of the 14 products approved by CDER, most were recombinant insulin or recombinant human growth hormone. *See* FDA, The Orange Book (2002); Usdin, S., *CDER's Abbreviated Route: Regulating Recombinant Proteins*, BioCentury: Bernstein Report on BioBusiness, Vol. 10, No. 17, at A6 (Apr. 15, 2002).

12/ Following approval of Genentech's original recombinant hGH product under the FDCA, the agency approved additional recombinant hGH products under this statute (*e.g.*, Bio-Tropin®,

products used to treat infertility (*e.g.*, Pergonal® (menotropins FSH/LH), Metrodin® (urofollitropin)); hormones used to relieve the symptoms of menopause and manage osteoporosis (*e.g.*, Premarin® (conjugated estrogens)); and two enzyme products used in the treatment of pulmonary embolism and Gaucher's disease, respectively (*e.g.*, Abbokinase® (urokinase) and Ceredase® (alglucerase), and Cerezyme® (imiglucerase recombinant)).

In an effort to demarcate the jurisdictional boundaries between CBER and CDER, FDA established an Intercenter Agreement between CBER and CDER in 1991. The Agreement preserved the existing regulatory classifications of therapeutic proteins, continued the practice of assigning new recombinant versions of products to the same center that handled the original version, and declared that any therapeutic proteins as well as any recombinant therapeutic products not specifically discussed would be classified as biologics.13/

The legal artifact of regulation of certain therapeutic proteins under the FDCA does not permit FDA to disregard the scientific and legal rationale on which the PHSA's prohibition against abbreviated applications for biologics was based. A coherent, forward-looking policy on the regulation of therapeutic proteins requires the agency to follow a consistent, science-based standard — the full complement of data standard — for approval of all biologically derived therapeutic products. Simply put, an historical anomaly should not serve as the basis for unjustified regulatory innovation that undercuts established scientific and legal principles.

3. Recent FDA Statements Cause BIO Concern.

Recent FDA statements suggest, however, that the agency is contemplating the possibility of allowing follow-on approvals, presented in 505(b)(2)

Nutropin®, Humatrope®, Norditropin®, Genotropin®, and Saizen®). Likewise, FDA approved recombinant insulin products under the FDCA (*e.g.*, Velosulin®, Novolin®, Novolog®, and Lantus®).

13/ The Intercenter Agreement attributed to CBER responsibility for all "biological products subject to licensure," including "protein, peptides or carbohydrate products produced by cell culture" except for certain named products that historically had been regulated as drugs (*i.e.*, insulin and hormones). FDA, Intercenter Agreement Between the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research, § III(B)(1)(f) (Oct. 25, 1991). www.fda.gov/oc/ombudsman/drug-bio.htm. FDA recently announced its plan to reorganize the responsibilities of CDER and CBER, and assigned to CDER the responsibility for "proteins intended for therapeutic use that are extracted from animals or microorganisms." *See* Memorandum from Murray M. Lumpkin and Theresa M. Mullin to FDA Staff (Oct. 28, 2002) (Lumpkin and Mullin Memo) and note 19, *infra*.

applications, of those therapeutic protein products regulated as new drugs under the FDCA, including recombinant products. A 505(b)(2) application is an NDA, described in § 505(b)(2) of the FDCA, for which one or more of the investigations relied upon by the applicant "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted." 21 USC § 355(b)(2). Permitting 505(b)(2) applications for therapeutic proteins would raise substantial and distinct scientific and public health questions, discussed in C.6., in addition to the legal and policy questions associated with FDA's current rethinking of its authority under § 505(b)(2).

BIO is especially concerned about reports of a recent speech by the Commissioner, confirming earlier agency statements:

> Speaking to the Food and Drug Law Institute in Washington, D.C., McClellan said that "human insulin and growth hormone present opportunities for approving generics under current law." . . . McClellan [stated] that FDA's long-term goals include creating a regulatory and scientific pathway for generic biologics. "I have a vision that includes effective and safe biogenerics potentially being available in the very long-term. . . . We are taking some baby steps now" toward creation of a biogenerics approval mechanism.14/

Also of concern to BIO is a 1999 Draft Guidance stating that an applicant seeking approval of a new drug under § 505(b)(2) of the FDCA may "rely on the agency's findings of safety and effectiveness for an approved drug to the extent such reliance would be permitted under the generic drug approval provisions of section 505(j)."15/ In addition, the generic drug industry has suggested various

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14/ Biocentury Extra on April 2, 2003, at 1. In his speech, Commissioner McClellan acknowledged the legal and scientific "hurdles" that must be overcome before sponsors can demonstrate bioequivalence of complex molecules. *Id.* *See infra* notes 17 and 71. The Commissioner's prepared remarks posted on the FDA website do not contain discussion of generic biologics. *See* http://www.fda.gov/oc/speeches/2003/fdli0401.html. Mark B. McClellan, M.D., Ph.D., Commissioner of Food and Drugs, prepared remarks to the Generic Pharmaceutical Association (GPhA) (Jan. 29, 2003) http://www.fda.gov/oc/speeches/2002/gpha.html; Yuan-Yuan Chiu, FDA Office of New Drug Chemistry, Biotechnology-Derived Drug Substances for AB-Rated Drug Products – A CDER Perspective, Presentation at the National Association of Pharmaceutical Manufacturers' Bulk Drug Program (Mar. 20, 2001). *See also* The Pink Sheet, *Generic Biologics Are Coming, Commissioner McClellan Tells [the Massachusetts Biotechnology Council]* (Feb. 24, 2003) ("McClellan is understood to have delivered a clear message during the meeting: the biotech industry needs to accept the inevitability that there will some day be a system for interchangeable biologics.").

15/ *See* 1999 Draft Guidance, *supra* note 3, and the text accompanying notes 52-54.

pathways, including the use of § 505(b)(2), for approval of follow-on therapeutic proteins.16/

BIO strongly disagrees with FDA's proposed interpretation of § 505(b)(2) as authorizing approvals based upon an FDA finding of safety and/or effectiveness for an approved drug product. This proposed interpretation would permit reliance, without any right of reference, upon proprietary information in an approved product's application, an approach that is not authorized by law. To date, FDA has neither finalized the existing Draft Guidance nor responded to industry's concerns. Use of the § 505(b)(2) pathway for approval of therapeutic proteins would raise not only questions regarding the propriety of reliance on an innovator's non-public data, but also a series of distinct and separate legal, regulatory and scientific questions about follow-on products.

C. GROUNDS FOR REQUESTED RELIEF

1. FDA Must Refrain From Approvals Of Follow-on Therapeutic Proteins.

FDA must refrain from approving — under any of the statutes it administers — any application for a therapeutic protein product that does not contain a full complement of original non-clinical and clinical data and that relies on any data or information contained in another product's application. BIO and its member companies believe that neither the law nor the current science permits such follow-on products. FDA lacks legal authority to approve follow-on therapeutic protein products under the biologics licensing provisions of the PHSA, the ANDA provisions in § 505(j) of the FDCA, and the § 505(b)(2) provisions of the FDCA.17/

a. FDA Cannot Approve Follow-ons Under The PHSA.

BIO appreciates FDA's informal reassurance that the agency continues to believe that follow-on applications are not contemplated for biological products licensed under the PHSA, and BIO requests that FDA affirm that position in its

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16/ Letter from Bill Nixon, GPhA, to Daniel Troy, Chief Counsel, FDA (Jan. 18, 2002) available at http://www.fda.gov/cder/ogd/GPHA_Jan_21.htm. The innovative industry disputes this view, as discussed in this petition. *See also* note 4.

17/ As reported in Biocentury Extra, *see supra* note 14, Commissioner McClellan stated that "FDA doesn't 'have the authority under current law for comprehensively approving and reviewing generic biologics.'" He also noted that an approval scheme for generic biologics "will require a lot more . . . legislation." *Id.*

response to this petition.18/ BIO also appreciates FDA's inclusion in its periodic updates on its plan to move responsibility for certain therapeutic proteins from CBER to CDER of statements addressing the continued regulatory requirements for biological products.19/ Because of the frequent FDA statements to this effect, this petition concentrates on the issue of follow-on approvals of therapeutic proteins under the FDCA and deals with the question of follow-on approvals under the PHSA only in the Appendix to this petition.

b. FDA Cannot Approve Follow-ons Of Therapeutic Proteins Under § 505(j).

The ANDA provisions in § 505(j) were not created, nor should they be used, to approve generic or follow-on versions of therapeutic protein products. The entire premise upon which § 505(j) is based is that one can establish "sameness" for two drugs. Because of the scientific complexities of therapeutic protein products, it

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18/ K. Coghill, *Waxman Criticizes FDA Process; FDA Head Encourages Innovation*, Bioworld Today, Apr. 2, 2003 ("Responding to a question following his speech [at the FDLI annual meeting], McClellan said the science related to developing biologics is just too complex to try to include them under a generics rule"); *Generic Biologics Are Coming, Commissioner McClellan Tells MBC*, The Pink Sheet (Feb. 24, 2003) (quoting the Commissioner as acknowledging the importance of "appropriate clinical and scientific standards"); Inside Washington, *McClellan Says Generic Biologics Would Require Legislation*, FDA Week, (Nov. 8, 2002); *Generic Biologic Science Must Evolve Before Legislative Debate-Lumpkin*, The Pink Sheet (March 21, 2003) ("FDA and industry need to work out the science of generic biologics before a legislative debate would be useful, FDA [Principal] Associate Commissioner Murray Lumpkin, MD, suggested. 'This is not something that FDA can make a decision on its own about. There are clearly science issues that have got to be answered, and there are very clear law issues that have got to be answered.'"); *Recent Developments Which May Impact Consumer Access To, and Demand For, Pharmaceuticals*, Hearing Before the Subcommittee on Health of the House Committee on Energy and Commerce, 107th Cong. 33 (2001) (statement of Janet Woodcock, MD) ("Products that are approved under the [PHSA] are often considered biologics . . . [T]hat statute does not have the provision for generics. So there's actually no statutory framework. There are also *major scientific issues* that relate to the approval of recombinant protein products.") (emphasis added). The recent FDA statements to the effect that generic biologics are scientifically and legally infeasible are consistent with FDA's long-standing view. *See, e.g.*, 39 FR 44602, 44641 (Dec. 24, 1974) (preamble to FDA's final public information regulations).

19/ In announcing its recent plan to move to CDER the responsibilities of CBER for "proteins intended for therapeutic use that are extracted from animals or microorganisms," Lumpkin and Mullin Memo, *supra* note 13, FDA indicated that "[c]urrent FDA policy on generic biologics will not be affected by this decision." FDA, *FDA To Consolidate Review Responsibilities For New Pharmaceutical Products* (Sept. 6, 2002), www.fda.gov/bbs/topics/NEWS/2002/NEW00834.html. Recently, FDA "reiterat[ed] that under the new structure the biological products transferred to CDER will continue to be regulated as licensed biologics." FDA, *FDA Completes Final Phase of Planning for Consolidation of Certain Products from CBER to CDER* (Mar. 17, 2003), http://www.fda.gov/bbs/topics/NEWS/2003/NEW00880.html.

is virtually impossible to isolate, much less compare, the active ingredients of two of these products. Therapeutic protein products differ in significant respects from chemical entities or traditional drugs. Primarily, therapeutic protein products are often comprised of many active components, both known and unknown, making it difficult to characterize the final product. Section 505(j), however, relies on active ingredient comparisons to determine "sameness." For therapeutic proteins, such an analysis would be of little relevance given the many unknowns about their composition. Because therapeutic proteins' effects in the body are often difficult to predict or explain, *i.e.*, immunogenicity incidents, the bioequivalence determinations made under § 505(j) would also prove to be of little relevance.

FDA may not use the ANDA process in § 505(j) to approve generic versions of therapeutic proteins characterized by a level of complexity in which the data needed are not satisfied by the requirements or analytical standards needed to answer the questions about product safety and effectiveness. Recent experience has shown the difficulty FDA has encountered in attempting to apply generic drug concepts to complex therapeutic protein products.20/ Recombinant products present additional issues, as discussed later in this petition.

The generic drug model is based on the concept that two drugs can be shown to be "the same" such that the clinical data developed using one drug can be applied in full to the other. Essentially, "sameness" is a surrogate; once established for a given drug, "sameness" takes the place of having to make an original showing of safety and effectiveness for that drug. Under the generic drug model, the sameness is shown primarily by comparing the active ingredients in vitro and the

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20/ *See, e.g.*, the discussion on Premarin® in section C.6. of this petition. In its final rule implementing the Hatch-Waxman Amendments, FDA responded to comments urging FDA to permit ANDAs for "duplicates of 'drug substances for which the specifications are very tightly drawn for both potency and purity, such as insulin preparations, and for copies of biotechnology products'":

> Section 505(j) of the act permits ANDA's only for duplicate and related versions of previously approved drug products. The ANDA applicant relies on a prior agency finding of safety and effectiveness based on the evidence presented in a previously approved new drug application. If investigations on a drug's safety or effectiveness are necessary for approval, an ANDA is not permitted. Thus, under the statute, an ANDA would only be permitted for a drug product with "tight specifications" or a biotechnology product *only if such a product is the same as a product previously approved under section 505 of the act or if FDA has approved the submission of an ANDA under a petition filed under section 505(j)(2) of the act.*" FDA, Abbreviated New Drug Application Regulations, 57 FR 17950, 17953 (Apr. 28, 1992) (emphasis added).

As discussed in note 56, FDA has taken the position that clinical studies are needed for biotechnology-derived products.

bioavailability of those ingredients in vivo. The assumption that the same approach can be used for biologically derived therapeutic proteins, with the same results is — without qualification — incorrect. The differences between prototypical pharmaceuticals (around which the generic drug model was designed) and biologically derived products (around which the biologics licensing process was designed) are profound. The size, structure, and heterogeneity, of these products, along with the inability to anticipate through assay, an unknown immune response, simply puts them beyond the realm of a responsible short-form approval process.21/ It is plain from the requirements of § 505(j) that Congress particularly meant for generic drugs to be the same as the listed drugs their applications reference.

FDA appears to believe the route to approval of follow-on versions of a therapeutic protein product is § 505(b)(2) rather than the ANDA provision in § 505(j). Accordingly, in its discussion of FDCA issues, this petition concentrates principally on why § 505 (b)(2) — the codification of FDA's very limited paper NDA policy for literature-supported applications) — is not a source of follow-on approval authority for therapeutic proteins.

c. FDA Cannot Approve Follow-ons Of Therapeutic Proteins Under § 505(b)(2).

Likewise, § 505(b)(2) of the FDCA was not written to provide authority for approving follow-on therapeutic proteins. Rather, § 505 (b)(2) was written to codify FDA's "paper NDA" policy, in which one or more of the investigations relied upon by the applicant was "not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted." 21 USC § 355(b)(2).

As discussed, through § 505(j) Congress chose to create an ANDA scheme only for products that are the "same," a statutory standard that follow-on versions of therapeutic proteins approved as new drugs under the FDCA cannot readily meet. The only logical conclusion that can be drawn from this construction is that therapeutic proteins were meant by Congress to be regulated, if at all under the FDCA, only under full NDAs as defined in § 505(b)(1). It is difficult to understand how a § 505(b)(2) applicant can scientifically demonstrate sameness.22/

21/ As discussed *infra* at C.5, the Court of Appeals decision in *Serono Laboratories v. Shalala*, 158 F.3d 1313 (D.C. Cir. 1998), does not change this basic conclusion.

22/ From a scientific point of view, it is problematic to presuppose that scientists have identified all the differences that exist between the innovator product and the follow-on. Scientifically, one

It cannot have been the intent of Congress for the carefully crafted ANDA provisions that were the centerpiece of the Hatch-Waxman Amendments of 1984[23] to be bypassed so easily, by a shift of agency decision-making to a separate statutory provision. All § 505(b)(2) was intended to cover was FDA's paper NDA policy for "duplicates" of already-approved drugs where published scientific literature obviated additional safety and efficacy testing.[24] There is no evidence that Congress intended for § 505(b)(2) to function as a catch-all provision for FDA to approve products that do not meet the approval standards of either the full application requirement of § 505(b)(1) or the sameness requirement of § 505(j).

FDA's paper NDA policy, put in place before the enactment of Hatch-Waxman, was an agency interpretation of its NDA regulations allowing reliance on published reports as the main support for findings of safety and effectiveness. This alternative approval route allowed applicants to receive approval of certain "duplicate" products without conducting full clinical investigations. A key element of this policy incorporated the doctrine that "no data in an NDA can be utilized without express permission of the original NDA holder,"[25] a long-standing FDA position that reflected the law. This law has neither been altered by Congress — except as to ANDAs regulated under § 505(j) — nor rescinded by the agency.

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never demonstrates sameness, rather, the follow-on applicant can demonstrate only the absence of differences according to a set of tests and criteria. If the applicant and the regulatory agency are unaware of the need to conduct certain tests or to apply certain criteria, an important product parameter can be missed and an unsafe or ineffective follow-on product approved. In sum, the best approach is not to seek short-cuts, but to require each manufacturer of a therapeutic protein to produce a full complement of data that demonstrates safety and effectiveness.

23/ Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417.

24/ *See* FDA, Publication of "Paper" NDA Memorandum, 46 FR 27396 (May 19, 1981) (publishing an internal FDA memorandum (the "Finkel Memorandum") dated July 31, 1978, and entitled, "NDA for Duplicate Drug Products of Post-1962 Drugs"); *see also* 45 FR 82052 (Dec. 12, 1980), Response to Petition Seeking Withdrawal of the Policy Described in the Agency's "Paper" NDA Memorandum. Like that policy, § 505(b)(2) allows a second or subsequent applicant to rely on those publications as a substitute for § 505(b)(1)'s requirement of "full reports" of investigations, even if the second applicant does not have a right of access to the full data underlying the publications.

