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

Re: *FDA Docket No. 01P-0323; Comments of Amgen Inc.*

Dear Sir or Madam:

Amgen Inc. ("Amgen") submits the following comments under 21 CFR 10.30(d) in support of the citizen petition submitted jointly by Pharmacia Corp. and Pfizer Inc. on July 27, 2001 (the "Joint Petition").

INTRODUCTION

The Joint Petition requests the Commissioner of Food and Drugs to recognize immediately that the Food and Drug Administration ("FDA") cannot rely upon confidential information submitted in support of one sponsor's new drug application ("NDA") to approve another sponsor's NDA. Among other things, the Joint Petition requests that the Commissioner amend the draft document titled *Guidance for Industry: Applications Covered by Section 505(b)(2)* (Oct. 1999) (the "*Draft Guidance*") to reflect this core legal principle. In addition, the agency must refrain from approving NDAs submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (the "FDCA") that rely on proprietary information submitted by another sponsor. Finally, the Joint Petition requests that the agency refrain from assigning "A" level therapeutic equivalence ratings to products approved under 505(b)(2) applications.

Amgen is the world's largest independent biotechnology company and stands as a world leader in molecular and cellular biology, target discovery, and therapeutic delivery. Amgen markets two of the most successful and renowned biotechnology products, EPOGEN® (epoetin alfa) and NEUPOGEN® (filgrastim), along with the recently approved products, Aranesp® (darbepoetin alfa) and Kineret® (anakinra). In addition, Amgen has a number of drug and biological products under development and several currently under FDA review.

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Amgen supports the arguments in the Joint Petition in all respects and believes strongly that the proposed interpretation of section 505(b)(2) is in excess of the agency's legal authority. In particular,

- FDA cannot incorporate by reference, nor permit an applicant to incorporate by reference, information in another sponsor's application without obtaining legal authorization from the first applicant to rely on the data, or without statutory authorization to do so (Joint Pet. at 3, 10-13).

- Outside of section 505(j) of the FDCA, the agency has no statutory authority to rely in whole or in part on a pioneer manufacturer's proprietary data (Joint Pet. at 13).

- Outside of section 505(j), the agency has no statutory authority to rely on "prior findings of safety and effectiveness" based in whole or in part on a pioneer manufacturer's data (Joint Pet. at 14).

- FDA's proposed use of section 505(b)(2) would represent an uncompensated taking of property (Joint Pet. at 17-25).

In addition to these points, Amgen's focus in submitting comments is on the proposed use of section 505(b)(2) for products that will be marketed as "pharmaceutical equivalents to" or "duplicates of" complex drug substances, including recombinant drug products. Specifically, the *Draft Guidance* states that section 505(b)(2) may be used for the review and approval of drug products with naturally derived or recombinant ingredients "where clinical investigations are necessary to show that the active ingredient is *the same as* an active ingredient in a listed drug." *Draft Guidance* at 5 (emphasis added). In various contexts, present and former FDA officials have suggested that such products, approved under section 505(b)(2), would also carry "A" level therapeutic equivalence ratings.[1]/

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[1]/ *See* Tab 1, Presentation of Yuan-Yuan Chiu (Director, FDA Office of New Drug Chemistry) at the National Association of Pharmaceutical Manufacturers' Bulk Drug Program (Mar. 20, 2001) titled "Biotechnology-Derived Drug Substances for AB-Rated Drug Products – A CDER Perspective" (arguing that section 505(b)(2) is a feasible pathway for approval of multi-source biotech protein products that could be interchangeable with a listed drug); Tab 2, Remarks of Roger Williams, U.S. Pharmacopoeia, reported in *FDA Week* (Mar. 23, 2001) (stating that 505(b)(2) was meant to address interchangeability of recombinant proteins); Tab 3, "Generic Recombinant Protein 'Paper' NDA Approval Process Outlined by FDA," *F-D-C Reports* (April

For the reasons stated in the Joint Petition and discussed below, we believe this proposed use of section 505(b)(2) is ill considered and unlawful. The idea of a "short-form" or "hybrid" application for the marketing of "generic" or "duplicate" recombinant products not only threatens the proprietary rights of pioneer sponsors, it also poses a direct threat to patient health and safety. Consequently, Amgen is compelled to file these comments.

COMMENTS

Comment 1: FDA cannot use section 505(b)(2) as a pathway for products that will be marketed as "A-rated" duplicates.

As applied to naturally occurring and recombinant drug products,[2/] the *Draft Guidance* violates the basic structure of the FDCA. FDA's proposed interpretation would, for all intents and purposes, allow the agency to turn "failed generics" under section 505(j) into "passing generics" under section 505(b)(2).[3/] The law cannot be bent and twisted in this way.

