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BY FEDERAL EXPRESS

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

Re: Docket No. 02N-0417; 67 Fed. Reg. 65448;
Patent Listing Requirments and 30-Months Stays

Ladies/Gentlemen:

On behalf of our client Alphapharm Pty Ltd of Glebe, New South Wales, Australia, we submit the following comments on one aspect of the above-referenced proposal, which was published in the Federal Register of October 24, 2002.

Although technically the comment period has closed, we respectfully request consideration of these comments, since they are address a single issue of importance to the drug industry.

## A. A Patent Claiming an Intermediate, Which Remains in Modified Form as a Drug Substance in a Finished Drug Product, is Required to be Listed in the Orange Book

1. All patents claiming an approved drug or a method of using an approved drug must be submitted to FDA for listing in the Orange Book. 21 U.S.C. § 353(b)(1). Such patents include "drug substance (ingredient) patents," where the drug substance (ingredient) is a component of an approved drug product. 21 CFR § 314.53(b). Both FDA's patent term extension and GMP regulations define the "active ingredient" (drug substance) in an approved drug product as:

> "any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure or any function of the body of man or of animals. **The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect."**

02N-0417

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21 C.F.R. §§ 60.3(b)(2), 210.3(b)(7), emphasis supplied.

2. An intermediate of a drug substance, which undergoes chemical change during the manufacturing process and remains as the active ingredient in a finished drug product, falls squarely within the second sentence of this definition. This is clear from the plain language of the above definition. It is also manifest from the following FDA guidance documents defining an intermediate:

- "What is an Intermediate?

  • A material produced during API processing that undergoes further molecular change or purification before it becomes the API"
  *ICH Q7A GMP Guidance for APIs and its Use During Inspections (8/20/02)*

- "Intermediate: A material produced during steps of the processing of an API that undergoes further molecular change or purification before it becomes an API."
  *Guidance for Industry: Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (August 2001)*

- "Intermediate: A material produced during steps of synthesis of a new drug substance that undergoes further chemical transformation before it becomes a new drug substance."
  *Guidance for Industry: Q3A Impurities in New Drug Substances (February 2003); Guidance for Industry: ANDAs: Impurities in Drug Substances (November 1999)*

- "Final Intermediate: The last compound synthesized before the reaction that produces the drug substance."
  *Guidance for Industry: BACPAC I: Intermediates in Drug Substance Synthesis; Bulk Actives Post-Approval changes: Chemistry, Manufacturing and Controls Documentation (February 2001); Guidance for Industry: Changes to an Approved NDA or ANDA (November 1999).*

3. In addition, the courts have held that patents claiming drug substances that are components of approved drug products are properly listed in the Orange Book. See *Ben Venue Laboratories, Inc. v. Novartis Pharmaceutical Corporation*, 10 F.Supp.2d 446 (D.N.J. 1998). In *Ben Venue*, the court determined that a patent claiming a pentahydrate form of the drug pamidronate disodium should be listed, because the pentahydrate compound was a component of pamidronate disodium.

The court cited FDA regulation 21 CFR § 314.53(b) as authority for its ruling.[1]

Accordingly, under the above authority: (i) an intermediate that remains after manufacturing in modified form as an active ingredient in a finished drug product is a drug substance; (ii) any patent claiming such an intermediate claims a drug substance; and (iii) such a patent must be listed in the Orange Book.

## B. FDA's Proposed Regulation Should Be Amended to Require the Listing of Patents Claiming Intermediates That Become Drug Substances

FDA's instant proposal to amend its patent listing regulations includes a provision that would preclude the listing of patents claiming intermediates (67 Fed. Reg. 65448, 65451-52, Oct. 24, 2002). This proposal is grounded upon the statement that intermediates "are not present in the final drug product." Id.

However, this assertion is clearly inconsistent with the above-cited FDA regulations and guidance documents, which: (a) recognize that many intermediates are present in modified form as the drug substance in a finished drug product, and (b) mandates the Orange Book listing of patents claiming such intermediates.

**FDA is urged to amend the proposal to allow the listing of patents claiming intermediates that are present in modified form as drug substances in finished drug products.**

Furthermore, under the *Ben Venue* decision, even patents claiming intermediates not present in a finished drug product may qualify for listing (see footnote 1 below).

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[1] Notably, the *Ben Venue* court determined that even though the pentahydrate compound was not present in the finished pamidronate drug product, it was nevertheless a component of the pamidronate drug substance, citing: (i) FDA's GMP regulation 21 CFR 210.3(b)(3), which defines "component" as "any ingredient for use in the manufacture of a drug product, including those that may not appear in such drug product," and (ii) FDA's NDA regulation 21 CFR § 314.50(d)(1)(ii)(a), which requires an applicant to provide a "list of all components used in the manufacture of the drug product (regardless of whether they appear in the drug product)." 10 F.Supp.2d at 457.

Thank you for the opportunity to submit these comments.

Sincerely yours,

Charles J. Raubicheck

CJR/bav
Encl.

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