25/ 46 FR 27396; 45 FR 82052 ("A drug marketed for the first time after 1962 under an approved New Drug Application may be marketed by a second firm only after the second firm has received the approval of a full New Drug Application for that product. Current Agency policy does not permit ANDAs for this purpose. *Present interpretation of the law is that no data in an NDA can be utilized without express permission of the original NDA holder.*" (emphasis added)).

In § 505(j), Congress enacted a detailed statutory mechanism for ANDAs for generic drugs meeting the "sameness test," while continuing in § 505(b)(2) a narrow FDA policy on literature-supported duplicate drugs. In enacting the "distinct regulatory scheme" laid out in these provisions "to address a given issue," Congress demonstrated its intention to legislate in the field, and "any attempt by FDA to intervene with an inconsistent regime shall be deemed in excess of its authority."26/

Neither the legal landscape at the time of enactment of Hatch-Waxman in 1984, nor FDA's interpretation of § 505(b)(2) since, would allow FDA to use § 505(b)(2) as an approval pathway for follow on therapeutic proteins, including hGH and insulin. Any agency effort to so use it would be unlawful.

1) Section 505(b)(2) Was Intended To Codify FDA's Paper NDA Policy.

The language of § 505(b)(2) is unclear. Likewise, its implementing regulations, 21 CFR §§ 314.50 and 314.54, provide little guidance as to what types of applications may be approved under § 505(b)(2). Thus, to best interpret the provision, we must look to other statutory provisions, judicial opinions at the time of its enactment, and the legislative history.27/ All strongly indicate that § 505(b)(2) simply codified FDA's then-existing paper NDA policy, a policy that would never have applied to follow-on versions of biological products and similarly complex products regulated under the FDCA. Also, nowhere was there expressed any intent to overrule a legal precept underlying that policy, which stated that "no data can be utilized without [the NDA holder's] express permission."28/

i) The Structure of § 505

The Hatch-Waxman Amendments reflect a compromise between the generic and innovative industries: Title I created a new avenue for generic approvals while Title II restored the patent term for pioneer products whose market launch is delayed by the regulatory review process. The hallmark of Title I was the

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26/ *Association of American Physicians and Surgeons, Inc. v. FDA*, Civil Action 00-02898 (HHK) (Oct. 17, 1992), slip op. at 26, *citing FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 154-55 (2000), *supra*, note 7.

27/ *See Chevron U.S.A. Inc. v. Natural Resources Defense Council Inc.*, 467 U.S. 837 (1984).

28/ 46 FR at 27396, *supra* note 24.

creation of a generic approval process for post-1962 approved drugs, termed an ANDA and authorized under § 505(j).

Section 505(j) established clear and extensive standards for submission, review, and approval of generic drugs. It provided clear mechanisms for approving duplicate or follow-on products that were not "the same" as the innovator's product. *See* 21 USC § 355(j)(2)(C) and the discussion in C.1.b., *supra.* It also provided a patent certification process designed to provide notice to patent holders when ANDAs were filed and an opportunity to litigate potential patent disputes before generic approval. And, it allowed ANDA sponsors to rely on the data submitted by another person in an NDA to support an agency finding of safety and effectiveness for the proposed generic.

Section 505(b)(2), on the other hand, required that applicants who rely on studies "not conducted by or for the applicant and for which the applicant has not obtained a right of reference," must certify to all patents that may claim the drug or its method of use. There is absolutely no indication that this provision was meant by Congress to do anything more than to codify FDA's then-existing paper NDA policy and apply to paper NDAs a patent certification process paralleling that enacted for ANDAs.

ii) Limited Scope of the Paper NDA Policy

A central issue in food and drug law in the late 1970s and early 1980s was the basis upon which "me too" drug applicants could receive FDA approval. This debate boiled down to one key issue: could FDA lawfully use proprietary information in an NDA to approve a competitor's product?

The paper NDA policy that FDA published in 1981 was limited to "duplicates," was limited to substitution of literature for original safety and effectiveness studies, and explicitly disavowed any ability of a second or subsequent applicant to rely on data generated by a pioneer sponsor in the original application. (Nor, of course, could FDA bypass this restriction by simply relying upon its own earlier findings of safety and effectiveness based on the pioneer sponsor's data.)

As the case law demonstrates, litigation spanning the period of Congressional consideration of Hatch-Waxman, its enactment, and its early FDA implementation established that, in implementing the paper NDA policy, FDA could not use one manufacturer's information in support of a competitor's paper NDA. Indeed, by 1984 the courts had made it clear that FDA could not approve an application in which one manufacturer relied on another's proprietary information. In 1981, a federal district court ordered FDA to publish in the Federal Register the

internal FDA memorandum that had first articulated its paper NDA policy *but also* enjoined FDA from including a paragraph in which FDA had stated that it could, in a second paper NDA, rely on the Summary Basis of Approval underlying FDA's approval of the first paper NDA. *See American Critical Care v. Schweiker*, Food Drug, Cosm. L. Rep. (CCH) 1980-81 Transfer Binder 38,110 (N.D.Ill. 1981). FDA obeyed the court's order and published a revised version of its policy with the paragraph in question stricken.29/ The court's holding showed clearly that FDA's proposal to rely on summary data published by FDA after consideration of an NDA was inconsistent with long-standing agency practice. *See id.* Likewise, in *Upjohn v. Schweiker*, 520 F. Supp. 58, 63 (W.D. Mich. 1981), the court held that FDA, in applying its just-issued paper NDA policy, could not rely on trade secret information in the innovator's NDA to approve a duplicate NDA.

With this background, it is improbable that Congress would have changed the law in this field without an explicit statement in the statute or, at the very least, the legislative history.30/ Quite simply, the holdings in these cases were, along with FDA's paper NDA policy as a whole, codified in § 505(b)(2). "Congress is assumed to know the judicial or administrative gloss given to particular statutory language, and therefore is assumed to have adopted the existing interpretation unless it affirmatively indicates otherwise." *Pfizer v. Shalala*, 753 F. Supp. 171, 178 (D. Md. 1990).

iii) Legislative History: § 505(b)(2)=Paper NDAs

The legislative history of § 505(b)(2) also demonstrates Congress' clear intent for this provision to continue FDA's paper NDA policy. The House Report, in particular, reflects this intent, providing that the FDA paper NDA policy that is the precursor to § 505(b)(2) allowed use only of scientific reports, or published studies,

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29/ 46 FR 27396 (May 19, 1981), *supra*, note 24.

30/ The legislative history shows that Congress knew how to express its intent to overrule judicial precedent. The Hatch-Waxman Amendments included a provision — now codified at 35 USC § 271(e)(1) — that reversed the holding in *Roche Products, Inc. v. Bolar Pharmaceutical Co.* 733 F. 2d. 858, *cert. denied* 469 U.S. 856 (1984). In this case, the court had held that U.S. patent law was violated when a generic company (Bolar) tested its product against that of the pioneer (Roche) during the patent life of the latter's pioneer product. Hatch-Waxman's "Bolar provision" permits the generic manufacturer to conduct bioequivalence testing of its product against the pioneer's drug during the patent life of the pioneer. The legislative history shows clearly the Congressional intent to overrule the *Bolar* decision: "The provisions of § 202 of the bill have the net effect of reversing the holding of the court in *Roche Prod., Inc. v. Bolar Pharms. Co.*" H.R. Rep. No. 98-857, pt. 2, at 27 (1984), *reprinted in* 1984, U.S.C.C.A.N. 2686, 2711. In contrast, no such intent is stated to overrule the *American Critical Care* or *Upjohn* decisions. *See also Burroughs Wellcome*, discussed in C.1.c.1.iv.

as opposed to *any* investigation for which the applicant has not obtained a right of reference to the underlying raw data. This report reviewed FDA's existing NDA approval processes, as follows:

> The FDA allows this ANDA procedure [under the Drug Efficacy Study Implementation] only for pioneer drugs approved before 1962. There is no ANDA procedure for approving generic equivalents of pioneer drugs approved after 1962. While the FDA has been considering since 1978 an extension of the pre-1962 policy to post-1962 drugs, it has not extended the regulation. Because of the agency's failure to act, Title I of H.R. 3605 is necessary to establish a post-1962 ANDA policy.
>
> Some have suggested that 'Paper NDAs' be used to approve generic equivalents of pioneer drugs approved after 1962. Under the paper NDA procedure, the generic manufacturer may submit *scientific reports*, instead of clinical trials, to support findings of safety and efficacy. This procedure is inadequate, however, because FDA estimates that satisfactory reports are not available for 85 percent of all post-1962 drugs.31/

This passage shows that Congress intended both to codify the existing paper NDA policy and to create an alternative ANDA route. Its intent was to retain and codify the long-standing requirement that one NDA applicant (including a paper NDA applicant and thus, now a 505(b)(2) applicant) may not, without permission, rely on another sponsor's unpublished data. At the same time, Congress specifically authorized such reliance for ANDAs, in the limited context of a carefully drawn statutory checklist, to assure product "sameness." Only in the case of ANDAs under § 505(j) did Congress change the previous law and the parallel long-standing agency interpretation forbidding reliance on another manufacturer's data without consent.32/

31/ House Report 98-857 Part 1, 98th Congress, 2d Session, June 21, 1984 (emphasis added). The characterization of FDA's paper NDA policy as "inadequate" was intended to demonstrate why an ANDA procedure for post-1962 drugs was necessary. The first paragraph quoted above demonstrates that Congress was concerned about the lack of an ANDA route for post-1962 drugs, and not about any perceived need to broaden the categories of information available to follow-on applicants, in the statute's version of a paper NDA policy. In the context of § 505(b)(2), there is no indication in the legislative history that the Congress thought it needed to broaden beyond published literature the categories of information upon which follow-on applicants could rely, without a right of reference or use.

32/ If an agency has characterized a certain regulatory procedure using a specific term, and Congress employs that term — here, paper NDA — the presumption is that Congress gave the term the same meaning as had the agency. *See Toilet Goods Ass'n v. Finch*, 419 F.2d 21, 26 (2d Cir. 1969) (where an agency used a certain definition, burden fell on the party challenging that definition to show that when, "Congress employed words similar to those previously in the FDA's regulations, it meant them to have a different effect."). Furthermore, it is a fundamental principle that "before a court will hold Congress to have made a basic change in regulatory procedures, legislators must either use plain language or give other clear manifestation of intent." *Id.* at 27. Congress certainly

iv) Post-Hatch-Waxman Interpretations

Shortly after enactment of the Hatch-Waxman Amendments, a court had occasion to discuss their meaning:

> Pursuant to the 1984 amendments, there are now two new kinds of drug applications: literature supported NDAs frequently termed "paper" NDAs (section 505(b)(2)), and abbreviated new drug applications (ANDAs) (section 505(j)). A "paper" NDA is one in which the required safety and effectiveness data are not the result of the original testing by the NDA applicant, but rather are obtained from *literature reports* of testing done by others.33/

Burroughs Wellcome Co. v. Bowen, 630 F. Supp. 787 (E.D.N.C. 1986). This decision affirms that Congress meant to codify FDA's paper NDA policy.

The government briefs and the Third Circuit's decision a year later in *Tri-Bio Laboratories v. FDA*, 836 F.2d 135 (3rd Cir. 1987) show that Hatch-Waxman changed FDA's authority to use the original sponsor's data in support of a generic applicant's abbreviated application *only* as provided in § 505(j) for ANDAs.34/ The

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would have forthrightly communicated its intent in the legislative history if it effected such a radical change in FDA's paper NDA policy to permit applicants to rely on proprietary information in pioneers' NDAs. *See also* note 30 (detailing plain language in Hatch-Waxman legislative history renouncing *Roche v. Bolar*).

33/ *Id.* at 789 (emphasis added). The leading textbook interprets § 505(b)(2) as codifying FDA's paper NDA policy. *See*, Hutt and Merrill, *Food and Drug Law 2nd Edition* (1991), at 571 ("FDA's abbreviated NDA policy for pre-1962 drugs and *its paper NDA policy for post-1962 drugs were codified* and extended to all new drugs . . . in the Drug Price Competition and Patent Restoration Act of 1984.") (emphasis added).

34/ The government's briefs in the district court and the court of appeals, submitted as exhibits to this petition, described the agency's long-standing interpretation that information in NDAs or new animal drug applications (NADA) is considered proprietary and confidential:

> Since 1938, FDA has consistently taken the position that unpublished safety and effectiveness data submitted as part of an NADA or NDA are confidential, proprietary information which can not, except in very limited circumstances not present here, be released to the public or used to support another manufacturer's application. This position, which is based on FDA's longstanding interpretation of 331 (j), 5 U.S.C. 552, *et. seq.* (the Freedom of Information Act), and 18 U.S.C. 1905 (the Trade Secrets Act) has been set forth in regulations promulgated by FDA, preambles published in the Federal Register, and in testimony by agency officials before several Congressional committees.

Tri-Bio court thus upheld the agency's decision not to allow a generic animal drug applicant to make reference to a pioneer's data, holding that the agency "routinely followed" and gave "consistent interpretation" to its regulation prohibiting reliance on data in previously submitted applications — a policy premised on the law and upon FDA's belief that "pioneer manufacturers possess a property interest in the test data they present to support their new drug applications." 836 F.2d at 140, 141.

Furthermore, in its reply brief in the district court, FDA characterized paper applications as dealing only with FDA acceptance of published studies, not FDA usage of an original sponsor's data in favor of a generic application:

> [T]he paper NADA policy does not, as plaintiff claims, create a third policy concerning applications for generic copies of previously approved animal drugs. . . . Paper NADAs . . . still must satisfy the 'full reports' requirement and so are full NADAs. Under the paper NADA policy, FDA simply accepts published studies from the scientific literature, where such studies are adequate to establish safety and efficacy, as the requisite 'full reports.' *See, e.g., Burroughs Wellcome Co. v. Schweiker*, 649 F.2d 221 (4th Cir. 1981).35/

In sum, the government's briefs in the post-Hatch-Waxman *Tri-Bio* litigation show unequivocally that the agency construed the new law as maintaining the legal barrier to reliance upon the pioneer sponsor's data (without the sponsor's consent) *except* in the context of ANDAs under § 505(j). Moreover, both parties' briefs in *Tri-Bio* discussed FDA's paper NDA policy, and neither the district court nor the Third Circuit disagreed with FDA's description of this policy.

Significantly, in 1990 the Supreme Court in *Eli Lilly & Co. v. Medtronic, Inc.* described a 505(b)(2) application as "a so-called paper new drug application (paper NDA), an application *that relies on published literature* to satisfy the requirement of animal and human studies demonstrating safety and effectiveness. See § 355(b)(2)." 497 U.S. 661, 676 (1990) (emphasis added). This

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Government's Br. at 62-63, (filed Apr. 3, 1986, M.D. Pa.). The brief also cites to 39 FR 44,602, at 44,612-14 and 44,633-38 (1974) (FDA's public information regulations). "Nothing in the new animal drug approval provisions of the Act, in the view of FDA, would permit FDA to breach the confidentiality of [the innovator's] safety and effectiveness data for [the generic] by expropriating those data to benefit an NADA for [the generic]." Government's Third Cir. Br. at 44. As the Commissioner explained, "It has been the agency's long-standing view that, with certain exceptions, every NADA must be supported by complete safety and effectiveness data. *The underlying rationale is that the safety and effectiveness data supporting an approval are proprietary and belong to the sponsor.*" *Id.* at 39 (emphasis added). It is noteworthy that the government's briefs discuss only § 505(j), and do not discuss § 505(b)(2), as new authority in the human drugs area permitting FDA to rely on a pioneer's data in support of a generic drug application.

35/ Government's Brief at 5 n.4 (filed June 2, 1986, M.D. Pa).

interpretation of the law by the highest court in the land was later-in-time than the FDA proposed rule discussed in section C.1.c.2.v., below, and should be treated as removing all doubt about the limited scope of § 505(b)(2).

2) Paper NDA Policy Was Intended For Duplicate Drugs, Not Highly Variable Therapeutic Proteins.

Because FDA limited its paper NDA policy to duplicates of drugs for which sufficient scientific literature had been published to make additional safety and effectiveness studies unnecessary, a paper NDA would *never* have been sufficient to support approval of highly variable products such as therapeutic proteins, nor would a 505(b)(2) application today. A literature search may well produce scientific articles attesting to the safety and effectiveness of a therapeutic protein product. A previous FDA approval should certainly attest to the safety and efficacy *of the approved product.* A follow-on manufacturer, however, particularly of a product derived from recombinant-DNA technology, cannot demonstrate through a paper NDA (or, as it is now called, a 505(b)(2) application), that its facilities and manufacturing process will produce the same product as the one described in the scientific articles (or in the original manufacturer's unpublished proprietary information in its NDA). As explained in section C.6., the follow-on product will be a different substance, because the manufacturing process for the follow-on version will necessarily differ in meaningful ways from that of the innovator.

Even if FDA had the legal authority — which it does not — to interpret § 505(b)(2) to permit reliance on unpublished, proprietary data in an innovator's application to support approval of a follow-on application, it is not clear how such *agency* reliance on undisclosed information provides any reassurance about the follow-on *manufacturer.* In such a circumstance, the *manufacturer* of a follow-on complex biopharmaceutical is unable to assure the safety and effectiveness of its own product, considering that it is not simply safety and efficacy data, but also *manufacturing processes,* that are critical to therapeutic proteins. Any notice published by FDA in response to this petition must deal with this issue as well as explain how the agency believes, given the legal constraints in the FDCA, it could rely upon one company's proprietary data about a therapeutic protein in support of another's therapeutic protein's application.

i) Policy-by-Approval Is Improper.