Section 505(b) of the FDCA establishes the requirements for the submission of NDAs. Among other things, section 505(b)(1) provides that an NDA must contain "*full reports of investigations* which have been made to show whether or not such drug is safe for use and . . . effective in use" (emphasis added). Section 505(b)(2) incorporates all of the requirements of

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[Footnote continued]

5, 1999) at 32 ("'We are postulating a path for a recombinant molecule that gets an AB rating in the Orange Book, that does not come in the "(j)" route, it comes in the "(b)(2)" route,' [Roger] Williams [FDA Director of Pharmaceutical Science] said.").

[2/] Most biological products are marketed under section 351 of the Public Health Service Act (the "PHS Act") and thus are not eligible for approval under section 505(b)(2) of the FDCA. Consequently, such products would not be subject to the *Draft Guidance*. However, for reasons that are largely historical, several categories of products with biological origins have been approved under section 505 of the FDCA and are regulated solely as new drugs (*e.g.*, insulin and human growth hormone).

[3/] We note and agree with the conclusion that recombinant drug products cannot be approved under section 505(j) because such products require the submission and review of independent clinical data. *See Draft Guidance* at 4 and references cited in footnote 1, above. Any other approach would necessarily put patients at risk.

505(b)(1), with one adjustment: 505(b)(2) allows the applicant to submit investigations that were conducted by another person and for which the applicant lacks a "right of reference." All other data requirements described in 505(b)(1) remain the same.

At the center of the *Draft Guidance* is the agency's argument that a 505(b)(2) applicant may rely on "prior findings of safety and effectiveness" in place of submitting "full reports of investigations." *Draft Guidance* at 7-8. According to the *Guidance*, an applicant under section 505(b)(2) may rely on prior findings for a pioneer product *to the same extent* that an applicant under section 505(j) may rely on such findings. *Id.* at 2-3.[4]/

This interpretation, without more, would render sections 505(b)(2) and 505(j) redundant. To guard against this problem, FDA makes clear that a 505(b)(2) application must incorporate *a significant change to the pioneer product*. On at least five occasions, the *Draft Guidance* states that the proposed product *cannot be or purport to be a duplicate* of the approved product. *Id.* at 2, 3, 4, 6, 8 ("Section 505(b)(2) permits approval of applications *other than those for duplicate products* . . . ." *Id.* at 2.). FDA's related regulation, 21 CFR 314.54, also includes this important qualifier. Otherwise, an applicant who cannot meet the standards set forth in section 505(j) could simply "end run" the statute by proceeding under section 505(b)(2). *See also* 21 CFR 314.101(d)(9).

In this light, the proposed use of section 505(b)(2) to demonstrate the "sameness" of recombinant drug products, is in error. Under FDA's proposed approach, a 505(b)(2) applicant would be permitted to rely on prior findings of safety and effectiveness as if the sponsor were proceeding under section 505(j). In addition, the 505(b)(2) applicant would be permitted to submit clinical studies in support of the application, studies which the applicant could *not* submit under section 505(j). At the end of the process, the applicant would be able to market its product as a "duplicate to" or as "interchangeable with" an approved pioneer. The 505(b)(2) product would be

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[4]/ Section 505(j) is intended for two categories of products: (1) those that will be marketed as duplicates of pioneer products (*i.e.*, "generic drugs" or "pharmaceutical equivalents"); and (2) those that include certain minor differences for which no clinical data is needed to support the difference (*i.e.*, "suitability petition products" or "pharmaceutical alternatives"). That is, section 505(j) is intended for products that are "the same as" an already-approved product.

marketed as if it had been submitted and approved under 505(j) when, in fact, the product cannot satisfy the legal requirements of section 505(j).[5]/

As applied to recombinant drug products, the agency's interpretation effectively reads section 505(j) out of the FDCA, in favor of the agency's own vision of a much more flexible "generic process" under section 505(b)(2). The agency would, of course, be legislating rather than merely interpreting, were it to embark down this path. FDA cannot through "interpretation" or "policy" rewrite the carefully structured requirements under 505(j) for the marketing of generic drug products.

Amgen urges the agency in response to the Joint Petition to strike from the *Draft Guidance* the proposed use of 505(b)(2) to demonstrate the "sameness" of recombinant products, where such products could be marketed as duplicates of approved pioneer drugs. *See Draft Guidance* at 5.

Comment 2: The proposed use of section 505(b)(2) cannot be scientifically sustained at this time.

