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VIA HAND DELIVERY

Dockets Management Branch
U.S. Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

**Re: Supplemental Comments on Apotex Corp.'s Suitability
Petition, Docket No. 2004P-0326/CP 1**

Ladies and Gentlemen:

Fujisawa Healthcare, Inc. (Fujisawa) submits these supplemental comments on the above-referenced suitability petition, in which Apotex Corp. (Apotex) seeks FDA approval to file an abbreviated new drug application (ANDA) for adenosine injection in strengths of 18 mg (6 mL vial) and 30 mg (10 mL vial). *See* Apotex Suitability Petition (July 16, 2004), FDA Docket No. 2004P-0326/CP 1. Apotex's proposed ANDA would rely on Fujisawa's Adenocard[®] product (adenosine injection) as the reference listed drug. *See id.* at 1.

As Fujisawa indicated in previous comments on the suitability petition, the proposed Apotex products present a major change in the strength of the drug product and raise significant safety concerns. *See* Comments of Fujisawa, Inc. (September 8, 2004), FDA Docket No. 2004P-0326/CP1 (Fujisawa September Comments) at 3-11. As further noted in Fujisawa's previous comments, Apotex's proposed ANDA can be viewed as an attempt to encourage use of the proposed new strengths as an off-label substitute for Fujisawa's Adenoscan[®] product, rather than for the reference product, Adenocard. *See id.* at 12-14. In these supplemental comments, Fujisawa submits additional evidence supporting denial of Apotex's petition.

I. The Proposed Apotex Products Cannot Be Safely Used Without Extensive Retraining of Medical Personnel

The dosage strength and format of Fujisawa's Adenocard product are well suited for the emergency context in which adenosine is generally administered for treatment of

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paroxysmal supraventricular tachycardia (PSVT). Under the approved labeling for Adenocard, the initial dose for treatment of PSVT is 6 mg, administered as a rapid intravenous bolus over a 1 to 2 second period. *See* Adenocard Prescribing Information (August 2003). If a patient fails to respond to the initial 6 mg dose, the label directs administration of a second rapid intravenous bolus, of 12 mg rather than 6 mg. A third dose, of 12 mg, is indicated only in the 8% of patients who fail to respond to the first two doses. *See id.* Fujisawa supplies both the 6 mg strength and the 12 mg strength in pre-filled syringes. Medical personnel can administer the full contents of the syringe each time a dose is needed, and are not required to stop and measure out amounts as they would have to do with the proposed Apotex products.

The safety concerns associated with the proposed Apotex products, which are supplied in multidose vials, have been set forth in Fujisawa's previous comments and are reinforced in the attached declarations. In short, because emergency personnel would have to insert an empty syringe into the Apotex vials and measure out the appropriate dose for each administration of adenosine (up to three times per patient), the proposed products present a significantly greater risk than Fujisawa's Adenocard with regard to dosing errors and product contamination. *See* Fujisawa September Comments at 3-11; *see also* Declaration of Dr. Richard V. Aghababian, M.D., F.A.C.E.P. (Aghababian Decl.) ¶¶ 4-6, 10; Declaration of Dr. Albert C. Wehl, M.D. (Wehl Decl.) ¶¶ 5-8. The concern about dosing errors, including overdose, is particularly marked because of the pressure injection technique that is used with adenosine. As stated by Dr. Albert Wehl, "adenosine, because of its extremely short half life, is likely to be ineffective unless administered as a forceful rapid bolus . . . Therefore, emergency room personnel and paramedics are trained to administer the drug with a pressure injection. Since these personnel are accustomed to administering the entire 6 mg or 12 mg vials or pre-filled syringes, if a larger vial is used, there is a real possibility that they may mistakenly inject an entire 30 mg vial into a patient." *See* Wehl Decl. ¶¶ 7-8. The risks of dosing error and contamination associated with the proposed Apotex products must be assessed through clinical studies or, at a minimum, should be reflected in the product labeling.

