
August 8, 2003

*ELECTRONIC AND U.S. MAIL*

Dockets Management Branch (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: *Docket No. 03P-0176: Follow-On Therapeutic Proteins*

Dear Sir:

The Biotechnology Industry Organization (BIO) respectfully submits this supplement to its Citizen Petition (Petition), dated April 23, 2003. Since April, representatives of BIO and its members have had several opportunities to meet with FDA representatives about our concerns. We greatly appreciate the opportunity to engage in this dialogue with the agency. Those events have raised several questions concerning FDA's interpretation of its legal authority with respect to follow-on therapeutic proteins -- and the potential impact of that interpretation on the industry -- that compel BIO to supplement its Petition to address these issues.

A. *Legal Issues Presented by Section 505(b)(2)*

*1. Chevron Deference*

The language of § 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) limits the deference courts may afford to the agency's interpretation of the provision. *See Chevron U.S.A., Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837 (1984). For example, as BIO's Petition discusses, § 505(b)(2) does not include language expressly authorizing an applicant or FDA to rely on clinical data submitted by another applicant. Without an express grant of authority – which is clearly provided by § 505(j) – no such authority exists. *See* Petition at 25. BIO does not believe that,

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were FDA to approve an application based on another sponsor's data, the agency's broad interpretation of the statute would be entitled to deference. [1]

And, for an additional reason, the language of § 505(b)(2) itself does not allow the broad interpretation FDA put forward in its *Draft Guidance For Industry: Applications Covered by Section 505(b)(2) (October 1999).* The plain language of the statute requires that each and every NDA applicant submit "full reports" showing that the particular drug product it proposes to market is safe and effective.

As the agency is aware, a § 505(b)(2) application is an "application submitted under paragraph (1)" of § 505(b) of the FDCA. Section 505(b)(1) provides that NDAs must contain, among other things, "full reports of investigations which have been made to show whether or not such [drug is] safe . . . and . . . effective . . . ." 21 USC § 355(b)(1). Section 505(b)(2), thus, represents a subset of § 505(b)(1) and incorporates all of its requirements, including the requirement that NDAs contain full reports of investigations. *Id.* § 355(b)(2).

The key difference between a section 505(b)(1) and a 505(b)(2) application lies in the "ownership" of the clinical studies. Under section 505(b)(2), applicants may submit studies (or reports of studies published in scientific or medical literature) that they did not conduct for which they have not obtained a "right of reference or use." In doing so, they must submit certifications for patents held by another applicant.[2] *Id.* § 355(b)(2)(A).

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[1] And, to the extent that FDA is using guidance documents to interpret § 505(b)(2) in ways that go beyond existing regulations, the policy FDA articulates in those guidances is not entitled to deference. *See,* e.g., *Christensen v. Harris County,* 529 U.S. 576 (2000) (no *Chevron* deference to agency opinion letter); *Reno* v. *Koray,* 515 U.S. 50, 61 (1995) (internal agency guideline, which is not "subject to the rigors of the Administrative Procedur[e] Act, including public notice and comment," entitled only to "some deference" (internal quotation marks omitted)); *EEOC* v. *Arabian American Oil Co.,* 499 U.S. 244, 256-258 (1991) (interpretative guidelines do not receive *Chevron* deference); *Martin* v. *Occupational Safety and Health Review Comm'n,* 499 U.S. 144, 157 (1991) (interpretative rules and enforcement guidelines are "not entitled to the same deference as norms that derive from the exercise of the Secretary's delegated lawmaking powers").

[2] As BIO explained in its Petition, there was ample reason for Congress to enact this provision -- in order to codify FDA's previous "Paper NDA" policy, which allowed approval of a "duplicate" product based on submission of published studies discussing the drug's safety and effectiveness in lieu of "full reports" of clinical investigations. Congress also sought to apply patent certification and related requirements to such "paper NDAs".

Nothing, however, permits the Secretary to approve an NDA that fails to contain the "reports . . . required to be submitted to the Secretary pursuant to subsection (b). . . ." *Id.* § 355(d). Moreover, FDA-produced summaries of the underlying data supporting a previously approved product cannot "constitute the full reports of investigations" requirement for an NDA. 21 C.F.R. § 314.430(e)(2).

The agency's *Draft Guidance* proposes to change this statutory requirement and allow approval based on "an Agency finding of safety and/or effectiveness for an approved drug product." *Draft Guidance* at 2. BIO does not believe that this interpretation is allowable given the FDCA's clear requirement that an NDA sponsor submit "full reports" about the safety and effectiveness of its product whether through submission of original research or of published literature discussing research results. And, as our Petition made clear, such a radical change in interpretation requires a process grounded first and foremost in public participation.

*2. Issues Unique to Biological Products Will Not Be Resolved in the Pfizer/Dr. Reddy's Dispute*

Many of the legal issues raised by BIO will not be resolved when the agency addresses the issues raised in Pfizer's Citizen Petition concerning FDA's review of a § 505(b)(2) application from Dr. Reddy's Pharmaceuticals for amlodipine. *See* FDA Docket No. 02P-0447. BIO is concerned about application of § 505(b)(2) to therapeutic proteins, which possess unique characteristics from those of small-molecule drugs like amlodipine. In short, application of § 505(b)(2) raises different issues when applied to therapeutic protein products where, inherently, the product is the process and the process is the product.