Given the cryptic nature of the statute, and the only slightly more detailed treatment in the regulation, discussed below, FDA cannot embark on a

path of applying rules without the benefit of a public process. If FDA seeks to define the scope of this provision through guidance or through an approval in which only the applicant is a participant, it violates the law and runs afoul of basic principles of public participation in the governing process. The very generality of the statute means that FDA in any individual decision must be applying definitive language that has a present, binding effect and that imposes "rights and obligations."36/ Each time the agency makes an *ad hoc* approval decision under § 505(b)(2), it is in essence adopting a rule without completing a rulemaking proceeding, which is contrary to principles of administrative law. And each time it adopts what amounts to a rule through individual approval decisions, and without going through a rulemaking procedure, the agency denies a fair process to anyone but the 505(b)(2) applicant.37/

At a minimum, FDA must initiate a meaningful public process in which the agency makes a diligent effort to collect enough legal and scientific information to adequately analyze this complex matter. FDA should comprehensively articulate the basis of the 1999 Draft Guidance (and any change in agency interpretation it is apparently intended to implement) and allow for public comment. As discussed in this petition, use of guidance documents cannot cure this problem, even where the agency uses a notice-and-comment process pursuant to Good Guidance Practices.

ii) FDA's § 505(b)(2) Interpretation Ignored Its Paper NDA Lineage.

Since enactment of Hatch-Waxman, FDA has never issued a regulation that implemented § 505(b)(2) as the present embodiment of the pre-enactment paper NDA policy, despite the fact that the Congressional purpose in enacting § 505(b)(2) was to continue FDA's paper NDA policy while applying to it the patent certification provisions also applied to ANDAs. Instead, as is discussed below, FDA decided that, because the usage of paper NDAs was confined to duplicates, and because Hatch-Waxman had made ANDAs available to duplicates, there was no

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36/ *See Community Nutrition Institute v. FDA*, 818 F. 2d 943, 946 (D.C. Cir. 1987).

37/ BIO is aware that agencies possess power to set industry norms through adjudication. Here, however, "the policy disputes are too sharp, the technological considerations too complex, the interests affected too numerous, and the missions too urgent" for FDA to rely upon adjudication. Judge Wright, *The Courts and the Rulemaking Process: The Limits of Judicial Review*, 59 Cornell L. Rev. 375, 376 (1974). *See also* Lars Noah, *Administrative Arm-Twisting in the Shadow of Congressional Delegations of Authority*, 1997 Wis. L.R. 873, 936-41 (discussing potentially "standardless" individualized approval decisions).

need to continue paper NDAs even if redesignated as 505(b)(2) applications. Although this position contradicted the legislative history, it apparently went unchallenged because of a general industry view that there was little need for paper NDAs due to the inauguration of ANDAs.

iii) Parkman Letter On § 505(b)(1) And (j), Not On § 505(b)(2).

During early implementation of Hatch-Waxman, questions arose about "the statutory mechanism by which ANDA applicants may make modifications in approved drugs if the modifications require the submission of clinical data," and, to answer these questions, in 1987 FDA issued an informal notice known as the "Parkman Letter."38/ In it, FDA described a new hybrid form of "ANDA plus" application for such cases, consisting of an ANDA, plus whatever clinical data was needed to justify the modification or new indication (*i.e.*, relying upon the original sponsor's submission pursuant to the ANDA provisions of § 505(j), while allowing the simultaneous submission of supplemental NDA-type data under § 505(b)(1)). FDA reasoned that:

> [The agency will] allow a generic applicant to submit a 505(b) "supplement" (a form of NDA) for a change in an already approved drug that requires the submission of clinical data, without first obtaining approval of an ANDA for a listed drug. This submission would include data only for those aspects of the proposed drug that differ from the listed drug. Changes in already approved drugs for which such applications will be accepted include changes in dosage form, strength, route of administration, and active ingredients for which ANDA suitability petitions cannot be approved because studies are necessary for approval as well as new indications. Like similar supplements to approved ANDAs, these applications will rely on the approval of the listed drug together with the clinical data needed to support the change. The applicant will thus be relying on the approval of the listed drug only to the extent that such reliance would be allowed under section 505(j): to establish the safety and effectiveness of the underlying drug.39/

In other words, the authority used by the agency for an "ANDA-plus" application was the § 505(j) ANDA authority for the aspects of the drug that are the same as the reference product *plus* the § 505(b)(1) full reports authority for the

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38/ Letter to all NDA and ANDA applicants from Paul Parkman, M.D., Acting Director, Center for Drugs and Biologics, FDA, (April 10, 1987) (attached as an exhibit).

39/ *Id.* at 1.

aspects of the new drug that are modified and were of the sort traditionally handled in NDA supplements. The authority to rely on the pioneer's data derives from, and is limited to the scope permitted by § 505(j), *i.e.*, only as to drug aspects meeting the sameness criteria for ANDAs. Although the authority for the "ANDA-plus" was derived from §§ 505(b)(1) and 505(j), to assure "due regard for the listed drug's patent rights and exclusivity . . . an application that relies in part on the approval of a listed drug and in part on new clinical data will, *for this purpose,* be considered an application described in section 505(b)(2) and must contain a certification to any relevant patents that claim the listed drug." (emphasis added).

iv) Parkman Letter Codified In § 314.54.

The policy announced informally in the Parkman Letter was later restated in 21 CFR 314.54, with a discussion in the preamble to the proposed rule that largely tracked the Parkman Letter.40/ The regulation's requirement that the application include reference, *inter alia,* to "Identification of the listed drug for which FDA has made a finding of safety and effectiveness"41/ must be read in light of its derivation from § 505(j). The Parkman Letter stated that the generic "applicant will thus be relying on the approval of the listed drug only to the extent that such reliance would be allowed under section 505(j)," *i.e.*, the reliance relates to the aspects of applicant's drug and the original drug that meet the sameness criteria for ANDAs.42/ In short, underlying § 314.54 is the assumption of follow-on sameness with the listed drug, but for the modification or new indication justified by the second applicant's clinical data.

40/ FDA, Abbreviated New Drug Applications Regulations, 54 FR 28875, 28891, 28892 (July 10, 1989). Although § 314.54 calls the application a "505(b)(2) application," the Parkman Letter, which it codifies, had made clear that, except in ensuring respect for patent and exclusivity rights, the authority for such "ANDA-plus" applications is traceable to § 505(b)(1) and (j), not (b)(2).

41/ § 314.54(a)(1)(ii).

42/ To ensure that § 314.54 does not create an avenue for approval of bio-inequivalent drugs, the preamble cautioned that this regulation cannot be used to "thwart Congress' clear intention to require that a duplicate of a listed drug be shown to be bioequivalent to that listed drug," 54 FR at 28893. Therefore, the regulation forbids use of § 314.54 for a drug product whose only difference from the reference listed drug is a lesser extent of absorption or rate of absorption, or other bioavailability, at the site of action. § 314.54(b).

v) Non-binding Preamble Statement Inconsistent With Administrative And Judicial Interpretations.

The preamble to the 1989 proposed rule on ANDAs contains a discussion (preceding the preamble accompanying § 314.54) in which FDA states that § 505(b)(2) "is broader than the paper NDA policy," downplays the legislative history linking the provision to the paper NDA policy, and then revokes the paper NDA policy (as all duplicates of approved drugs can be handled under the ANDA provisions of § 505(j)).43/ Then, in a statement seemingly unanchored to any particular proposed regulation, and therefore at best a hortatory advisory opinion,44/ the preamble finds in the "plain language of the statute" the ability "to apply [§ 505(b)(2)] to any application that relies on investigations which the applicant has not conducted, sponsored, or obtained a right of reference to, regardless of the similarity or dissimilarity of the drug product to an already approved drug product."45/

Although the quoted language is similar to that of the statute, it plainly would be incorrect for FDA to read into it a scope other than that indicated by the accompanying statutory provisions, the contemporaneous judicial interpretation, and the legislative history: § 505(b)(2) codifies the FDA paper NDA policy, reflecting the established law on data non-reliance. The 1989 preamble statement did not state clearly any agency intent to overrule previous law; nor did it state any agency intent to use *NDA data* for 505(b)(2) applications.46/ Drug

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43/ 54 FR at 28890. *See* 21 CFR 314.101(d)(9). The legislative history contains no indication that Congress was bothered by the overlap between FDA's paper NDAs — codified in § 505(b)(2) — and ANDAs. Both applied to duplicate products. However, FDA decided to create an administrative demarcation in which ANDAs, only, could be used for duplicate products. 54 FR 28891.

44/ Under 21 CFR § 10.85(d)(1), a statement of policy or interpretation made by FDA in any portion of a Federal Register notice other than the text of a proposed or final regulation is treated as an advisory opinion, unless the statement is subsequently repudiated by an agency or overruled in court. Of course, statements that are nominally FDA "advisory opinions" under this regulation cannot overrule provisions in an agency's statutory mandate. *United States v Articles of Drug . . . Promise Toothpaste*, 826 F. 2d 564, 571 (7th Cir. 1987) (*Promise Toothpaste*) (disregarding an FDA preamble statement at odds with other agency statements, as discussed in note 46, *infra*).

45/ *Id.* The agency went on to say that "Such applications may be for variations of approved drug products, or, rarely, for new chemical entities." Although § 314.54 might be said to cover the "variations of approved drug products," there is no FDA regulation on its criteria and requirements for its intent, "rarely," to apply 505(b)(2) to follow-on versions of new chemical entities.

46/ Nowhere in the preamble to the 1989 ANDA proposed ruledid FDA include an explanation of how this statement can be reconciled with the agency's long-standing interpretation that a "me-too"

industry officials reading the preamble may well have thought that the discussion related only to the paper NDA policy, the Parkman Letter as restated in proposed § 314.54, or both. In any event, as was recognized by the Court of Appeals in *United States v. Articles of Drug . . . Promise Toothpaste*, "deviation from the statutory and regulatory norm to which the agency has otherwise adhered hardly establishes an administrative policy or regulatory interpretation upon which appellants can rely." 826 F.2d at 571 (referring to an FDA statement in the preamble to a proposed rule that was at odds with its interpretation of the statute and regulations in the litigation).

FDA cannot grant itself authority beyond that which has been delegated by Congress.47/ To the extent that FDA believes that § 505(b)(2) is anything more than a statutory codification of its paper NDA policy, the provision is an impermissible delegation of authority in that it lacks a clear articulation of statutory standards for administrative decision-making. Plainly, Congress knows how to write a law that lays out the standards for new drug approvals. Section 505(b)(1) for full NDAs and § 505(j) for ANDAs are clear examples. Where we have (1) a clear articulation of decision-making standards in these related statutory provisions, (2) an utter lack of correspondingly clear substantive standards ("an intelligible principle") for decision-making in § 505(b)(2) (except in describing the application as one filed under (b)(1)), and (3) a legislative history which refers repeatedly to paper NDAs as the antecedent to § 505(b)(2), we have a situation where § 505(b)(2) may be unconstitutionally vague unless it is construed as the legislative embodiment of FDA's paper NDA policy.48/

In any case, the 1990 opinion of the U.S. Supreme Court in *Eli Lilly v. Medtronic, supra,* shows definitively that the Supreme Court viewed § 505(b)(2) as

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applicant cannot, under the law, rely upon the safety and efficacy data of another, except in the context of an ANDA or with the data owner's consent, *see United States v. State Farm Mutual Automobile Ins. Co.*, 463 U.S. 29, 43 (1983), despite the regularity with which the agency has defended this interpretation in court, including in the *American Critical Care, Upjohn, Burroughs-Wellcome* and *Tri-Bio* cases discussed in notes 30, 33-35 and accompanying text.

47/ *See supra* note 7.

48/ Congress may confer decision-making authority on agencies if it establishes by legislation an "intelligible principle" to which the agency must conform. *EPA v. American Trucking Ass'ns, Inc.*, 121 S.Ct. 903 (2001) (Scalia, J., *quoting J.W. Hampton, Jr. & Co. v. United States*, 276 U.S. 394, 409 (1928). Agency efforts to prescribe an intelligible principle that Congress had failed to supply would itself constitute an unlawful exercise of legislative power. 121 S.Ct. at 912. In sum, unless FDA respects the legislative history of § 505(b)(2), stating that it codifies the FDA paper NDA policy, § 505(b)(2) is an impermissibly vague statute.

referring to paper NDAs, characterizing these submissions as literature-supported applications. 497 U.S. at 676. There is no hint of the Court's adopting the "broader" interpretation mentioned in the FDA preamble several months before the Medtronic decision was argued. The Court's interpretation should be treated as definitive.

vi) Lack Of Adequate Notice Of Agency Plans For § 505(b)(2).

FDA's limited amendments to 21 CFR § 314.50, the existing rule on contents of NDAs, provided little guidance on 505(b)(2) applications.49/ A new proposed rule, § 314.54, did little more than codify the Parkman Letter, by setting forth several scenarios in which § 505(b)(2) applications could be submitted to obtain approval of product *modifications* for small molecule chemical drugs.50/ Beyond the discussion of the carefully defined provisions of § 314.54 — whose derivation stems from § 505(b)(1) and (j), and (except on patent certification) not (b)(2) — FDA has not articulated in regulations how it would use § 505(b)(2). FDA received *no* comment on proposed § 314.50 and only *two* comments on proposed § 314.54, neither concerning use of proprietary, unpublished data in the applications of other sponsors.51/ Had there been any clear and well-reasoned explanation in the 1989 proposed rule, or even in the 1992 final rule of how, outside the constraints of ANDAs including the "ANDA-plus" mechanism of the Parkman Letter, FDA intended to allow reliance upon a manufacturer's *non-public, proprietary* information for follow-on approvals, FDA surely would then have been bombarded with comments and other filings, comparable in volume and vehemence to the petitions and filings submitted to Dockets Management Branch in response to the 1999 Draft Guidance.

3) 1999 Draft Guidance Is A Radical Expansion Of § 505(b)(2).

The only FDA regulations that purport to implement 505(b)(2) are 21 CFR §§ 314.50(a)(2) and 314.54. Neither regulation is sufficiently broad in scope, or

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49/ 54 FR 28872, 28915.

50/ 54 FR 28892-3 (discussing relatively minor changes in products).

51/ 57 Fed. Reg. 17950, 28890-92 (Apr. 28, 1992). FDA characterized § 314.54 as "permit[ing] any person seeking approval of a drug product that represents a modification of a listed drug and for which investigations other than bioequivalence or bioavailability studies are essential to the approval of the change to submit a § 505(b)(2) application." Investigations showing bioequivalence or bioavailability are core features of ANDAs.

comprehensive in detail, to serve as an adequate regulatory precursor to the 1999 Draft Guidance.

Specifically, § 314.54 allows an applicant to submit a 505(b)(2) application for products originally intended for an ANDA under § 505(j), only if both of the following two conditions are met:

(1) the drug product "represents a modification of a listed drug (*e.g.* a new indication or a new dosage form) and
(2) for which investigations, other than bioavailability or bioequivalence studies, are essential to the approval of the changes."

21 CFR § 314.54(a). Thus, ANDA-plus applications under § 314.54 that do not represent a "modification" or "change" to a listed drug are not eligible for approval. The regulation is not drafted to allow products that are "slightly different from" a listed drug and need further investigation for approval of the "slight difference" to use the § 505(b)(2) process. Indeed, as is shown by the Parkman Letter, underlying § 314.54 is the bedrock foundation of drug sameness, with additional clinical studies to support the applicant's proposed modification or new indication. Both the term "modification" and the examples listed (new indication or new dosage) suggest that the difference from the listed drug must be quantifiable and can be tested in and of itself. Section 314.54 states that, "This application need contain only that information needed to support *the modification(s)* of the listed drug" (emphasis added). One would need to be able to isolate the change or modification to be able to submit information solely to support that change. These steps can be difficult, if not impossible, to achieve in the therapeutic protein drug development process.

In contrast to the lack of specificity *vis a vis* 505(b)(2) applications in § 314.50, and the narrow scope of § 314.54 on modifications, FDA's 1999 Draft Guidance was sweeping in scope. The 1999 Draft Guidance, if finalized, would go well beyond the regulation by suggesting that § 505(b)(2) applicants may rely not only "on literature," but also on "*an Agency finding of safety and/or effectiveness for an approved drug product.*" The Draft Guidance seems to permit *the agency* to rummage through its files for proprietary information underlying its findings of safety and effectiveness and then to use this information by "rely[ing] on [those] findings of safety and effectiveness for an approved drug to the extent such reliance would be permitted under [ANDAs]."52/ This, however, the agency cannot do. Such reliance by the agency on its own findings of safety and/or effectiveness is, of course, tantamount to reliance upon a pioneer's data in approving a follow-on application.

52/ 1999 Draft Guidance, *supra* note 3.