An essential element of the *Draft Guidance* is the concept of "bridging" from one application to another. According to the *Draft Guidance*:

> Complete studies of safety and effectiveness may not be necessary if appropriate bridging studies are found to provide an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s).

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[5]/The *Draft Guidance* refers to the April 10, 1987 "Parkman Letter" and the "hybrid NDA" regulation, 21 CFR 314.54, to suggest that the agency is simply building on prior policies. These prior interpretations, however, are inapplicable to recombinant therapeutic proteins. The Parkman Letter and the regulation rely on the idea that the underlying product – *without the proposed change or modification* – could have been approved under section 505(j). *See* 54 FR 28872, 28892 (July 10, 1989). The Parkman Letter and the regulation were intended to streamline the application process, where the underlying product could have been approved under 505(j) and the change could have been approved through a 505(b) supplemental NDA. Rather than submit both applications, FDA resolved that the 505(j) step could be eliminated. The sponsor could go directly to 505(b) and submit only the additional data needed to support the change (along with bioequivalence data). Nevertheless, the premise is that the *product must have been eligible in the first instance to be approved under section 505(j).* Otherwise, neither the applicant nor FDA would be authorized to rely on prior findings of safety and effectiveness. Again, reliance on "prior findings" is authorized under, and only under, section 505(j). The reasoning behind the Parkman Letter simply does not apply to recombinant and other difficult-to-characterize products, where such products in the first instance could not have been approved under 505(j).

Draft Guidance at 8. The "bridging" concept, however, lacks meaning when applied to complex drug substances, including recombinant DNA products.

The regulation of biologically derived products is premised on the idea that the physical and pharmacodynamic properties of such products are dependent on source materials, assays, specifications, and on the specific manufacturing process. Each element contributes to the characteristics of the final product such that a second manufacturer with different materials or a different process is, despite best efforts, likely to yield a product with clinically meaningful differences. Simply comparing the rate and extent of absorption of such products may overlook crucial differences. Indeed, even seemingly minor or subtle differences in the quantity or quality of the variations in each product can have a significant impact on potency, pharmacodynamics, and immune response.[6]/

Even more, the ability to characterize these differences is limited, and the ability to predict whether these differences will lead to immunogenic responses, antibody production, or non-recognition by the host is perilous absent a full clinical program. Unlike small molecule drugs, end-product comparisons for biologics manufactured from different materials using different processes are simply inadequate. For all intents and purposes, the clinical data developed by the manufacturer of such a product is specific to that manufacturer's own cell line and production process.[7]/

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[6]/*Compare* approved labeling for Saizen® (somatropin (rDNA origin) for injection) (stating that half-life for subcutaneous administration is 1.75 hours); Humatrope® (somatropin (rDNA origin) for injection) (stating that half-life for subcutaneous administration is 3.8 hours); and Norditropin® (somatropin (rDNA origin) for injection) (stating that half-life may be as long as 10 hours and that "the absolute bioavailability for Norditropin® after the SC route of administration is currently not known.").

[7]/ This is consistent with FDA's April 1996 "Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-Derived Products." The guidance outlines how a single sponsor may demonstrate "product comparability" before and after a manufacturing change, through analytical and functional testing rather than full clinical study. As described in the guidance, "comparability" involves the evaluation of incremental changes made to a carefully controlled manufacturing process, performed by the individuals who developed that process. The raw materials, master cell bank, equipment, process controls, key intermediates, assays, and validation studies are all within the control of the sponsor who undertakes a showing of comparability. This level of intra-manufacturer control is not present when a new and different sponsor undertakes to make the "same" biologically-based product using different cellular materials, equipment, and processes. The end result of an original attempt at making "the same" biological product is a new and unique biological product.

There may be no better illustration of this point than the recent disclosure of an unexpected cluster of approximately forty cases reported worldwide of patients suffering from antibody positive pure red blood cell aplasia after being treated with the recombinant product known as Eprex® (epoetin alfa recombinant), manufactured by a subsidiary of Johnson & Johnson.[8]/ In contrast, in the twelve years since the introduction EPOGEN®, Amgen's epoetin alfa recombinant product, there has been only one reported case of an antibody positive patient suffering from pure red blood cell aplasia after treatment with EPOGEN®. Even though the two products are marketed for the same uses and bear the same generic name, they are manufactured by different companies in different locations. To date, the cause of this phenomenon is unknown.

A full discussion of the science is well beyond the scope of the Joint Petition and these comments. More significant, however, is the fact that FDA included in the *Draft Guidance* an approach to the approval of "duplicate" recombinant products *without* a full analysis of the basic science.