The FDCA presumes that a small-molecule chemical drug can be expected to behave the same way in the body if certain conditions are met -- the drug has the same active ingredient, route of administration, dosage form, and strength, and is shown to be bioequivalent to the reference listed drug. 21 USC 355(j)(2)(A). This assumption is simply not relevant to therapeutic proteins because comprehensive specifications do not exist for the final formulations. In fact, when a biological product manufacturer proposes to change its own tightly-controlled manufacturing processes, FDA often requires original new data to ensure that the product produced through the revised process behaves the same way in the human body as the drug on

which original clinical studies were performed.[3] *See Guidance Concerning Comparability of Human Biological Products* (April 25, 1996).

Although the amlodipine approval decision may settle some questions about the interpretation of § 505(b)(2) as applied to chemical drugs, it will not answer many questions about its application to therapeutic proteins. For example, BIO questions whether FDA can make equivalence or "bridging" decisions when comparing a proposed follow-on biological product to a pioneer therapeutic protein without relying on trade secret information contained in the innovator's Biologics License Application (BLA).[4] Even a comparison of two applicants' manufacturing processes, whether or not sufficient scientifically, could violate express prohibitions on the release and use of a manufacturer's trade secret data. 21 USC 331(j). These issues should be addressed through a comprehensive, public process that considers all relevant scientific, legal, and policy issues surrounding the review and approval of these unique products.

Moreover, BIO contests the notion that FDA's past approval decisions lead inexorably to approval of "different" new drug products after review of the innovator's safety and effectiveness data plus a limited amount of data needed to support the safety and effectiveness of the "different" product. *See* Dr. Reddy's April 9, 2003 response to Pfizer Citizen Petition, FDA Docket No. 02P-0447. Pfizer and Dr. Reddy's have provided numerous examples of products allegedly approved under various interpretations of the FDCA. BIO does not have access to detailed information about the data

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[3] Moreover, FDA has an established policy that products derived from biotechnology, and/or therapeutic proteins, require a full complement of data before approval. *See, e.g.*

- December 24, 1974 statement by FDA in its public information preamble (cited at footnote 109 of BIO's Petition).
- 1984 and 1986 biotechnology policy statements (*id.*, footnote 56).
- April 10, 1985 points to consider document (*id.*, footnote 56).
- October 25, 1991 CBER-CDER intercenter agreement (*id.*, at 7)
- April 6, 1992 supplement to 1985 points to consider (*id.*, footnote 56).
- April 28, 1992 response to comment on ANDA final rule (*id.*, footnote 20).
- June 25, 2002 CBER FAQs (*id.*, footnote 120).
- March 2002 FDA Draft Guidance for Industry, Exposure-Response Relationships (*id.*, footnote 119).

The wisdom of this traditional policy is supported by the relevant science, as discussed in BIO's Petition at 40-51.

[4] Nor does BIO agree that there is a principled difference between relying on information contained in an innovator's NDA and reliance on a previous agency finding based on that data. *See* FDA Docket No. 02P-0447.

underlying these approval decisions. That fact alone demonstrates the opaque nature of FDA's reliance on approval-by-approval decisionmaking to establish important policies. Of course, if there are additional approvals at issue that were not discussed by Pfizer or Dr. Reddy's, that would contribute to the conclusion that policy-making by approval is opaque, standardless, and unsound public governance. *See* Petition at 21.

*B. Regulatory Certainty Is Essential for the Future of the Industry*

On June 23, 2003, President Bush addressed BIO's annual meeting. There, he credited biotechnology as essential to "the future of medicine in the United States of America." Commissioner McClellan, who also spoke, stated that due to biotechnology "the most important innovations are still ahead of us -- as new scientific insights from genomics, proteomics, information technology and other emerging fields are increasingly translating into better health and better lives for patients throughout the country and the world." Indeed, the Commissioner has reached out to the scientific community and encouraged greater cooperation between FDA's regulators and those at the forefront of scientific innovation, whether in government or industry.

Despite all this, the biotechnology industry relies, in large measure, on regulatory certainty for its growth and health. As Commissioner McClellan recognized, it costs more than $ 800 million and typically takes well over a decade to develop a new drug. Indeed, "the vast majority of the treatments that enter clinical testing don't succeed," and, once approved, the "life expectancy" of a drug is perhaps a few decades.[5]

When deciding whether to invest the time and money required, and whether to risk that investment, investors and companies need certainty -- about the manner in which FDA will evaluate the scientific issues presented, about the legal and regulatory standards the agency will apply to the product and its potential competitors, and about their ability to participate in these processes. To provide that certainty, FDA should make a clear statement with respect to its approval authority and policies governing therapeutic protein products and provide the industry with an opportunity to participate in open, public, and meaningful debate about proposed actions with respect to those products. A piecemeal, approval-by-approval approach

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[5] Commissioner McClellan's remarks are available on FDA's website at http://www.fda.gov/oc/speeches/2003/biotechnology0623.html.

based on guidance documents is simply not an appropriate vehicle for deciding major policy issues concerning follow-on biological products. Indeed, such an approach fails to meet the basic minimum of good government – public discussion of critical economic, scientific, and public health issues.

Moreover, such an approach does not allow an on-going, public assessment of what the current science will support. Scientific advances allowed the creation and growth of the biotech industry and will likely dictate the nature and scope of follow-on products. BIO strongly believes that, to be credible, FDA must first evaluate the science in a public forum and, only then, establish appropriate regulation through consistent application of recognized scientific principles to all manufacturers. We welcome the opportunity to participate in a transparent and inclusive debate about the scientific principles underlying follow on biologics and how best to apply various regulatory approaches that may emerge from that scientific discussion.

*C. Conclusion*

We appreciate your attention to the issues raised in our Petition and this comment and look forward to an opportunity to continue this public dialogue.

Sincerely yours,

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