The Draft Guidance purports to provide "further information and amplification regarding FDA's regulations at 21 CFR § 314.54" and states that, "The requirements for 505(b)(1) and 505(b)(2) applications are stated at 21 CFR 314.50." In fact, § 314.50 says almost nothing about 505(b)(2) applications, and the scope of the Draft Guidance far exceeds that of § 314.50 and § 314.54. The Draft Guidance thus creates out of whole cloth what amounts to a new regulation on 505(b)(2) applications other than the "ANDA-plus" applications under § 314.54. While § 314.54 covers only limited modifications of approved drugs, the Draft Guidance covers an entire range of follow-on applications. While § 314.54 allows reliance on agency findings of safety and effectiveness only in the context of relatively modest product changes, the Draft Guidance allows follow-on applicants to enjoy wholesale reliance on FDA findings on pioneers' data. The scope of the Draft Guidance thus is considerably broader than that of the regulations it purports to interpret. The 1999 Draft Guidance is therefore itself a regulation that both goes beyond the agency's authority and is being promulgated without benefit of compliance with the Administrative Procedure Act (APA).

An administrative agency cannot through a rulemaking grant itself advance permission to adopt later, through procedurally deficient means, a new initiative outside the scope of the rulemaking notice.53/ Nor can it promulgate a rule describing one set of circumstances for product modifications (combining an ANDA and an NDA supplement into the ANDA-plus, a more convenient one-step process) but then go back and informally reinterpret the rule itself — or preamble statements seemingly ungrounded to regulatory text — to encompass situations outside the ambit of the original regulation.

Indeed, FDA's 1999 Draft Guidance essentially proposes to reinstate a variation of the enjoined provision from the original FDA version of the FDA paper NDA policy.54/ The Draft Guidance suggests that FDA can rely on its past approval of an innovator's product when reviewing an application submitted under § 505(b)(2), even where the applicant does not reference published literature and where the applicant does not meet § 505(j)'s "sameness" provisions. An approval on this basis would in principle be the same as an approval based on another applicant's summary data – the very policy FDA is enjoined from implementing due to its inconsistency with the law. *See American Critical Care, supra.*

53/ *See Appalachian Power Co. v. EPA*, 208 F.3d 1015, 1025 (D.C. Cir. 2000) (rejecting agency's argument that statements in preamble authorized subsequent adoption, without notice and comment rulemaking, of policy beyond the scope of previous rulemaking); *see also Sprint Corp. v. FCC*, 315 F.3d 369 (D.C. Cir. 2003) (describing scope of notice requirement).

54/ *See American Critical Care, supra* note 29 and accompanying text.

Considering Congress' clear intent to codify in § 505(b)(2) FDA's previous paper NDA policy, any inclusion in FDA's regulations or guidance implementing § 505(b)(2) of a provision enabling reliance upon innovators' data, or FDA findings of safety and efficacy, would be beyond the scope of the statute. Were the agency to go one step further and reinterpret the law as permitting the approval of a follow-on such as a recombinant therapeutic protein product approved under the FDCA, the agency clearly would exceed its authority and could even allow potentially harmful products to reach the public.

In short, the 1999 Draft Guidance (and the use of § 505(b)(2) in approving certain applications) goes far beyond what the Parkman Letter and the codified 1992 regulation contemplated. The 1999 Draft Guidance is a new proposed rule, issued in a procedurally inadequate way, and in many respects at odds with substantive law. In the case of recombinant hGH or human insulin, the applicant could *not* receive approval of an ANDA, because there would be no way to provide assurance to FDA that the active ingredient is sufficiently similar to be deemed the "same" for purposes of § 505(j). Thus, there is no lawful way that FDA can extend § 505(b)(2) to allow approval of an ANDA-plus application for a therapeutic protein.

2. FDA Must Hold a Meaningful Public Process On The Issue Of 505(b)(2) Applications.

BIO submits that FDA would benefit from a meaningful public participation process to permit submission of comments and views on the subject of 505(b)(2) applications. BIO believes that particular attention should be devoted to the questions of unauthorized use of the pioneer sponsor's undisclosed data (given the legal restraints on such use of data), as well as the significant scientific questions that exist concerning the adequacy of testing of therapeutic proteins to avoid public health concerns. BIO is concerned that FDA might decide to finalize the 1999 Draft Guidance without a meaningful public process, follow its policies without finalizing the Guidance, issue a product-specific guidance on human growth hormone or insulin, or, worse, approve a product without any further public process.

Policy-by-approval, like policy-by-guidance, undercuts the administrative procedures created by Congress in the APA, and by FDA in its administrative practices and procedure regulations, for thoughtful, deliberative, and prospective policy formulation in which all interested persons can fully participate.55/ Moreover, it is unlawful for FDA to proceed in this manner since

55/ *See supra* note 37. *See also infra* note 60 on the *Serono* case (illustrating the shortcomings of policy-by-approval and policy-by guidance).

substantive change involving a significant departure from long-standing policy must be accomplished through rulemaking.

Although FDA allowed comment on the 1999 Draft Guidance, and received petitions and comments from several concerned manufacturers, including numerous questions about its legal validity, the agency's public statements suggest a determination to proceed unilaterally. The confusion and uncertainty regarding FDA's activities in this area are disrupting the ability of innovative companies to make plans.

FDA must recognize that it does not possess the legal authority to proceed in this manner. To assist the agency in reaching this determination, it should commit to initiating and completing a meaningful public process on 505(b)(2) applications (notice, docket, public meetings, and consideration of comments). The agency presently has not established a legal or scientific basis for follow-on approvals of therapeutic proteins, under *any* of the statutes it administers.

The initial Federal Register notice should (1) lay out the legal, scientific, and policy basis that FDA believes would justify follow-ons for therapeutic proteins under any statute it administers; (2) invite comments on the quantity and quality of data required for 505(b)(2) applications; and (3) withdraw the 1999 Draft Guidance. The requested public participation process would enable the full vetting of the entire range of issues through adequate notice of the basis for the agency's action, creation of a docket, the holding of public meetings and other opportunities for structured and meaningful stakeholder participation, and publication of a final notice responding to comments. In analogous situations involving important and complex issues, FDA has successfully used a docket and request for comment process. *See, e.g.,* FDA, Request for comment on First Amendment Issues, 67 FR 34942 (May 16, 2002); FDA, Pharmaceutical Good Manufacturing Practices for the 21st Century: A Risk-Based Approach; Establishment of a Public Docket, 68 FR 9092 (Feb. 27, 2003).

The agency should also create a transparent timetable for the steps involved in the process, so that the public knows the agency's direction and the status of each step along the way. A notice-and-comment process and public meetings would allow essential input from members of the public who are intimately aware of the issues at hand. It also would ensure that the clarity and contours of the new interpretation are robustly discussed and well-defined, along with a clear explanation of how the new interpretation comports with the law.

Although the endpoint of the requested public participation process might be a decision by FDA to engage in rulemaking, what BIO is requesting at this

point is for FDA to create a process that includes the public in FDA's deliberations on 505(b)(2) applications, particularly as to therapeutic protein products such as insulin and human growth hormones that, for historical reasons only, are approved as new drugs, rather than licensed as biologics.

During the public process requested by this petition, there must be no approvals of follow-on therapeutic protein products regulated as new drugs under the FDCA (and certainly not of follow-on biologics, as discussed in the Appendix).

3. Changes In Long-standing Agency Interpretations May Be Achieved Only Through Rulemaking.

Two long-standing FDA policies, both reflecting underlying law, would be reversed by the approval of 505(b)(2) applications for therapeutic proteins through reliance on other manufacturers' proprietary data. First, FDA has long interpreted the safety and effectiveness requirements of the FDCA and its implementing regulations as satisfied only by full, original data on each unique therapeutic protein product approved as a new drug under the FDCA.56/ This interpretation is closely linked to the underlying science. Given the inherent uniqueness and complexity of therapeutic proteins, there is a necessity for manufacturer-specific clinical information.

Second, FDA has long interpreted the FDCA as not allowing reliance, without permission, by one manufacturer upon another's proprietary data, except

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56/ According to FDA, protein drug substances produced by recombinant DNA technology cannot be assumed to be the same as one another. For each product, a Notice of Claimed Exemption for an Investigational New Drug and a full Biologics License Application or New Drug Application is required. *See* Draft Points to Consider in the Production and Testing of New Drugs and Biologicals Produced by Recombinant DNA Technology at 3 (April 10, 1985) ("New license applications or new drug applications are required before marketing products made with recombinant DNA technology, even if the active ingredient in the product is thought to be identical in molecular structure to a naturally occurring substance or a previously approved product produced in an established manner,"); *id.* at 13 ("Clinical trials will be necessary for products derived from recombinant technology to evaluate their safety and efficacy."). This Points to Consider document is referenced in FDA's Final Statement of Policy for Regulating Biotechnology Products, 51 FR 23309, 23311 (June 26, 1986) ("The marketing of new drugs and biologics for human use, and new animal drugs, requires prior approval of an appropriate new drug application (NDA), biological product license, or new drug application (NADA)," at 23310; FDA, CBER, Supplement to the Points to Consider in the Production and Testing of New Drugs and Biologics Produced by Recombinant DNA Technology, Apr. 6, 1992 ("At present, it is believed that analytical data derived from either nucleic acid testing or protein structural testing alone do not allow for a complete evaluation of the identity and purity of a recombinant protein product," at 8), available at http://www.fda.gov/cber/gdlns/ptcsupdna.pdf. *See* note 70 (describing FDA's guidance document on how a manufacturer may, as to its own products, show product comparability following changes in manufacturing methods).

under the strict framework for § 505(j) ANDAs.57/ FDA could not, through a policy statement such as the original paper NDA policy (permitting reliance on published studies) or the 1999 Draft Guidance on § 505(b)(2) (permitting reliance on *another's* data), satisfy the legal requirements required to change such long-standing interpretations (a change that, in this case, can be achieved only through statute). The APA requires agencies such as FDA to promulgate only regulations and guidance that comport with their statutory mandates; they also must conduct notice-and-comment proceedings to change established agency interpretations of their rules and provide a reasoned analysis for the change, an analysis that may well go beyond what was required in establishing the initial interpretation.58/

Recently, the U.S. Court of Appeals for the District of Columbia Circuit held that an agency interpretation that "significantly revises" an agency's prior "definitive interpretation" of a regulation cannot be implemented except through notice-and-comment rulemaking, *Alaska Prof'l Hunters Assoc. v. Federal Aviation Administration*, 177 F.3d 1030, 1034 (D.C. Cir. 1999), and the agency must of course possess the authority to issue the regulation in question. As the court explained, when an agency revises its previous interpretation of a rule, it "in effect amend[s] its rule, something it may not accomplish without notice-and-comment." *Id.* at 1034. Put simply, "[w]hen an agency has given its regulation a definitive interpretation, and later significantly revises that interpretation," notice-and-comment proceedings are required. *Id.* Agency policy that becomes an "administrative departmental interpretation" necessarily rises to the level of *"administrative common law,"* requiring formal procedures for its amendment. *Id.* at 1035 (emphasis added).

Since *Alaska Professional Hunters*, courts have consistently held that agencies may not significantly alter their established interpretations of regulations without engaging in notice-and-comment proceedings. *See Shell Offshore Inc. v. Babbitt*, 238 F.3d 622, 629-30 (5th Cir. 2001) (significant departure from agency's "long established and consistent practice" requires notice-and-comment

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57/ *See* the government's brief in *Tri-Bio*, notes 34-35 and accompanying text; 21 CFR § 314.50(d) (requiring evidence of safety and effectiveness); Alan H. Kaplan, *Fifty Years of Drug Amendments Revisited: In Easy to Swallow Capsule Form*, 50 Food Drug L.J. 179, 188-89 (1995) (discussing FDA's belief that "essential preclinical and clinical data" submitted in an NDA is "proprietary" unless the product is one subject to a proper ANDA).

58/ *See supra* note 7. An agency may not "rel[y] on factors which Congress has not intended it to consider, entirely fail to consider an important aspect of the problem, offer an explanation for its decision that runs counter to the evidence before the agency, or is so implausible that it could not be ascribed to a difference in view or the product of agency expertise." *United States v. State Farm Mutual Automobile Ins. Co.*, 463 U.S. 29, 43 (1983) (*State Farm*).

rulemaking); *Iyengar v. Barnhart*, 233 F.Supp.2d 5, 13-15 (D.D.C. 2002) (same); *Torch Operating Co. v. Babbitt*, 172 F.Supp.2d 113, 124-28 (D.D.C. 2001) (same); *United States v. American Nat'l Can Co.*, 126 F.Supp.2d 521, 530 (N.D. Ill. 2000) (same); *cf. Sugar Cane Growers Coop. v. Veneman*, 289 F.3d 89, 95-96 (D.C. Cir. 2002) (agency announcement that imposed requirements affecting subsequent agency actions and having "future effects" on other parties is a rule subject to APA notice-and-comment requirements); *Tozzi v. United States Dep't of Health & Human Servs.*, 271 F.3d 301, 310-11 (D.C. Cir. 2001) (agency action that had "binding effect" is reviewable under APA). *See also Darrell Andrews Trucking, Inc. v. Federal Motor Carrier Safety Admin.*, 296 F.3d 1120, 1125 (D.C. Cir. 2002) (significant revisions of definitive agency interpretation require notice-and-comment rulemaking); *Air Transport Assoc. of America, Inc. v. FAA*, 291 F.3d 49, 56 (D.C. Cir. 2002) (same); *Assoc. of American Railroads v. Dep't of Transportation*, 198 F.3d 944, 947 (D.C. Cir. 1999) (same).59/

Whether therapeutic proteins have been regulated as new drugs under the FDCA or as biological products under the PHSA (*see* Appendix), a full complement of data has historically been required for each application. This was true before and after enactment of the Hatch-Waxman Amendments and holds true today.60/ FDA's long-standing, general *de facto* practice of demanding a full

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59/ *See also State Farm*, 463 U.S. at 43 (1983).

60/ As discussed in section C.5, *Serono Laboratories, Inc. v. Shalala*, 974 F.Supp. 29 (D.D.C. 1997), 158 F.3d 1313 (D.C. Cir. 1998), involved FDA's approval of Ferring Pharmaceuticals' follow-on generic menotropins product, an approval that many in the innovative industry find at odds with FDA's traditional approach. The precise meaning of the *Serono* decision is unclear. The decision was based on a limited record and dismissed before the full merits could be fully considered. Possibilities include that the case was (1) wrongly decided; (2) *sui generis* [in a class by itself]; (3) an exemplification of an unannounced FDA exception — to the long-standing agency administrative common law that a full complement of data is required for therapeutic protein products — allowing approvals of follow-on applications for this type of therapeutic protein products (menotropins); (4) an exemplification of an unannounced FDA exception — to the same administrative common law — that allows approvals of follow-on products that copy early versions, but perhaps not later versions derived from recombinant biotechnology; or (5) as the generic industry might have it, a precedent showing that any product can be a follow-on product, including even therapeutic protein products.

Confusing the significance of *Serono* as a precedent is that the decided case involved an effort by the pioneer to obtain equitable relief in which the court would decree that FDA must refrain from approving, or withdraw any approval of, the follow-on application. Another confusing feature of the approval is that the subject of the litigation was FDA's Jan. 30, 1997 approval under § 505(j) of an *ANDA* (#073599) for Ferring's drug Repronal (injectable menotropins), with the parties' briefs and the court's opinion focused on § 505(j). However, FDA approved the Ferring menotropins product as "Repronex" under § 505(b)(2). Letter from L. Rarick, FDA, to R. Nardi, Ferring (Aug. 27, 1999) (referring to NDA 21-047 dated Oct. 26, 1998 submitted pursuant to section 505(b)(2) for Repronex (menotropins for injection)), http://www.fda.gov/cder/foi/appletter/1999/21047ltr.pdf. In sum, the

complement of original data for biologically derived new drugs rises to the level of administrative common law that, if there is a statutory and factual basis for changing it at all, can be changed only through notice-and-comment rulemaking. Clearly, any decision by FDA to approve follow-on applications for therapeutic protein products relying on another's NDA data would be a reversal of two long-standing interpretations in violation of basic principles of administrative law. As a result, such action would be considered beyond the agency's legal authority, arbitrary and capricious, and an abuse of discretion in violation of the APA, 5 USC § 706(2)(A).

4. An Agency Cannot Avoid APA Requirements By Issuing Guidance Documents.

The Office of Management and Budget (OMB) recently cautioned agencies about the use of "guidance documents" to carry out programs that, as a matter of law, require notice-and-comment rulemaking:

> Through guidance documents, agencies sometimes have issued or extended their "real rules," *i.e.*, interpretative rules and policy statements, quickly and inexpensively — particularly with the use of the Internet — and without following procedures prescribed under statutes or Executive orders.61/

Likewise, the D.C. Circuit has often cautioned agencies against short-circuiting APA requirements. In *Appalachian Power Company v. EPA*, the court explained that an agency may not escape notice-and-comment requirements "by labeling a major substantive legal addition to a rule a mere interpretation." 208 F.3d 1015, 1024 (D.C. Cir. 2000). Instead, courts must look to whether "the interpretation itself carries the force and effect of law," *id.*, as evidenced by whether an agency treats the interpretation as "controlling in the field," "bases enforcement actions on the [interpretation]," or "leads private parties . . . to believe" that it will enforce the interpretation. *Id.* at 1021.

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meaning of *Serono* is unclear, and the decision serves principally as a caution about the drawbacks of an agency's use of individual licensing decisions to embark upon new directions. For example, the administrative record was incomplete, and Serono was permitted to see only part of it. As the *Serono* case illustrates and as was stated in the introductory section of this petition, policy-by-approval, like policy-by-guidance, undercuts the processes created by Congress for thoughtful, deliberative, and prospective policy formulation in which all interested persons can fully participate.

61/ *See Draft Report to Congress on the Costs and Benefits of Federal Regulations*, 67 FR 15014, 15034 (Mar. 28, 2002) (discussing *Appalachian Power Co. v. EPA*, 208 F.3d 1015 (D.C. Cir. 2000)). FDA's Chief Counsel has stated that the agency must "[employ] guidance where appropriate and promulgate rules where appropriate." The Pink Sheet, Apr. 29, 2002 at 22.