In addition, the increased risks associated with the proposed Apotex products would create a need for extensive and costly retraining of the medical personnel who administer adenosine in emergency situations, including paramedics, emergency room nurses, and physicians. *See* Aghababian Decl. ¶ 8; Wehl Decl. ¶ 10. Under emergency treatment protocols, personnel are trained to respond to medical emergencies such as PSVT in an almost automatic fashion. *See* Aghababian Decl. ¶ 8. As part of these conditioned responses, personnel learn to rely on packaging that is adapted to the dosage strengths associated with a particular emergency treatment protocol -- such as the pre-filled syringes in which Adenocard is supplied. *See* Aghababian Decl. ¶¶ 6-7; Wehl Decl. ¶ 3.

If a generic form of Adenocard is introduced in the new dosage strengths proposed by Apotex, institutions will have to revise their emergency protocols for treatment of PSVT, and all emergency personnel subject to those procedures will have

to be retrained. This retraining will be critical to patient safety given the risk of dosage errors associated with multidose vials, particularly in emergency situations. *See* Aghababian Decl. ¶¶ 6, 8; Weihl Decl. ¶¶ 6, 10. Protocols will also have to be revised to address the danger of contamination from opened vials, which is particularly significant given that the second and third doses of adenosine can be administered up to half an hour apart or longer. *See* Aghababian Decl. ¶ 10.

In addition, a black box warning should be placed on the proposed larger vials to ensure that emergency personnel understand that the larger vials are a different product strength. *See* Weihl Decl. ¶ 10. The warning should also state that no studies have been performed to evaluate adverse events associated with mistaken administration of the entire 30 mg vial at once. This black box warning is particularly important given that generic manufacturers are unlikely to provide in-service training to medical personnel. *See id.*

Given the costs associated with retraining emergency response personnel and emergency room physicians and staff, there is no guarantee that institutions will perform sufficient training to mitigate the risks presented by the proposed Apotex products. *See* Weihl Decl. ¶ 11. In addition, the costs associated with this retraining erode Apotex's argument that the proposed products will result in cost savings. *See* Apotex Suitability Petition at 2-3.

II. The Primary Utility of The Proposed Apotex Products Is As An Off-Label Substitute For Adenoscan

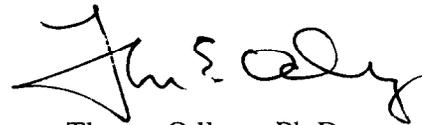
As discussed in Fujisawa's September comments, the proposed Apotex products -- whose dosage strength renders them impractical, as well as unsafe, as generic versions of Adenocard adenosine injection -- are actually intended to be used as off-label substitutes for Adenoscan, another Fujisawa product¹ containing adenosine solution at the same concentration used in Adenocard. Specifically, the proposed 30 mg vials of generic adenosine can be readily combined to yield dosage strengths of 60 mg or 90 mg, the strengths at which Adenoscan is supplied. *See* Fujisawa September Comments at 12.

The primary utility of the larger, 30 mg vial of generic adenosine is to provide an off-label substitute for Adenoscan. This conclusion is strongly reinforced by the actions of another healthcare entity, Biotech Pharmacy of Las Vegas, Nevada. Fujisawa understands that Biotech is repackaging generic Adenocard and selling it in larger units to nuclear cardiology practices and freestanding radiology clinics for use in pharmacological stress tests, the use for which Adenoscan is indicated.

¹ Adenoscan is used in a non-emergency setting as an adjunct to thallium-201 myocardial perfusion scintigraphy in patients unable to exercise adequately. Adenoscan is administered as a slow infusion of adenosine at 140 mcg/kg/minute over a period of six minutes.

An ANDA referencing Adenocard is not the appropriate vehicle for approval of Apotex's proposed 18 mg and 30 mg strengths, whose primary utility is as an off-label substitute for Adenoscan. Apotex should be required to conduct clinical investigations to assess the safety risks associated with use of generic Adenocard as a substitute for Adenoscan, which is subject to more stringent endotoxin controls under USP standards.² At a minimum, even if the proposed Apotex products can be approved as a substitute for Adenocard, the proposed products would require additional warnings -- including a black box warning -- about the risk of serious side effects and the need for retraining of emergency room personnel. Either of these requirements provides grounds for denial of the Apotex suitability petition.

Respectfully submitted,



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² Under USP standards, a generic Adenocard product could contain up to twice the level of endotoxins deemed safe for Adenoscan, and therefore the use of a generic Adenocard as an off-label substitute for Adenoscan raises significant safety concerns that have not yet been studied. *See* Fujisawa September Comments at 12-13.