CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-536

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of New Drugs Quality Assessment
Biopharmaceutics Review

NDA NUMBER:	22-536
Submission Type:	Original NDA
Submission Date:	May 8, 2009
Applicant Name:	APP Pharmaceuticals, LLC
Brand Name:	Indomethacin for Injection
Generic Name:	Indomethacin for Injection
Dosage Form:	Sterile lyophilized powder for IV administration
Dosage Strength:	Single use vials containing 1 mg of indomethacin as a sterile, lyophilized powder or plugs for reconstitution
Proposed New Indication:	To a hemodynamically significant patent ductus arterious in premature infants weighing between 500 mg and 1750 g
ONDQA:	Biopharmaceutics Group
OND Division:	Cardiovascular and Renal Products
Biopharmaceutics Reviewer:	Angelica Dorantes, PhD
Biopharmaceutics Supervisor:	Patrick Marroum, PhD

Biopharmaceutics Review Summary

SUBMISSION:

NDA 22-536 was submitted by APP Pharmaceutics. LLC on May 8, 2009, in accordance with Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act to seek marketing clearance for Indomethacin for Injection. The Reference Listed Drug, INDOCIN® IV (Indomethacin for Injection), is manufactured by Ovation Pharmaceuticals. APP Pharmaceuticals, LLC will manufacture this product in its manufacturing facility located in Barceloneta, Puerto Rico.

BIOWAIVER REQUEST:

In accordance with 21 CFR § 320.22(a), APP Pharmaceuticals, LLC is requesting a waiver for the requirement to submit in vivo bioavailability/bioequivalence data for Indomethacin for Injection. This request is based on 21 CFR § 320.22(b), which states that for certain drug products, the in vivo bioavailability or bioequivalence of the drug product may be self-evident. The drug product's self-evident in vivo bioavailability or bioequivalence is based on the fact that the drug product is sterile lyophilized intended solely for administration by intravenous injection, having the same active ingredient in the same concentration as the reference listed drug product that is the subject of an approved full new drug application.

BACKGROUND

The following information is provided in 21 CFR Section 320.22.

320.22. Criteria for waiver of evidence of in vivo bioavailability or bioequivalence.

(a) Any person submitting a full or abbreviated new drug application, or a supplemental application proposing any of the changes set forth in Sec. 320.21(c), may request FDA to waive the requirement for the submission of evidence demonstrating the in vivo bioavailability or bioequivalence of the drug product that is the subject of the application. An applicant shall submit a request for waiver with the application. FDA shall waive the requirement for the submission of evidence of in vivo bioavailability or bioequivalence if the drug product meets any of the provisions of paragraphs (b), (c), (d), or (e) of this section.

(b) For certain drug products, the in vivo bioavailability or bioequivalence of the drug product may be self-evident. FDA shall waive the requirement for the submission of evidence obtained in vivo demonstrating the bioavailability or bioequivalence of these drug products. A drug product's in vivo bioavailability or bioequivalence may be considered self-evident based on other data in the application if the product meets one of the following criteria:

(1) The drug product:

(i) Is a parenteral solution intended solely for administration by injection, or an ophthalmic or otic solution; and

(ii) Contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application.

INFORMATION SUPPORTING THE BIOWAIVER

Conditions of Use: The conditions of use, prescribed, recommended or suggested in the labeling proposed for Indomethacin for Injection have been previously approved for the reference listed drug (RLD), INDOCIN IV®.

Active Ingredients: The active pharmaceutical ingredient (API) of the proposed drug product is Indomethacin which is the same active ingredient as that of the RLD.

RLD uses Indomethacin Sodium to make the finished product. APP uses Indomethacin base since the sodium salt is not available. Due to Indomethacin base's extreme hydrophobicity, APP adds phosphate buffers to (b) (4) help keep the pH of the solution between (b) (4) 8 at which the API dissolves well and solution maintains stability. (b) (4) . At the same time Sodium Hydroxide serves as a pH adjuster. Hydrochloric Acid will also be needed to adjust the final pH of the finished product at which it is stable.

Inactive Ingredients: There were no inactive ingredients listed on the RLD's package insert. Since APP converted the API base to sodium salt, APP needs to add phosphate buffers (b) (4) dissolve at certain pH level. Additionally, Sodium Hydroxide will be added as a pH adjuster. Hydrochloric Acid will also be needed to adjust the final pH of the finished product at which it is stable.

Route of Administration, Dosage Form and Strength: The route of administration, dosage form and strength of the proposed drug product are the same as those of the reference listed drug. The proposed drug product is a sterile lyophilized drug product containing 1 mg/vial of Indomethacin, USP which is intended for intravenous injection.

Side-by-Side comparison: The side-by side comparison of reference and test products is below:

Comparison of APP Pharmaceuticals, LLC's and Innovator's Formulation

	Reference Listed Drug	**Proposed Drug Product**
Name	INDOCIN IV®	Indomethacin for Injection
Conditions of Use (Indications)	It is indicated to close hemodynamically significant patent ductus arteriosus in premature infants.	It is indicated to close hemodynamically significant patent ductus arteriosus in premature infants.
Dosage Form	Lyophilized	Sterile Lyophilized Drug Product
Route of Administration	Intravenous Injection	Intravenous Injection
Active Ingredient	Indomethacin	Indomethacin, USP
Strength	1 mg/vial	1 mg/vial
Excipients (amount/mL)	**1 mg/3-mL vial**	**1 mg/3-mL vial**
Sodium Phosphate Monobasic Monohydrate, USP	not listed	0.2898 mg
Sodium Phosphate Dibasic Anhydrous, USP	not listed	0.4117 mg
Sodium Hydroxide, NF	not listed	(b) (4)
Water for Injection, USP	q.s. to 1 mL	q.s. to 1 mL
(b) (4)	not listed	as required
	not listed	as required

BIOPHARMACEUTICS RECOMENDATION

The Office of New Drugs Quality Assessments-Biopharmaceutics Group has reviewed the information provided in NDA 22-536 for Indomethacin for Injection. From the Biopharmaceutics perspective the provided information supports the sponsor's request for a waiver of the CFR's requirement to submit in vivo bioavailability/bioequivalence data for their product. Therefore, a biowaiver is granted to APP Pharmaceuticals, LLC for their Indomethacin for Injection (1 mg/vial) product submitted under NDA 22-536 on May 8, 2009.

Angelica Dorantes, Ph.D.
Biopharmaceutics Reviewer
Office of New Drugs Quality Assessment

Date: 09/17/2009

Signed by:

Patrick Marroum, Ph.D.
Biopharmaceutics Supervisor
Office of New Drugs Quality Assessment

Date: 09/17/2009

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22536	ORIG-1	APP PHARMACEUTICALS PARTNERS LLC	INDOMETHACIN

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANGELICA DORANTES
09/24/2009

PATRICK J MARROUM
09/28/2009