In other words, courts will look at how the agency in practice regards its statement to determine if it is a rule, as compared to a mere policy statement. If an agency statement "seek[s] to authoritatively answer an underlying policy or legal issue," as demonstrated by the agency's application and enforcement of the statement, it will be treated as a rule. *Tozzi v. United States Dep't of Health & Human Servs.*, 271 F.3d 301, 313 (D.C. Cir. 2001) (Silberman, J., concurring).

Most recently, the D.C. Circuit struck down a Federal Communications Commission order for failure to comply with APA notice requirements. *Sprint Corp. v. FCC*, 315 F.3d 369 (D.C. Cir. 2003). Distinguishing "mere policy statement[s], which 'lack[] the firmness of a [prescribed] standard,'" the *Sprint* court noted that "an agency's imposition of requirements that 'affect subsequent [agency] acts' and have a 'future effect' on a party" triggers APA notice-and-comment requirements. *Id.* at 373 (citing *Sugar Cane Growers Coop. v. Veneman*, 289 F.3d 89, 95-96 (D.C. Cir. 2002)). When new agency interpretations "change the rules of the game," so that parties shoulder increased significant burdens, "more than a clarification has occurred," and, therefore, APA notice-and-comment requirements apply. *Id.* at 374. "Although [an agency] must have flexibility to adjust a regulatory scheme as concerns and problems arise in an obviously complex and developing area, it must conform its conduct to the APA notice requirement." *Id.* at 377. "That [FDA's Import] Alert is entitled guidance by the agency does not mitigate the tone of the language that follows its title." *Bellarno Int'l, Ltd. v. FDA*, 678 F. Supp. 410 (E.D.N.Y. 1988).

The significance of these cases is clear: FDA cannot use guidance documents to announce its proposed interpretation as to use of proprietary data, to announce its intention to approve therapeutic protein products similar to biological products but historically regulated as new drugs under the FDCA, *or* to lay out eligibility standards for 505(b)(2) applications.62/

As the D.C. Circuit held in *General Electric Co. v. EPA*, a guidance document that would "[impose a] binding obligation . . . upon the [a]gency not to question an applicant's use" of a certain set of data, as a guidance approving follow-on biological products invariably would do, constitutes a legislative rule. 290 F.3d

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62/ FDA's 1999 Draft Guidance document, *supra* note 3 at III., listed "Naturally derived or recombinant active ingredient" as an example of a product suitable for a 505(b)(2) application (without acknowledging the scientific impossibility of showing "sameness" of "the active ingredient" in clinical investigations): " *Naturally derived or recombinant active ingredient.* An application for a drug product containing an active ingredient(s) derived from animal or botanical sources or recombinant technology where clinical investigations are necessary to show that the active ingredient is the same as an active ingredient in a listed drug."

377, 385 (D.C. Cir. 2002); *cf. Community Nutrition Inst. v. Young*, 818 F.2d 943, 949 (D.C. Cir. 1987). The intended effect of such a guidance document would be clear — an applicant could rely on another product's proprietary information for approval of its product — a policy that would represent a sea change in FDA's view of the legal and regulatory bases for approval, is inconsistent with the statute, and goes beyond the agency's regulations implementing § 505(b)(2) (21 CFR §§ 314.50, 314.54).

Such a drastic change would not only impose significant additional burdens on innovators whose proprietary information would be subject to use without any compensation, but very possibly would constitute a taking. BIO is particularly concerned with FDA's proposed assertion that, to approve follow-on products, the agency may rely on its findings as to the safety and effectiveness of other manufacturers' products, findings that in turn are based on proprietary data. In BIO's view, a meaningful public participation process would demonstrate to FDA that such a course of action is not legally permissible under the FDCA and the Takings Clause of the Fifth Amendment.63/

In *Ruckelshaus v. Monsanto*, 467 U.S. 986 (1984), the U.S. Supreme Court held that proprietary data submitted to an agency in support of an application to market a product constitutes a property interest that is protected by the Takings Clause of the Fifth Amendment. In reaching that conclusion, the Court stressed that the economic value of this type of property right lies in the competitive advantage that the owner enjoys by virtue of his exclusive access to, and use of, the data. If an agency were to use a company's proprietary information to evaluate or approve the applications of competitors, that action could effect a taking of the owner's property interest for which just compensation would be due. Applying that test here, FDA's use of proprietary information to evaluate or approve a follow-on product would require FDA to make payments of just compensation. As no statutory provision exists for such compensation, the Takings Clause bars FDA's use of one sponsor's data in support of another's application, except with the data owner's permission or in the context of ANDAs under § 505(j). *Tri-Bio v. United States*, 836 F.2d 135 (3d Cir. 1987). Only as to ANDAs has Congress altered the reasonable, investment-backed expectation of innovative sponsors that their data will not be used for approval of competing products. As to § 505(b)(2), Congress intended only to codify FDA's paper NDA policy and apply to it the patent

63/ The pending Pfizer-Pharmacia petition referenced in note 4 discusses this issue in more detail. *See also* 21 CFR §§ 20.21 and 20.61; *Anderson v. Dep't of Health and Human Services*, 907 F.2d 936 (10th Cir. 1990); *Tri-Bio v. United States*, 836 F.2d 135 (3d Cir. 1987); *Public Citizen Health Research Group v. FDA*, 704 F.2d 1280 (D.C. Cir. 1983); *Serono v. Shalala*, 35 F.Supp.2d 1 (D.D.C. 1999); *Public Citizen Health Research Group v. FDA*, 997 F.Supp. 56 (D.D.C. 1998).

certification process. The fact that Hatch-Waxman's ANDA provisions for duplicate drugs may have rendered largely unnecessary the § 505 (b)(2) statutory codification of the paper NDA policy did not justify the transfiguration of this provision into another form of application entirely.

The notice-and-comment process used for the 1999 Draft Guidance on 505(b)(2) — now part of Good Guidance Practices (GGPs)64/ — has not been a sufficiently robust administrative procedure for scientific, legal, and policy issues of this magnitude. The agency needs to conduct a much more comprehensive public participation process, consisting of not only a Federal Register notice laying out the agency's views and the legal and scientific justification therefore, but also the creation of a docket for interested persons to submit comments, public meetings, and agency response to comments received.

As a component of the public participation process, FDA should hold public meetings on these issues under the agency's procedural regulations, such as meetings under 21 CFR § 10.65(b), advisory committee meetings under 21 CFR Part 14, or public hearings under 21 CFR Part 15.65/

The contemplated process would be similar in many respects to rulemaking, in ensuring that the agency action is legally authorized, supported by an adequate scientific and public health policy basis in the administrative record, and issued only after ample opportunity for public participation.66/ Neither the safeguards of rulemaking nor the precepts of GGPs were present when the agency issued the 1999 Draft Guidance on 505(b)(2) applications, where virtually no explanation accompanied the document despite the presence of legal and scientific

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64/ § 701(h) of the FDCA, 21 USC § 371(h); 21 CFR § 10.115.

65/ *See also* § 903(b)(4) of the FDCA, 21 USC § 393(b)(4): " [FDA] shall, as determined to be appropriate by the Secretary, carry out [its mission] in consultation with experts in science, medicine, and public health, and in cooperation with consumers, users, manufacturers, importers, packers, distributors, and retailers of regulated products."

66/ The notice required by the APA "must disclose in detail the thinking that has animated the form of a proposed rule and the data upon which that rule is based". *Home Box Office v. FCC*, 567 F.2d 9, 35 (D.C. Cir. 1977). The APA's notice-and-comment procedures "are intended to assist judicial review as well as to provide fair treatment for persons affected by a rule." *Id.* Participation includes not only the right to comment, but also receipt of an agency response to significant comments in the preamble to a notice published at the close of the meaningful public participation process. *Cf. Asiana Airlines v. FAA*, 134 F.2d 393, 396 (D.C. Cir. 1998) ("The opportunity to comment is meaningless unless the agency responds to significant points raised by the public."); *United States v. Nova Scotia Food Products Corp.*, 568 F.2d 240 (2nd Cir. 1977).

issues of utmost complexity.67/ In no way did the bare-bones process followed in FDA's issuance of the 1999 Draft Guidance come close to the substantive and procedural safeguards that are cardinal principles of rulemaking proceedings and even of GGPs under the statutory provision enacted in 1997. Moreover, the petitions and comments filed subsequently on the 1999 Draft Guidance demonstrate such serious flaws in the document itself that FDA must abandon that document and start over with a meaningful process. GGPs do not assure that there will be any agency response to comments received, even as to the most significant category of guidance document.

FDA has consistently asserted that: (1) each application for approval of a therapeutic protein needs a full complement of original data and (2) FDA cannot rely on one manufacturer's data in support of another's application, except with permission or in the § 505(j) ANDA context. Considering the strong scientific, public health, legal and policy reasons why these long-standing interpretations should not be changed at all, BIO does not see how FDA could legally deviate from these views. The creation by FDA of a meaningful public participation process would provide the agency an opportunity to collect complete information on these complex and contentious issues and provide the public an effective means of participation.

5. No Case Law Authorizes Approval Of Follow-On Products Without A Full Complement Of Data.

Although two courts have rejected challenges by a manufacturer to an FDA decision allowing marketing of a competitor's complex product on the basis of something less than what previously had been required, *Serono Laboratories, Inc. v. Shalala*, 974 F. Supp. 29 (D.D.C. 1997), 158 F.3d 1313 (D.C. Cir. 1998) (*Serono*) and *Berlex*, no court has decided that FDA has authority to approve follow-on recombinant products under the FDCA or the PHSA.

In *Serono*, the Court of Appeals' decision was in the context of review of the district court's grant of the pioneer company's request for equitable relief to nullify FDA's decision to approve a generic version of Pergonal,® a non-recombinant hormone product regulated as a new drug, for historical reasons, under the FDCA. Reversing the district court, the Court of Appeals held that a review on the merits

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67/ *See* 21 CFR § 10.115(g)(ii) (requiring agency to publish notice of availability and draft guidance, but not scientific or legal bases for draft guidance); *id. at* § 10.115(g)(iv) (providing for agency review of public comments on certain types of guidance documents, but not requiring agency to respond to comments); *see also* 61 FR 9181 (March 7, 1996) (stating that, "[r]egardless of the [level of guidance], FDA would not be required to respond to each comment . . .").

of FDA's approval decision would likely be upheld and deferred to the agency's scientific determination that the active ingredients in Pergonal and the generic product were the "same" for the purposes of § 505(j).68/ The *Serono* decision focused on the propriety of FDA's findings under § 505(j) of the FDCA — not § 505(b)(2). The *Serono* case does not support the view that FDA may approve follow-on recombinant products under § 505(b)(2).69/

Berlex is a decision under the biological products provisions of the PHSA in which the court upheld FDA's decision to approve an Interferon beta recombinant product – Avonex® (BG9216) — on the basis of, among other things, a clinical study of a "comparable" Interferon beta product (BG9015). *Berlex Laboratories, Inc. v. FDA*, 942 F Supp. 19 (D.D.C. 1996). FDA's decision reflected an agency view that Biogen had satisfied the required steps for a manufacturer to demonstrate that changes to *its own* product are permissible under the PHSA.70/ Underlying the decision is the principle that product comparability can be assured if a manufacturer has legitimate access to trade secret data about the first product's manufacturing process and to the raw data in unpublished clinical study results — assuring both product safety and intellectual property protection. However, a wholly different scenario would be presented if a *different* manufacturer, lacking knowledge of the innovator's manufacturing process and other critical data, attempted to rely on such information without access to it, were to seek approval for a follow-on product that would, of necessity, be a *different product*.

68/ Serono had argued that the active ingredients were different because they contained different isoforms, and therefore the generic approval was unlawful under 21 USC § 355(j)(3)(C)(ii) and 21 CFR § 314.92(a)(1). The court upheld FDA's decision since (1) the generic applicant showed "chemical identity to the extent possible;" (2) FDA "guarantee[d] the greatest degree of sameness possible for this kind of product" by reducing natural batch-to-batch variation to the same degree as that found in the pioneer drug; and (3) FDA had relied on its earlier approval of another menotropins product in which head to-head clinical trials showed no differences in the efficacy and safety of the two products based on isoform variation. *Serono*, 158 F.3d at 1320-21.

69/ *See* Appendix to this petition (explaining why there cannot be follow-on products regulated under the PHSA). The *Serono* decision provides no support for a contrary view.

70/ According to an FDA guidance document, "when a biologics manufacturer institutes a change in *its* manufacturing process . . . it may not be necessary for the manufacturer to perform additional clinical studies to demonstrate that the resulting product is still safe, pure, and potent." (emphasis added). FDA, Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-Derived Products (Apr. 25, 1996) (available at www.fda.gov/cber/gdlns/comptest.pdf). Under the FDCA, as well as the PHSA, manufacturers may, *only as to their own products*, demonstrate that changes in manufacturing process have not affected the safety and effectiveness of the product without additional clinical studies.

Therefore, the limited holding of *Berlex* does not authorize the approval of follow-on biologics of different lineage. Although the Berlex decision was under the PHSA biological licensing provisions and not the FDCA, it is discussed here because its underlying rationale applies equally to decisions on therapeutic proteins regulated by FDA only under the FDCA. Follow-on approvals must be limited to analogous instances in which a manufacturer has legitimate access to trade secret data about the first product's manufacturing process and to the raw data in unpublished clinical study results, such that the comparability issue is "intra-manufacturer" not "inter-manufacturer."

6. The Science Does Not Support A Regulatory Change.

The current science is not adequate to assure the safety and effectiveness of any follow-on therapeutic proteins based on less than a full complement of original non-clinical and clinical data.71/ The inherent complexity and variability of these products require different and more stringent requirements for marketing approval than those governing smaller-molecule synthetic products. Similarly, there is no scientific basis for FDA to change its long-standing scientific policy that a full complement of non-clinical and clinical data is needed for approval of those therapeutic proteins that are regulated for historic reasons under the FDCA, particularly those products derived from recombinant DNA technology. A decision by FDA that such products may be marketed through follow-on approvals would not only reverse such long-standing policy, but present scientific and public health challenges as well.

The same issues arise as to biological products licensed under the PHSA and similar therapeutic protein products approved under the FDCA — grouped here under the names "therapeutic proteins" or "biologically derived products." No discernable scientific differences distinguish these two classes of products, regulated under different statutes for purely historical reasons.

Biologically derived products are vastly different from chemical drug products. Most fundamentally, biologically derived products are highly complex and generally large molecules derived from living organisms, while chemical drugs are typically smaller and synthesized. Biologically derived products are thus complex, heterogeneous mixtures without specifications in the classical chemical

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71/ Commissioner McClellan recently has recognized the inadequacy of the current science to support the approval of follow-on biologics. In his April 1, 2003, speech to FDLI, he noted that "a number of scientific hurdles must be overcome before sponsors could demonstrate the bioequivalence of more complex molecules," and that the approval of generic biologics would "require a lot more science." *See supra* note 14.

sense. Often, manufacturers do not know precisely which of the identified components constitutes the "active ingredient," and often it is the sum rather than the parts that is effective. Regulatory authorities cannot treat biologically derived and chemical drug products in the same manner for the purposes of approving follow-on products. In fact, there are substantial differences between biological products and other drug products, and any regulatory scheme allowing for biologically derived products must carefully consider these important distinctions.

The discussion that follows shows how these clinically meaningful differences manifest themselves, in illustrative examples of the challenges in this area.

a. Biologically Derived Protein Products Differ Significantly From Other Drug Products.

As is shown in the examples below, the active substances of biologically derived products, particularly recombinant products, generally are much larger and more complex than synthetic molecules, and a broad range of sizes exists within the class of recombinant biologically derived products.

Product	Comment	Molecular Weight (Dalton)	Number of Amino Acids
Propranolol	average size synthetic drug	259	NA
Calcitonin	relatively small recombinant product	4,500	32
Human growth hormone	regulated as new drug under FDCA	22,000	121
Factor VIII	large recombinant product	264,000	2332

The structure of a small synthetic molecule is relatively simple and it is, in general, correspondingly well-characterized. In contrast, even a relatively small-molecule biologically derived products is difficult, if not impossible, to characterize. Even with products from a single manufacturer it is possible, through small changes, to produce a dramatically different product, *e.g.*, the intentional alteration of Humulin® (insulin recombinant) that resulted in Humulog®.

Small changes in biologically derived products can thus cause concomitant changes in the highly complex three-dimensional structure. Changes may be based upon the amino acid sequence (primary structure), disulfide bonds (secondary structure), elaborate bending and folding of the protein chain (tertiary structure), and often assembly or aggregation of multiple chains (quarternary structure). Substitution of a single amino acid, or even small changes within an amino acid, can alter dramatically (and often have dramatically altered) the biological activity and immunogenicity of a protein. In addition, many, although not all, recombinant products are glycosylated (they have attached sugar or other, more complex carbohydrate molecules) and have multiple isoforms (shapes). They can form an array of various complexes among themselves and with other compounds in the mixture. The three-dimensional structure, degree and location of glycosylation, 72/ as well as the isoform profile, all are critical factors with regard to pharmacokinetic and pharmacodynamic profiles, biological activity, clinical efficacy, and clinical safety. This broad range of sizes and the diversity of structural features give rise to a significant number of structural variations within and among products. In addition, the biologically derived product is often a complex mixture of various forms of the protein, in contrast to what is usually a highly purified form for small molecule products.

b. The Manufacturing Process Can Determine The Characteristics Of A Biologically Derived Product.