The idea of using 505(b)(2) to approve "duplicate" recombinant drug products is ill considered and flawed. To "bridge" from one manufacturer's product to another manufacturer's version in this context represents a significant and untested departure for the agency *and the public*. The science has not been publicly vetted and, suffice to say, brief mention in a draft guidance is not an appropriate vehicle for addressing these issues.

Comment 3*: *The proposed use of 505(b)(2) would create an unlawful regulatory imbalance.

Most biological products are marketed under licenses issued pursuant to section 351 of the PHS Act by FDA's Center for Biologics Evaluation and Research ("CBER"). All such products, including therapeutic recombinant DNA products, are subject to CBER's full clinical data requirements. *See* 21 CFR 601.2. Moreover, CBER continues to emphasize that, unlike small molecule drugs, biological products present unique technical and medical issues. As the Director of CBER recently explained:

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[8]/ *See, e.g.,* Tab 4, Medicines Control Agency, "Important Safety Message: Eprex (epoetin alfa): Reports of Pure Red Cell Aplasia (PRCA)," 11/19/01.

> One cannot completely characterize the biological product and that in itself is an issue, and quite frankly with biological products you really don't have a homogeneous product, you have a defined range of biological components for which you find consistency in a particular clinical outcome. The challenges of analytical technology are still very great for characterizing biologics.

Remarks of K. Zoon, Ph.D., as noted in *FDA Week* (April 20, 2001), attached under Tab 5. CBER officials have consistently expressed concern about the introduction of adventitious agents into biological manufacturing processes and genetically engineered cell lines, the risks of propagating infectious agents, and the need for immunogenic studies on recombinant and modified protein products.[9]/ *See also* Tab 6, FDA letter dated Nov. 8, 1999 ("[CBER] has no means of establishing that two biological products from different sponsors can be expected to have the same effectiveness and safety.").

Most biologically-derived protein products remain under the jurisdiction of CBER, where there is no regulatory path for the approval of "duplicates" and where officials remain cautious about the underlying science. It would be arbitrary and capricious, in this context, for CDER to move forward with its own approach, and to begin approving "A-rated" or "duplicate" therapeutic proteins based on clinical data derived from other sponsors' applications. *See generally Bracco Diagnostics, Inc. v. Shalala*, 963 F.Supp. 20, 27 (D.D.C. 1997) (it is unlawful for an agency to apply different legal standards to similarly situated products).

CONCLUSION

The issues involved in trying to establish therapeutic equivalence among biological products, including proteins manufactured using rDNA technology, are complex. The brief mention in a draft guidance of the use of section 505(b)(2) for the approval of recombinant products is a poor vehicle for vetting these fundamental scientific and medical issues.

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[9]/ *See, e.g.*, K. Stein, Ph.D, Director (CBER Division of Monoclonal Antibodies), "Immunogenicity of Recombinant Proteins" (Feb. 22, 2001) (available on the FDA/CBER website); K. Zoon, Ph.D., Director (CBER), "Points to Consider in the Characterization of Cell Lines Used to Produce Biologicals (May 17, 1993) (available on the FDA/CBER website); *see also* 66 FR 4688, 4690 (Jan. 18, 2001) (discussing the ongoing work of the rDNA Advisory Committee under the National Institutes of Health's Office of Biotechnology Activities).

Amgen vigorously supports the legal analysis and conclusions reached in the Joint Petition and urges the agency, for the reasons described above, to grant the Petition. In doing so, the agency must revoke all proposals and policies that would allow for the use of section 505(b)(2) (or any other abbreviated or "hybrid" process) to approve recombinant drug products.

ENVIRONMENTAL IMPACT

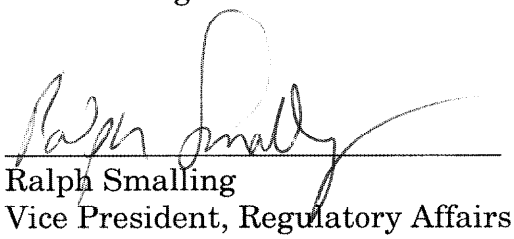
The actions requested in these comments are not within any of the categories for which an environmental assessment is required pursuant to 21 CFR 25.22.

ECONOMIC IMPACT

Information on the economic impact of this proposal will be submitted if requested by the Commissioner.

CERTIFICATION

The undersigned certifies, that, to the best knowledge and belief of the undersigned, these comments include all information and views on which the comments rely and representative data and information known to the undersigned which are unfavorable to the comments.



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