In contrast to other drug products, biologically derived products' manufacturing processes involve numerous complicated steps based upon the production and secretion of the biologically active molecule by living cells or organisms, the responses of which are inherently variable. Product heterogeneity and contamination can result during any manufacturing step. The impurity profile and degree of protein aggregation can have significant impact on the clinical profile, and both depend critically on the manufacturing process. Biologically derived

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72/ Control of carbohydrates can have a marked effect on disease target specificity and efficacy. For example, Ceredase® is a modified version of the naturally occurring enzyme, glucocerebrosidase (GCR). Ceredase is approved for the treatment of Gaucher's disease, a rare genetic disorder in which a functional deficiency in GCR results in the accumulation of lipids in tissue macrophage cells. Both GCR and Ceredase contain the same 497 amino acids, but naturally occurring GCR is approximately 12% sugar while the modified Ceredase is approximately 6% sugar. That difference was enough to produce markedly different results in clinical trials, with GCR producing only modestly helpful results in one patient and with Ceredase demonstrating clinical efficacy in virtually every treated patient. *See* Copmann,T., et. al., *One Product, [One] Process, [One] Set of Specifications—A Proven Quality Paradigm for the Safety and Efficacy of Biologic Drugs*, BioPharm (March 2001) (*One Product, One Process*).

products are also very sensitive to physical conditions such as temperature, shear forces, enzymatic activity, and formulation changes.

The basic steps in manufacturing biologically derived products are:

1) Naturally sourced products: Some biologics manufacture uses plants, animals or isolated micro-organisms as the starting material. The active ingredient is isolated using biochemical techniques of various levels of sophistication, and there may or may not be an in vitro growth step. The key is that the source material for the subsequent isolation be available in sufficient quantities, with enough consistency and absence of contaminants, from which to reliably derive the biologic product. Various levels of "purification" are used to concentrate the components, which are then formulated into the product. *The key to a consistent final product is the use of the same source material, the same process and the same formulation, as well as consistent storage conditions.*

2) Development of a Host: A host cell is developed by isolating the DNA sequence that codes for the desired protein, selecting a vector to carry the gene and then inserting it into a suitable bacterial or eukaryotic cell or by fusion of a producer cell with a cell containing the desired DNA sequence. *The types of cells used, and exact sequence of genes used, determine the characteristics of the protein product.*

3) Establishment of a Cell Bank: A cell bank is then established using an iterative and elaborate cell screening and selection process yielding a unique master cell bank. *No two cell master cell banks are ever exactly alike.*

4) Production System: The "engineered" cells are then cultured on a large scale under growth conditions to optimize cellular production and secretion of the desired protein. This culture serves as the protein production system. *The vessels used, the components of the solution (e.g., nutrients, serum, growth factors, carbohydrates), the type of fermentation process used, and the physical conditions of the culture can affect the protein in ways that alter its eventual biological behavior in patients.*

5) Purification: Along with producing the desired protein, often in various forms, the cultured cells also produce undesired proteins and impurities. So, after culture, fractions containing the desired protein are harvested and isolated, and the undesired proteins and impurities are separated from the desired protein by a series of carefully selected and validated steps designed to optimize the purity and yield of the desired protein. Furthermore, as the protein may take an inappropriate form during production or purification, the purification process must assure that the final protein is in the desired form. *Any change in the purification process can*

alter the purity profile of the product and/or the mixture of forms of the active ingredient and affect its clinical efficacy and safety, including immunogenicity.

6) Analysis: During and after purification, the protein mixture must be analyzed to determine if it is uniform in terms of structure, character, and potency; and free of impurities and contaminants. Various analytical tools, including physiochemical and biological tests, are used to examine amino acid sequence, glycosylation patterns, protein aggregation, isoform profile, heterogeneity, strength and potency. It is not unusual to conduct several thousand analytical tests per single batch of product. Tests are conducted at multiple stages during product manufacture and form process controls crucial for consistency and confidence in the final product, and provide key data for regulatory assurance. *These tests have become more sophisticated and are critical, but they remain limited in their ability to detect all product variations that may affect clinical efficacy and safety.*

7) Formulation: The therapeutic protein is then formulated. As with all of the steps, *the components of the formulation and the process used can significantly affect the product, its stability, and its eventual behavior in patients.*

8) Distribution: Finally, the formulated product is stored, distributed and delivered to health care professionals and ultimately to patients. Like the bulk drug, the formulated product is extremely sensitive to environmental conditions such as temperature changes and must be stored carefully under conditions optimal for product integrity and stability over time. *Poor adherence to cold storage requirements could affect clinical efficacy and safety, including immunogenicity.*

This series of intricate steps — described above in simplified terms — produces a biologically derived protein product. Within each basic step are numerous smaller substeps that must be controlled and validated. *To ensure batch uniformity and reproducibility, changes in the steps must be modest and made in a conservative manner with extensive validation of comparability of the resultant product. Experienced personnel familiar with the subtle nuances and proclivities of the distinct process are essential for a consistent and productive operation.* If an ingredient or a processing step is changed for any reason, the *comparability*[73] of the product *before* and *after* the change must be demonstrated.

73/ The term *comparability* is used to describe the comparative evaluation of biologically derived products produced before and after introducing a manufacturing change. Extensive historical results from analytical and validation tests, are needed to ensure that the product produced *before* the change is comparable to that produced *after*. Physiochemical testing may suffice for minor changes in the process, whereas non-clinical and clinical studies may be needed for major changes. *This term "comparability" should not be applied to a comparison of an innovator's biologic product to another manufacturer's follow-on biologic product* because the second manufacturer will not have

These manufacturing features and realities represent the well-established and accepted challenges for all manufacturers of biologically derived products. Both the innovators and any would-be follow-on producers must be held to the same very high standards as to controls over product and process if the public is to be protected.

c. Therapeutic Protein Products Of Biological Origin May Elicit Immunogenic Responses That Can Affect Efficacy And Safety.

Unlike small synthetic molecules, all biologically derived products possess the potential for immunogenicity. For example, for vaccines immunogenicity is intended but still must be appropriate and predictable. Even small, and *sometimes undetectable*, changes in a biologic product can cause it to become more immunogenic in the patient. This immunogenicity causes the patient to produce antibodies that may inactivate a therapeutic protein resulting in *loss of efficacy and disease progression*, or may inactivate one of the body's naturally occurring proteins resulting in *side effects that can be severe*. In some cases, immunogenicity causes no measurable effects on efficacy or safety, while in other cases the effects can be severe. Factors that have been shown to influence protein product immunogenicity include: amino acid sequence variation, glycosylation, other host cell proteins, manufacturing-related contaminants and impurities, aggregate formation, formulation, deamidation, oxidation, and storage, route of administration, dose and length of treatment, and patient characteristics, while other factors remain unknown.74/

Examples of biologically derived products that have exhibited changes in immunogenicity include Factor VIII75/, interferon-alph76/, interferon-beta77/,

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access to the innovator's historical data nor to in-process and bulk product materials from the innovator, so a comparison of *before* and *after* is not relevant.

74/ Schellekens, H., Bioequivalence and the immunogenicity of biopharmaceuticals. *Nature Reviews* Vol. 1, June 2002.

75/ Jacquemin, M.G. and Saint-Remy, J.M.R., Factor VIII Immunogenicity. *Haemophilia* 4:552-557, 1998.

76/ Hochuli, E., Interferon immunogenicity: Technical evaluation of interferon-alpha 2a. *J. Interferon and Cytokine Res.* Supplement 1:S15-S21 (1997); Oberg, K., et al., Treatment of malignant carcinoid tumors with recombinant interferon alpha2b: development of neutralizing antibodies and possible loss of anti-tumor activity. *J. Natl. Cancer Inst.* 81:531-535, 1989.

interleukin-278/, erythropoietin79/, granulocyte macrophage colony stimulating Factor80/, growth hormone81/, calcitonin82/, denileukin-diftox83/, and megakaryocyte-derived growth factor84/.

For example, interferon-alfa is a biological product with an extensive marketing history. It stimulates antiviral, anti-proliferative and immunological activities and is used to treat a variety of carcinomas and viral diseases, including several forms of leukemia and chronic hepatitis C. One manufacturer has reported a multi-fold difference in potency, as well as a difference in immunogenicity (antibody production), among closely related interferon alpha subtypes.85/ After extensive investigation, it was found that the differences were likely due to a number of technical aspects related to formulation and storage conditions.

Similarly, recombinant human TNFR55-IgG1 fusion protein was under development for the treatment of rheumatoid arthritis, multiple sclerosis, and sepsis. Although the product was clinically active, the formation of antibodies in

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77/ Zang, Y.C.Q., Immunoregulation and blocking antibodies induced by interferon beta treatment in MS. *Neurology* 55:397-404, 2000.

78/ Prummer, O., Treatment-induced antibodies to interleukin-2. *Biotherapy* 10: 15-24, 1997.

79/ Casadevall, N., et al., Pure red cell aplasia and antierythropoietin antibodies in patients treated with recombinant erythropoietin, *New Eng. J. Med.* 346 (No. 7) 469-475, 2002.

80/ Ragnhammar, P. and Wadhwa, M., Neutralizing antibodies to granulocyte-macrophage colony stimulating factor (GM-CSF) in carcinoma patients following GM-CSF combination therapy. *Medical Oncology* 13:161-167, 1996.

81/ Grumbach, M.M., et al., The growth hormone cascade: progress and long term results of growth hormone treatment in hormone deficiency. *Horm. Res.* 49 Suppl. 2:41-57, 1998.

82/ Grauer, A., et al., Clinical significance of antibodies against calcitonin. *Exp. Clin. Endocrinol. Diabetes* 103(6):345-51, 1995.

83/ Olsen, E., et al., Pivotal phase III trial of two dose levels of denileukin diftitox for the treatment of cutaneous T-cell lymphoma. *J. Clin. Oncol.* 15:19(2):376-88, 2001.

84/ Zipkin, I., *Amgen Lays MGDF to Rest BioCentury: Bernstein Report on BioBusiness;* Sep 14, 1998 at A8.

85/ Bausch, J., Schering, Plough Research Institute, *Comparability of Biotech Products: Issues for Alpha Interferons,* Presentation, Washington, D.C. (Oct. 3, 2000).

the majority of patients hampered its use.86/ Recombinant human ciliary neurotrophic factor (rHCNTF) was shown to enhance the survival of motor neurons and was being developed for the treatment of amyotrophic lateral sclerosis, a severe motor neuron disease. More than 90% of the patients in early clinical testing developed antibodies. The lack of efficacy was believed to be attributable to immunogenicity.87/

More recently, an increase in immunogenicity has been observed with an epoetin-alpha product, and the cause is currently under scientific investigation by the manufacturer and regulatory authorities. During the last three years, there has been an increase in post-marketing reports of antibody-mediated pure red blood cell aplasia in patients with chronic renal failure after treatment with exogenous epoetin-alpha.88/ As a result of these serious reactions, many patients become dependent on blood transfusions, while others have been reported to recover with a variety of therapies. Before this incidence of immunogenicity, epoetin-alpha was considered to possess low immunogenic potential compared to other biologics.

Many questions about the immunogenicity of recombinant protein products await answers: "The factors triggering immune reactions against biotechnology-derived proteins are often not fully understood in individual cases."89/ Regulatory policy should not get out ahead of the relevant science.

d. Analytical Testing Methods Cannot Detect All Product Characteristics.

Because even small changes in a biologically derived product can have a significant impact on clinical outcome, all manufacturing processes must have extensively validated process controls, well-established reference standards at all stages, and definitive release specifications to ensure, to the degree possible with

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86/ Christen, U., et al., Immune response to a recombinant human TNFR55-IgG1 fusion protein: auto-antibodies in rheumatoid arthritis and multiple sclerosis have neither neutralizing nor agonist activities. *Hum. Immunol.* 60(9):774-90, 1999.

87/ ALS CNTF Treatment Study (ACTS) Phase I-II Study Group. A phase I study of recombinant human ciliary neurotrophic factor (rHCNTF) in patients with amyotrophic lateral sclerosis. *Clin. Neuropharmacol.* 18(6):515-32, 1995.

88/ Casadevall, N., et al., Pure red cell aplasia and antierythropoietin antibodies in patients treated with recombinant erythropoietin, *New Eng. J. Med.* 346 (No. 7) 469-475, 2002.

89/ *CPMP Note for Guidance on Comparability of Medicinal Products Containing Biotechnology-Derived Proteins and Drug Substances*, 30 Jul. 2002, sec. 5.1.

today's technology, that the product is *as safe and effective as the previously manufactured and clinically tested product.*

Although analytical tests have become more advanced and will always be critical in any manufacturing process, these tests remain limited in their ability to detect all product changes that may affect clinical efficacy and safety:

> Physiochemical assays may not fully characterize a product, may not discriminate all variants and impurities, and may change the product while testing. Bioassays may be imprecise, may not measure all activities, and may not measure a clinically important activity.90/

Biological assays of potency are critically important but rarely can be made precise enough to ensure that a new product has an activity level comparable to a predecessor. Furthermore, complex biological products frequently have multiple activities (*e.g.*, interferons as mentioned above) and not all may be identifiable or measurable in potency assays.

Examples abound of immunogenicity resulting in reduced efficacy or side effects with biologically derived products, even when the manufacturer is the same and analytical requirements have been met.91/ Current analytical methods do not always dependably predict the clinical properties of a biologically derived product when the manufacturer is unchanged and minor changes are made in the production process. Increasingly in such cases, FDA requires immunogenicity, pharmacokinetic, and/or other clinical data to validate the process change. So, the clinical outcome becomes even less predictable when the manufacturer is different — along with a different master cell bank, manufacturing process, analytical armamentarium, facilities, equipment and personnel.

Furthermore, a manufacturer of a follow-on biologically derived product will not have access to the innovator's historical data; key intermediates, including unformulated bulk protein; specifically designed or adapted reagents and analytical procedures; validation results; in-house standards; and experienced

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90/ Jay P. Siegel, then Director, Office of Therapeutics Research and Review, CBER, FDA, *Comparability of Biotechnology Derived Protein Products: Lessons from the US Experience,* DIA Meeting (Basel 2002).

91/ Schellekens, H., Bioequivalence and the immunogenicity of biopharmaceuticals. *Nature Reviews* Vol.1, June 2002.

personnel familiar with the subtle nuances and proclivities of the process.92/ In fact, the transfer of many of these analytical methods within a manufacturing company requires extensive training, close monitoring, and continuous trending to ensure that analytical drift between sites does not occur.

The argument that analytical methods and established release specifications would prevent unexpected clinical effects with a follow-on biologic is not sound. Analytical methods and specifications for a biologically derived product are based on historical data from a single manufacturing process and are linked to the demonstration of clinical safety and efficacy of the product made with that unique process. The analytical methods and specifications have meaning for only a single combination of process, product and test methods and cannot be transferred from innovator to another manufacturer.

A good example of the challenge in this area involves the conjugated estrogen product, Premarin,® a biologically derived pharmaceutical regulated as a new drug by CDER. Although Premarin has been on the market for 60 years and is not a recombinant product, synthetic generic versions of it are impracticable, according to FDA. After many years of considering the issue, the Director of CDER issued a decision that FDA would not approve an ANDA for a synthetic version of this product "as the reference drug Premarin is not adequately characterized at this time [and] the active ingredients of Premarin cannot now be definitively defined."93/ The agency explained that part of the difficulty in characterizing the active ingredients in Premarin stems from the fact that it is derived from natural sources: "Products such as Premarin, that are derived from natural source material, frequently are not characterized as completely as synthetic products at the time of marketing."94/ In particular, the recent studies demonstrating that a biological component of Premarin, previously not thought to contribute significantly to the drug's effectiveness, might have an important therapeutic effect "underscore[d] the lack of precise knowledge of the makeup of Premarin and the relative importance of its components, and therefore the lack of a standard on which

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92/ *See* Copmann, T., et. al., *One Product, One Process* at 3 (finding that there is "clearly" no way to establish comparability for generic biologics because the generic biological manufacturer will "have a totally different 'living' host or vector system, manufacturing processes, facilities and equipment, and analytical armamentarium").

93/ Memorandum, Director, CDER to Director, Office of Generic Drugs (May 5, 1997), at 1 ("Premarin Memorandum") available at www.fda.gov/cder/news/celetterjw.htm.

94/ *Id.* at 12.

to evaluate a generic copy."95/ In sum, the agency's experience with generic Premarin demonstrates, that even as to non-recombinant biologically derived products, determining the composition of products derived from natural sources is complex, and often any determination will change as the science evolves. "As with any such complicated scientific issue, differences in scientific opinion arose and continue to exist concerning how available data are to be interpreted and applied in the regulatory context."96/

Today, unpredictable changes in a product's safety profile (*i.e.*, changes in pharmacokinetics, pharmacodynamic efficacy and safety, including immunogenicity) due to manufacturing changes present major dilemmas for developers of biologically derived products. There is no validated laboratory or pre-clinical test system that can be used to predict whether a molecule produced by a new process will or will not result in adverse clinical consequences.

Science must drive the issue whether follow-on biologics are safe. Relatively simple modifications to the manufacturing process of a biologically derived product can alter the clinical profile of the product, causing it to be more or less effective or to result in more or fewer side effects. The potential for altering the clinical profile exists even when the manufacturer remains the same and the product passes analytical tests. It is therefore not surprising *that a follow-on biologically derived product made by another manufacturer using its own distinct manufacturing process would likely produce a different product with its own clinical and side effect profile.* That is, a follow-on biologically derived product — including a therapeutic protein regulated as a new drug under the FDCA — can be *fundamentally different* from the innovator product it purports to copy.

95/ FDA Statement on Generic Premarin, (May 5, 1997) (available at www.fda.gov/cder/news/cepressrelease.htm). Furthermore, the finding that the component, DHES, that could have such a significant effect was, according to the agency, "completely unexpected and illustrate[d] the long-standing inadequate characterization of Premarin." FDA Backgrounder on Conjugated Estrogens at 2 (available at www.fda.gov/cder/news/cebackground.htm). In its May 1997 announcement that it would not approve any ANDAs for Premarin, CDER acknowledged that "[b]ased on new scientific information" and "improved techniques for compositional analysis," it was reversing its position on the composition of Premarin and could "no longer support the position taken in the current USP monograph" for the drug. Synthetic Conjugated Estrogens: Questions and Answers at 3, May 5, 1997 (available at www.fda.gov/cder/news/ceqa.htm).

96/ Premarin Memo at 7. FDA subsequently approved a 505(b)(2) application for certain estrogen products on the basis that all but one of the amino acids thought to be relevant to the drug's action had been demonstrated to be the same.

In light of the inherent complexity of biologically derived products, and the susceptibility of such products to change, scientists and regulatory authorities do not fully understand what to test for, when considering the comparability of products from different manufacturers, much less follow-on products. Until science advances, there are more sophisticated analytical methods to detect all product changes, and there is enhanced understanding of the impact of product changes on clinical outcome, testing requirements must be extensive and further developed in order to assure the safety and efficacy — including consistent quality — of follow-on therapeutic proteins. At a minimum, extensive non-clinical testing and clinical trials involving follow-on therapeutic protein products are essential to ensure that products perform as intended and without serious and unexpected adverse effects. These test requirements should be clear and distinct for the wide variety of therapeutic proteins — whether complex biological products or similarly complex therapeutic proteins historically regulated as new drugs. As discussed above, FDA's process for developing these standards must allow ample scientific discussion and debate.

For the above reasons, an application — such as an ANDA or a 505(b)(2) application — based on less than a full complement of original data cannot possibly show the safety and efficacy of inherently variable products such as therapeutic proteins. Rather, scientific understanding of such products is not to the point where truncated applications, such as ANDAs and 505(b)(2) applications, offer sufficient information about these products. Therefore, regulators typically demand full applications for them, *i.e.*, in the United States, BLAs or full NDAs under § 505(b)(1).97/ Full applications for such products are a well-established, general regulatory practice, supported by what is known about the significance of small, sometimes undetectable differences among seemingly similar biologically derived therapeutic protein products.

In the end, science must drive the critical question whether a follow-on therapeutic protein product is safe and effective for use in this country.

97/ It is noteworthy that, in the European Union (EU), where no legal distinction is made between "drugs" and "biologics" (all are "medicinal products") and where no legal barrier forbids approvals of abridged marketing authorization applications, in practice the EU has never approved the equivalent of an ANDA or a § 505(b)(2) application for a biotechnology medicinal product. Experience in the EU thus confirms that "generic" approval processes are inappropriate for such a product. R. Kingham, European Experience with Second-Entrant Biotechnology Products (Oct. 18, 2002) (an exhibit to this petition).

7. A Meaningful Public Participation Process Would Give The Public An Opportunity To Help FDA Answer Relevant And Difficult Questions.

The 1999 Draft Guidance is now over three years old. It appears that FDA is wrestling internally with defining the contours and boundaries of a proper 505(b)(2) application. The public should be allowed to be part of this process. FDA champions guidance documents as allowing the agency and regulated industry greater flexibility, and no doubt such documents can at times be more easily prepared, cleared, and published than proposed and final rules. However, in choosing guidance rather than rules, an agency must neither cut out the public nor violate the law.

Guidance documents, even if labeled as non-binding and intended as aids to industry, are highly influential. They can have the effect of creating substantial pressure to follow the "guidance." Accordingly, any agency decision to use guidance for a significant and complex issue should not forego the administrative safeguards of a rulemaking process and should be reserved for situations where the agency is adding technical details to a regulatory framework that already has been created though a notice-and-comment rulemaking process. Draft guidance needs to be accompanied by adequate explanation, cannot be used for initial announcements of new policies, and certainly cannot be used to make changes in laws or in long-standing interpretations of regulations.

With all due respect for the agency's desire for the flexibility that guidance documents may offer, that flexibility cannot be at the expense of the safeguards to ensure administrative accountability enshrined in legal requirements discussed in this petition, *i.e.*, the APA, FDCA, and takings clause of the Fifth Amendment. If the agency articulates its policy on 505(b)(2) applications through a guidance document, it still would shoulder the burden of developing standards that are scientifically sound, protective of public health, legally supported, and procedurally fair.

What is missing from the guidance process, as it is being carried out in this case, is the public. Neither the 1999 Draft Guidance itself, nor the agency's GGP process, would meet APA requirements. A robust discussion of the issue through a meaningful public participation process by parties acutely aware of the characteristics of the products in question — because they develop and manufacture them — could only aid the agency in formulating sound policy.98/

98/ Input from industry participants is of particular importance in areas, such as this, that involve scientific complexity. *See generally United States v. Bioclinical Systems, Inc.*, 666 F. Supp.

As part of the Federal Register notice that inaugurates the public participation process, FDA should discuss the following questions and seek comments from the public on these issues, among others:

1. What is the intended scope of § 505(b)(2)?

2. Does § 505(b)(2) have a broader applicability than the pre-Hatch-Waxman paper NDA? If so, what are the other situations that it covers and how can FDA articulate in its regulations this additional coverage?

3. Considering the 505(b)(2) applications that FDA has approved since the Hatch-Waxman Amendments became law, what are the principles underlying such approvals that should be described in FDA regulations?

4. What authority does FDA have to construe § 505(b)(2) as enabling the agency to rely upon a prior agency finding of safety and effectiveness of another sponsor's drug, if the effect of this approach is to allow use of unpublished proprietary data, without permission?

5. If FDA believes that it has authority to construe § 505(b)(2) to allow reliance, how is such an approach squared with the new drug provisions, as longstanding interpretation of the statute's new drug provisions and the specific legislative action on this point under Hatch-Waxman do not allow one manufacturer to rely on another's unpublished proprietary data, except as permitted for ANDAs? Would not such an approach constitute an unconstitutional regulatory taking?

6. Are there any steps an innovative manufacturer can take to guard against such unintended reliance?

7. What internal mechanisms does FDA employ to ensure that its review staff do not rely improperly, as to subsequent applicants, upon innovators' proprietary data *or* agency findings of safety and effectiveness based on proprietary data?

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82 (D. Md. 1987) (holding that FDA could not unilaterally adopt a new technically-laden compliance standard, but instead, that notice-and-comment procedures should be used to "resolve an issue of [that] magnitude"). These types of agency decisions are most likely to benefit from broad participation by those with specialized expertise, including industry and academia. *See* § 903(b)(4) of the FDCA, 21 USC § 393(b)(4).

8. How can FDA assure the public that it will be adequately protected if the follow-on manufacturer is not required to submit the full complement of data that ordinarily must accompany full NDAs?

9. Does not the history of FDA's long, and ultimately failed, effort to permit ANDAs for drugs purported to be the same as Premarin® show the difficulty of follow-on approvals of biologically derived products, even if regulated as a new drug under the FDCA for 60 years and even if non-recombinant?

10. Considering FDA's many responsibilities and priorities, is it good use of scarce public resources for FDA to expend countless hours trying to craft regulatory short-cuts for generic or follow-on applicants, instead of looking to applicants to carry the burden of persuasion assigned them under the statute?

11. Should therapeutic proteins, regulated as new drugs under the FDCA for historical reasons, simply be excluded from eligibility for follow-on approvals, in view of the complex scientific issues presented in this petition?

12. Should products derived from recombinant DNA technology be excluded from eligibility for follow-on approvals? Has scientific understanding of how to assure inter-manufacturer comparability of conventionally derived versions of therapeutic proteins advanced to the stage that FDA could accept follow-on applications containing less than a full complement of data and information?

13. As to therapeutic proteins, particularly recombinant products, how can anything less than a full complement of original data assure product safety and effectiveness?

14. Considering FDA's frequent statements about the difficulty (or impossibility) of assuring comparability of biopharmaceuticals from two different manufacturers, how can there be follow-on approvals of such products considering that the information relied on — whether in the published literature or other sources — may have no bearing on the follow-on manufacturer's product?

15. How can we be sure that a move to allow follow-on applications for therapeutic protein products, and particularly recombinant versions of such products, will not be followed by sharply rising immunogenicity due to insufficient testing of the follow-on products?

16. Does it make sense for FDA to invest scarce governmental scientific resources in the production of guidance documents aimed at facilitating

follow-on approvals of products acknowledged to present such difficult scientific challenges?

17. Should not the agency instead invest those resources into developing proposed regulations on the criteria for, and quantity and quality of data and information required in, NDAs for therapeutic proteins — and look to each manufacturer to assure through a full complement of original data that its products meet these requirements? Should not the agency focus its § 505(b)(2) rulemaking on products other than therapeutic proteins?

18. Is not there a need for separate guidance documents — each issued through a meaningful public participation process — on the criteria and data and information requirements for *each* category of drugs that FDA finds eligible for a 505(b)(2) application?

19. Given the long-standing interpretation that FDA may not allow a sponsor to rely upon data in another sponsor's application, how can FDA consider an administrative policy change, when industry believes such action both legally impermissible under the FDCA (except as to ANDAs under § 505(j)) in the absence of a law amending the FDCA and providing for compensation as required by the Takings Clause of the Fifth Amendment?

These and other questions should be raised and answered in a public participation process in response to this petition.

8. BIO Requests That FDA Withdraw The Draft Guidance On 505(b) Applications.

BIO requests that FDA withdraw the document, "Draft Guidance for Industry: Applications Covered by Section 505(b)(2)99/ as this document needs to be revised in light of this petition as well as earlier petitions and comments.100/ Moreover, applicable administrative law dictates that the agency actions contemplated in this Draft Guidance document be handled through rulemaking. BIO requests that any FDA public participation process in response to the instant petition also consider the issues raised by the 1999 Draft Guidance comments filed

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99/ *See supra* note 3.

100/ *See supra* note 4 on Citizen Petition of Pfizer and Pharmacia (July 27, 2001) (Docket No. 01P-0323) and comments thereon as described in that note.

with the agency on the Draft Guidance, the issues raised in earlier citizen petitions and comments,101/ and this BIO petition.

In addition, withdrawal of the Draft Guidance is necessary if FDA is to comply with the Data Quality Act of 2001, which requires each Federal agency to "establish administrative mechanisms allowing affected persons to seek and obtain correction of information maintained and disseminated by the agency that does not comply with the required "guidelines ensuring and maximizing the quality, objectivity, utility, and integrity of information...disseminated by the agency."102/ BIO believes that FDA's 1999 Guidance document fails to meet the statutory, departmental,103/ or agency104/ standards for information quality and therefore needs to be withdrawn for it to be "corrected" under the Data Quality Act.

In implementing the Data Quality Act, FDA has stated that the agency "develop[s] regulations and guidance documents to help ensure that the data submitted to us result from the best available studies, that the studies are conducted in accordance with sound and objective scientific practices, and that the data are collected using scientifically accepted methods."105/ These laudable data quality standards are not met in the case of the 1999 Draft Guidance, particularly as it would relate to follow-on approvals of therapeutic proteins, insofar as FDA appears to contemplate approval of difficult-to-produce products without manufacturers' submitting a full complement of data. Under OMB and Department of Health and Human Services policies implementing the Data Quality Act, where

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101/ *See id.*

102/ Pub. L. No. 106-554, 114 Stat. 2763 (2001) § 515. FDA's guidelines implementing this law are found at http://www.hhs.gov/infoquality/fda.html.

103/ Department of Health and Human Services (HHS), Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated to the Public (HHS Guidelines). http://www.hhs.gov/infoquality/part1.html.

104/ FDA, Guidelines for Ensuring the Quality of Information Disseminated to the Public (FDA Information Quality Guidelines). http://www.hhs.gov/infoquality/fda.html.

105/ *Id.* FDA Information Quality Guidelines, at 9. FDA states that "FDA regulations specify the format and content of the clinical studies that are submitted in support of an application to market a new drug product. They specify how the data are to be collected and the types of analyses that are to be performed." *Id.* This FDA statement is true as to full NDAs under 505(b)(1) of the FDCA yet, as to 505(b)(2) applications, the agency has proposed, through a mere GGP process rather than a rulemaking proceeding, to grant competitors a much easier route to market. This proposed approach is inconsistent with the principle that agency decisions need to be based on high quality information.

documents are highly influential, *i.e.*, "the agency can reasonably determine that dissemination of the information will have or does have a clear and substantial impact on important public policies or important private sector decisions," an agency is obliged to provide "a high degree of transparency"106/ as to how it arrived at the information in question. Clearly, FDA regulations and guidance relating to product approvals are highly influential and the agency must offer a "high degree of transparency" as to their issuance.

The 1999 Draft Guidance falls far short of the expectations of the Data Quality Act. The agency has not provided the legal, scientific, and policy basis underlying the information in this document, nor has it met APA requirements.

BIO may in the future file a request for a correction of the 1999 Draft Guidance under § 515 (b)(2)(A) of the Data Quality Act. The purpose of such a correction would be to seek withdrawal of the 1999 Draft Guidance as not meeting the requisite standards under this statute and the implementing guidelines. A decision by FDA to withdraw that guidance would make it unnecessary for BIO to file such a correction request.

9. BIO Requests That FDA Refrain From Issuing Any Guidance Describing The Requirements For Approval Of A Specific Class Of Therapeutic Protein Under § 505(b)(2).

In particular, BIO requests that FDA refrain from preparing, publishing, circulating or issuing any new guidance for industry, whether in draft or final form, concerning follow-on applications filed under § 505(b)(2) seeking approval of therapeutic proteins, particularly human growth hormone or insulin. Informal public statements by some FDA officials have indicated that the Agency has drafted guidance documents describing in detail the amount and type of data it would require for approval of follow-on versions of recombinant human growth hormone and insulin. Because FDA does not possess the authority to approve a product in this class through the § 505(b)(2) pathway, dissemination of such a guidance, even in draft format, would be contrary to law.

106/ OMB guidelines at www.omb.gov; HHS Guidelines, note 79, at 5-6.

D. ENVIRONMENTAL IMPACT

The actions requested in this petition are subject to categorical exclusions under 21 CFR §§ 25.30 and 25.31. To the best of our knowledge, they cannot be expected to have any impact on the environment.

E. ECONOMIC IMPACT

Information about the petition's economic impact will be submitted on request of the Commissioner.

F. CONCLUSION

BIO petitions FDA to conduct and complete a meaningful public process that includes a Federal Register notice, creation of a docket for the notice-and-comment process, public meetings, and formal responses to comments. BIO also petitions FDA to refrain from approving any therapeutic protein products under § 505 of the FDCA based on applications that do not contain a full complement of original non-clinical and clinical data and rely on any data or information contained in another applicant's application.

What would be enormously injurious to patients and the innovative industry would be a decision by FDA to approve follow-on applications, including 505(b)(2) applications, for therapeutic proteins based upon less than a full complement of non-clinical and clinical studies — and using an innovator's proprietary information without a right of reference. This scenario is particularly of concern when one considers the scientific and public health concerns at stake, such as the inherent heterogeneity, variability and in some cases potential immunogenicity of these products (*see* C.6.c). Also, there has so far been a complete lack of any meaningful opportunity for participation in this vitally important area of agency scientific and regulatory policy formulation.

BIO and its members believe that there are substantial legal issues concerning FDA's authority to relax long-established approval standards through administrative action, and we would point out that such action would appear to constitute a regulatory taking. More importantly, the paramount issue of patient safety must be addressed, no matter what direction the agency takes.

G. CERTIFICATION

The undersigned certifies, that, on knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,

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Attachments

cc : Daniel E. Troy, Office of Chief Counsel

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APPENDIX:

BIOLOGICAL PRODUCTS UNDER THE PUBLIC HEALTH SERVICE ACT:

FOLLOW-ON PRODUCTS ARE NOT PERMITTED

This appendix discusses why biological products licensed under the Public Health Service Act (PHSA) are ineligible for follow-on applications.

1. Science Demonstrates That Follow-On Applications Are Inadequate For Biologic Products.

As fully discussed in BIO's citizen petition at C.6., therapeutic protein products differ significantly from non-biologic products with regard to size, complexity, heterogeneity, as well as sensitivity to changes in the manufacturing process. It is well known that a change in biologic manufacturing process can change the product in a way that increases its immunogenicity and results in reduced efficacy or increased side effects. *See* Petition at C.6.c. The relationship between product changes and immunogenicity is not fully understood. Furthermore, currently available analytical methods are often inadequate to detect all product changes. There are many examples of biologic products that have developed immunogenicity sometimes without an understanding of the cause. Given the complexity and numerous unanswered questions surrounding the development of biologic products, a follow-on approval system for these products is clearly inadequate.

2. FDA Has Long Taken The Position That Each BLA Must Be Supported By A Full Complement Of Non-clinical and Clinical Data.

The statute supports the agency's long-established position. The statutory approval standard has been substantively unchanged for a century. Biological products are regulated under a 1902 statute,107/ now § 351 of the PHSA, 42 USC § 262.108/ A biological product manufacturer must obtain FDA's premarket approval of a license. FDA approves a license only upon a demonstration that

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107/ S. Rep. No. 1980, 57th Cong., 1st Sess. 2 (1902). Manufacturers could ship products only from establishments that were licensed and subject to inspection. Product licenses were inaugurated later.

108/ In 1944, the biologics control provision was revised and incorporated into a larger set of statutes governing the authority of the Public Health Service. Pub. L. No. 85-410, 58 Stat. 702 (1944); § 351 of the PHSA, 42 USC § 262. From 1944 until 1997, the PHSA required approval of both

> (I) the biological product that is the subject of the application is safe, pure, and potent; and
>
> (II) the facility in which the biological product is manufactured, processed, packed, or held meets standards designed to assure that the product continues to be safe, pure and potent . . .

42 USC § 262(a)(2)(B). Through a century of federal biologics regulation, the consistent theme has been the key importance of the source materials and manufacturing process to the safety, purity, and potency of the finished product.

FDA's biologics regulation supports the agency's long-established position. To obtain a Biologics License Application (BLA), a manufacturer "shall submit data derived from non-clinical laboratory and clinical studies which demonstrate that the manufactured product meets prescribed standards of safety, purity, and potency." 21 CFR § 601.2(a). The agency's long-standing interpretation of this regulation is that the required data must be submitted for *each* biological product.

FDA's three-decades-old FOIA policy supports this position. In 1974, the agency explained that all biological products require clinical testing to demonstrate safety, purity, potency and effectiveness before licensing, "regardless whether other versions of the same product are already marketed or standards for the product have been adopted by rulemaking."109/ As FDA elaborated, specific clinical testing of each and every biological product is required because "all

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an Establishment License Application and a Product License Application for each product – reflecting the importance of the manufacturing facility to the safety, purity and potency of the product. Although the Food and Drug Administration Modernization Act of 1997 (FDAMA) amended the PHSA to require a single license, the BLA, the statute continues to emphasize both the product and the manufacturing facility. Pub. L. No. 105-115 (1997).

109/ 39 FR 44602, 44641 (Dec. 24, 1974) (preamble to FDA's final regulations implementing the Freedom of Information Act, or FOIA). Upon approving a BLA, FDA releases full safety and effectiveness data to the public immediately. 21 CFR § 601.51. Safety and effectiveness data for a biological product do not constitute confidential commercial information for the simple reason that every producer must develop and submit its own non-clinical and clinical data showing safety, purity and potency. In contrast, safety and effectiveness data contained in NDAs are treated as confidential commercial information and are not released in full until a pioneer drug becomes eligible for generic competition or until an NDA is abandoned by a sponsor. *Compare* 21 CFR § 601.51(e) (requiring disclosure of all safety and effectiveness data in an approved BLA) *with* 21 CFR § 314.430(e)(2) *and* (f) (requiring disclosure of a summary of safety and effectiveness data relating to an approved NDA). Of course, trade secret methods and processes in both NDAs and BLAs are exempt from disclosure. § 301(j), FDCA, 21 USC § 331(j); 21 CFR § 20.61.

biological products are to some extent different and thus must be separately proven safe, pure, potent, and effective. . . . There is no such thing as a 'me-too' biologic." *Id.* The context of this statement was a rulemaking by FDA to implement the Freedom of Information Act (FOIA), which generally requires agencies to disclose records unless, among other things, disclosure would cause competitive harm. 5 USC § 552(b)(4). In deciding to release safety and effectiveness information on biological products, FDA found that no harm would occur since, in contrast to new drugs, a competitor could not use the data under the PHSA to gain approval of its product but would have to conduct its own tests.

Subsequent agency statements reaffirm its traditional view. After both the 1984 Hatch-Waxman Amendments110/ and the 1997 Food and Drug Administration Modernization Act (FDAMA)111/ FDA affirmed that nothing in these laws changed its views on how biological products would be approved under the PHSA. Shortly after the 1984 amendments, FDA advised Congress that biological products are not subject to approval under Title I of the amendments112/ and, in its 1992 regulations implementing Hatch-Waxman, the agency reiterated its position that the new ANDA procedures for duplicate versions of drugs are "inapplicable to . . . biological drug products licensed under 42 USC § 262."113/ More recently, in connection with an effort to clarify a FDAMA provision addressing the relationship between the FDCA and the PHSA as to products subject to both laws, FDA once again declared that biological products are not subject to approval under Title I of Hatch-Waxman.114/

110/ Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417 (1984).

111/ Pub. L. No. 105-115 (1997).

112/ Letter from H. Meyer, Director, Center for Drugs and Biologics, FDA (Nov. 16, 1984): "There is no specific provision in Title I that includes . . . biologicals . . . . The Act refers to generic versions of those drugs originally approved under section 505(b) . . . of the Federal Food, Drug and Cosmetic Act. Biologicals are approved under the Public Health Service Act . . . . Accordingly, we do not consider these products to be covered by Title I." More recently, at a 1999 Advisory Committee Meeting, Basil Golding, Director of Plasma Derivatives in CBER's Division of Hematology, elaborated on the scientific reasons for FDA's rejection of abbreviated approval routes for biologics. "[V]ariations in the [manufacturing] process can have far-reaching effects on both safety and efficacy [so] . . . each product should be regarded as unique, and immune globulins should not be treated as a single generic biologic. In fact, there are no biologics that are considered generic." Blood Products Advisory Committee, 62nd Meeting, Day 2, transcript at 18 (Mar. 26, 1999).

113/ *See* 57 FR 17950, 17951 (Apr. 28, 1992).

114/ *See also* The Pink Sheet, *In Brief: FDA Modernization Act* (Dec. 8, 1997) (discussing post-FDAMA exchange of letters between Senators J. Jeffords and E. Kennedy and FDA, which expressed concern that FDAMA not be construed as permitting generic biologics); and D. Thompson, Assoc.

3. Approval Of Follow-On Biologics Under The PHSA Or The FDCA Is Contrary To Congressional Intent.

For almost a century, Congress has maintained separate approval schemes for biological products and drugs, and, for seven decades, responsibility for approval of each class of products was assigned to different health agencies.115/ Products that meet the definition of a biological product generally also meet the definition of a "drug" in § 201(g)(1) of the FDCA and are subject to most of the drug provisions of the FDCA.116/ Licensed biological products are not, however, required to obtain "new drug" approval under § 505 of the FDCA, under a 1997 amendment confirming a long-standing FDA interpretation. FDAMA § 123, Pub. L. No. 105-115 (1997), *codified at* 42 USC § 262(j);117/ *see also* 21 CFR §§ 310.4, 314.101(e)(1) (FDA will refuse to file an NDA or an ANDA for any product licensed under the PHS Act).

The demarcation between FDCA approval and PHSA approval derives from the heightened scrutiny accorded by the PHSA to manufacturing processes for all products enumerated in the statute, including products "analogous" to the others named.118/ Biological products are inherently variable and complex products

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Comm. for Legislative Affairs, FDA (Jan. 28, 1998) ("The agency does not view the new section 351(j) as changing the current status of the law with respect to biological products".)

115/ In 1972 the biologics program was transferred to FDA from the National Institutes of Health.

116/ Certain biologics, principally *in vitro* diagnostic products, are regulated as medical devices.

117/ With adoption of this provision, Congress also confirmed FDA's long practice of regulating (but not approving) biological products under the FDCA. *See, e.g.*, Biological Products, Procedures for Review of Safety, Effectiveness and Labeling, 37 FR 16679 (1972) and 38 FR 4319 (1973).

118/ A biological product is, "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product . . . applicable to the prevention, treatment, or cure of a disease or condition of human beings." 42 USC § 262(i). Most modern biotechnology products are "analogous to" or derivative of live cellular products and, as such, meet the definition of a "biological product." 42 USC § 262(i). According to FDA, "analogous products" include any product prepared from a virus, any product prepared from an agent that is actually or potentially infectious, any product that contains an organic constituent, other than a hormone or amino acid, that is derived from whole blood, and any product, irrespective of its source, that is intended to prevent, treat, or cure disease through a specific immune process. 21 CFR § 600.3. Virtually all products manufactured using recombinant DNA technology, also referred to as biotechnology-derived products, fall within this definition. Because the manufacturing process for biologics is so critical for products regulated under the PHSA, use of the term "analogous" in this statutory definition shows Congress' intent to encompass products that implicate the same types of

derived from living sources, and they are susceptible even to slight changes in the manufacturing process.119/ Accordingly, they require the especially significant oversight under the PHSA, a law that, according to FDA, "emphasizes the importance of manufacturing control for products that cannot be defined."120/

The criticality of individual biological product manufacturing processes was understood by Congress when it chose *not* to extend the paper NDA provisions and the generic approval procedures to biologic products with enactment of the Hatch-Waxman Amendments in 1984. Specifically, Hatch-Waxman was divided into two separate titles: Title I modified the FDCA by adding new §§ 505(j) and 505(b)(2) to address premarket review and approval of generic drugs,121/, and Title II added a new § 156 to Title 35 of the U.S. Code to authorize an extension of the "term of a patent which claims a product, a method of using a product, or a method of manufacturing a product." 98 Stat. 1598. In this connection, Title I used the term "new drug" and not the terms "drug" or "biological product" only when referring to the filing of an application. On the other hand, Title II defined the term "product" to mean a "human drug product" and to include the active ingredient of a "human biological product." 35 USC 156 (f)(1) and (f)(2). In sum, while Congress expressly chose to apply the patent extension provisions to biological products, it declined to apply the FDCA's generic and paper NDA premarket approval schemes to biological products.122/

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manufacturing issues as those applying to products named in the statute. Therapeutic protein products, including recombinant products, present similar questions about manufacturing process.

119/ "Changes in the manufacturing process of biological drugs often lead to subtle unintentional changes in the product, resulting in altered pharmacokinetics. In cases in which the change in product can be determined not to have any pharmacological effects (e.g., no effect on unwanted immunogenicity), exposure-response information may allow appropriate use of the new product. Exposure response data are not likely to obviate the need for clinical data when formulation or manufacturing changes result in altered pharmacokinetics unless the relationships between measured responses, and relevant clinical outcomes are well understood." FDA, Draft Guidance for Inudstry, Exposure-Response Relationships: Study Design, Data Analysis, and Regulatory Applications (March 2002), at 7-8.

120/ *See* FDA, Center for Biologics Evaluation and Research, Frequently Asked Questions (June 25, 2002), available at www.fda.gov/cber/faq.htm.

121/ 98 Stat. 1585, *codified at* 21 USC § 355(j) and (b)(2).

122/ *City of Chicago v. Environmental Defense Fund*, 511 U.S. 328, 338 (1994) ("[I]t is generally presumed that Congress acts intentionally and purposely when it includes particular language in one section of a statute but omits it in another.") (internal quotations omitted).

Since adoption of the Hatch-Waxman Amendments, Congress has sought to ensure that nothing disturbs its decision that Title I *not* govern approval of biologic products under the PHSA. For example, shortly after enactment of FDAMA, the innovative industry became concerned that new § 351(j) might be interpreted as authorizing FDA to approve follow-on biologic products under Title I. That provision states that the FDCA "applies to a biological product subject to regulation under this section, except that a product for which a license has been approved under this section shall not be required to have an approved application under section 505 of such Act." 42 USC § 262(j). To confirm that this provision *could not* be construed to authorize approval of follow-on biological products, the House quickly passed a technical corrections bill.123/ Although this bill was never considered by the Senate, two key Senators subsequently advised FDA that "the provisions of section 123(g) of FDAMA, amending 42 USC 262 to add new paragraph (j) were not intended by Congress to change the status of biological products under the provisions of Title I of Pub. L. 98-417."124/

In light of the plain language of the PHSA, and the decision of Congress not to extend the abbreviated approval provisions to biologic products through Title I of Hatch-Waxman, it should not be surprising that FDA has maintained the long-standing position that "follow-on" biological products cannot be approved. Contemporaneous interpretations of the statute are accorded especially strong deference by the courts. In fact, where an agency changes its long-standing interpretation of a statute, the courts do not accord the new interpretation the usual degree of deference. *See, e.g., Good Samaritan Hosp. v. Shalala,* 508 U.S. 402, 414 (1993) ("of particular relevance is the agency's contemporaneous construction which 'we have allowed . . . to carry the day against doubts that might exist from a reading of the bare words of a statute'").

4. FDA's Position On The Amount And Type Of Data Required In A BLA Rises To The Level Of Administrative Common Law.

As discussed above, FDA has long interpreted the PHSA and its implementing regulations as requiring full, original data on each and every unique biological product. *See* 39 FR at 44641 (FOIA preamble); 21 CFR § 601.2 (data requirements for BLAs). FDA cannot change a rule without first conducting notice-and-comment proceedings. Courts invalidate agency actions that attempt to effect a change in an agency's well-established interpretation without use of a notice-and-

123/ *See supra* note 114, H.R. Con. Res. 196, 105th Cong. (1997).

124/ Letter from Senator James Jeffords and Senator Edward M. Kennedy to FDA (Dec. 3, 1997), *see supra* note 114.

comment process. As is discussed in greater detail in the BIO citizen petition, recently, the U.S. Court of Appeals for the District of Columbia Circuit has held that an agency interpretation that "significantly revises" an agency's prior "definitive interpretation" of a regulation requires notice-and-comment rulemaking. *Alaska Prof'l Hunters Assoc. v. Federal Aviation Administration*, 177 F.3d 1030, 1034 (D.C. Cir. 1999).

5. Recent FDA Statements Cause Concern That FDA Might Change Its Long-Standing Interpretations.

No one could seriously argue that the PHSA expressly authorizes FDA to rely on the non-public proprietary information in another company's BLA to approve a follow-on product, and therefore BIO's citizen petition does not cover this issue. FDA officials, including the Commissioner of Food and Drugs, have made a number of recent public statements that legal and scientific barriers block serious consideration of the concept of "generic biological products."125/ Unlike § 505(j) of the FDCA as amended in 1984 by the Hatch-Waxman Amendments, 21 USC § 355(j), the PHSA contains no explicit mechanism for approval of abbreviated applications on the basis of an innovator's information. Nowhere does the PHSA authorize BLA applicants to take advantage of the FDCA's approval schemes to seek marketing authorization of follow-on biological products. Moreover, complex scientific and public health issues — matching or exceeding those described in the BIO petition as to similar FDCA-regulated products — stand in the way of change to this long-established legal framework for biological products.

Notwithstanding the clarity of the PHSA and the scientific challenges, the Generic Pharmaceutical Association (GPhA) contends that FDA has authority to establish a regulatory mechanism for approval of "generic biologics" under the PHSA on the basis of "articles and pivotal studies demonstrating safety and effectiveness."126/ According to GPhA, these "paper BLAs" would mirror the paper

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125/ *See supra* notes14 and 18.

126/ Letter from Bill Nixon, President, Generic Pharmaceutical Association, to Daniel Troy, Chief Counsel, FDA (Jan. 18, 2002), available at www.fda.gov/cder/ogd/GPHA_Jan_21.htm. For example, GPhA suggests that §118 of FDAMA (111 Stat. 2316) – a provision that directs FDA to issue a guidance document that specifies when abbreviated reports may be submitted in lieu of full reports — may be read as supporting the establishment of a scheme for paper BLAs. Rather, this section contemplates submission only of abbreviated reports that are *not* intended to contribute to an evaluation of a product's safety or efficacy, a view that is supported by FDA's implementation of this provision. FDA, Guidance for Industry: Submission of Abbreviated Reports and Synopses in Support of Marketing Applications (Aug. 1999).

NDAs that FDA approved for generic drugs prior to passage of the Hatch-Waxman Amendments.127/

There is no statutory basis for the scheme suggested by the generic drug industry, and it suffers from a fatal flaw. To obtain approval of a BLA, a manufacturer must demonstrate that it satisfies the relevant standards for *both* the product and the establishment where the biologic is manufactured. 21 CFR §§ 601.2 (a), 601.4. While a literature search may well produce scientific articles attesting to the safety and effectiveness of a product, there is no way that a follow-on manufacturer can demonstrate through a "paper BLA" that its establishment will produce the same product as the one described in the articles. The follow-on product will be a different product, since the manufacturing process for the follow-on version will necessarily differ from that of the innovator.

6. Conclusion

Given the critical role that manufacturing processes and facilities play in the BLA approval process, applications for follow-on products clearly are not permitted under the PHSA. Any such follow-on application could not meet the statutory or regulatory requirements for demonstrating the safety, purity, and potency of the follow-on product, which inherently includes assurances about the manufacturing process. *See* 42 USC § 262(a)(2)(B); 21 CFR §§ 601.2(a), 601.4. The legislative history of the Hatch-Waxman Amendments and congressional statements following enactment of FDAMA reinforce the proposition that follow-on biologicals are not permitted under PHSA. Finally, the agency has long interpreted the PHSA as requiring nothing short of clinical data demonstrating the safety, purity, and potency for *each* product seeking a BLA. To change this well-settled policy would contravene the clear statutory intent, and administrative common law. As such, there is simply no place for follow-on biologics under the PHSA.

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In sum, follow-on biologics are neither permissible under the PHSA nor scientifically feasible.

127/ Other arguments have focused upon a theory that § 505(b)(2), added to the FDCA by the Hatch-Waxman Amendments at the same time as the abbreviated NDA (ANDA) provision in § 505(j) offers a pathway for approval of follow-on biological products. 21 USC § 355 (b)(2), (j); Letter from Bill Nixon, Generic Pharmaceutical Association, to Daniel Troy, Chief Counsel, FDA (Jan. 18, 2002); Roger Williams, U.S. Pharmacopoeia, FDA Week (Mar. 23, 2001).