CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 077908

BIOEQUIVALENCE REVIEW

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.:	77-908
Drug Product Name:	Propofol 1% Injectable Emulsion
Strength:	10 mg/mL
Route of Administration:	Intravenous
Applicant Name:	Hospira, Inc.
Address:	275 North Field Drive, Dept. 389, Bldg. H2-2, Lake Forest, IL 60045
Submission Date(s):	September 30, 2005
Amendment Date(s):	
Reviewer:	Sandra Suarez-Sharp, Ph.D.
First Generic:	No
File Location:	V:\firmsam\Hospira\ltrs&rev\77908W0905.doc

I. Executive Summary

Hospira Inc. has requested a waiver of *in vivo* bioequivalence requirements for Propofol 1 % Injectable Emulsion, 10 mg/mL. This is a resubmission of ANDA 75-599 submitted on March 8, 1999 and withdrawn on April 21, 2003 by Abbott Laboratories for the same drug product. The Test formulation is not Q1 and Q2 the same as the RLD product, Diprivan® (propofol) Injectable Emulsion, 10 mg/ml manufactured by AztraZeneca. The proposed formulation for the Test product differs from the RLD only in that the RLD contains edetate disodium and the Test formulation contains the benzyl alcohol/sodium benzoate preservative system, which was found acceptable under ANDA 75-599.

The DBE agreed that the information submitted by Abbott Laboratories under ANDA 75-599 demonstrated that the formulation of Propofol 1% Injectable Emulsion, 10 mg/ml, was acceptable under 21 CFR 314.94(9)(iii). Therefore, the test product was deemed bioequivalent to the currently approved Zeneca's Diprivan® (propofol) Injectable Emulsion, 10 mg/ml, under 21 CFR 320.24(b)(6). Since then, there have been no changes to the qualitative or quantitative formulation (including the globule size) of Propofol 1% Injectable Emulsion. Therefore, the test product in the current application is acceptable per 21 CFR 320.24 (b)(6).

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Propofol 1% Injectable Emulsion
Reference Product	Diprivan® 1% (propofol injectable emulsion, 10 mg/mL)
RLD Manufacturer	AztraZeneca
NDA No.	19-627
RLD Approval Date	05/11/1996
Indication	for use in the induction and maintenance of anesthesia or sedation

B. PK/PD Information[1]

Distribution	Following an IV bolus dose, there is rapid equilibration between the plasma and the highly perfused tissue of the brain. Plasma levels initially decline rapidly as a result of both rapid distribution and high metabolic clearance. Distribution accounts for about half of this decline following a bolus of propofol. The rate at which equilibration occurs is a function of the rate and duration of the infusion. When equilibration occurs there is no longer a net transfer of propofol between tissues and plasma. Propofol has a steady state volume of distribution (10-day infusion) approaching 60 L/kg in healthy adults.
Food Effect	N/A
Metabolism/excretion	Propofol clearance ranges from 23-50 mL/kg/min (1.6 to 3.4 L/min in 70 kg adults). It is chiefly eliminated by hepatic conjugation to inactive metabolites which are excreted by the kidney. A glucuronide conjugate accounts for about 50% of the administered dose.
Half-life	The terminal half-life of propofol after a 10-day infusion is 1 to 3 days.
Relevant OGD or DBE History	Control correspondence found for propofol injectable emulsion: • 96-331, 11/28/96, ESI Lederle. Confirmation of acceptance of in vitro BE for propofol. • 97-059, 4/25/97, Ohmeda. Requesting a pre-meeting for ANDA # 74-719 on safety issues. • 97-328, 11/11/97, Gensia. Propofol with Sodium Metabisulfite. • 98-114, 11/6/87, Zeneca. Questions regarding regulatory consequences of newly issued Zeneca patents • 98-236, 7/24/87, Bedford. Request OGD's advice or recommendation to proceed with a propofol injectable emulsion containing (b) (4) mg/mL benzyl alcohol instead of EDTA. • 99-206, Morgan/Zeneca, 6/19/1999. Propofol citizen's Petition. Request FDA refrain from approving Bedford's propofol injection ANDA (74-848) because: 1) ANDA does not have identical active ingredients, 2) benzyl alcohol is not a proper substitution for EDTA, 3) no change in formulation for an ANDA can effect the safety and efficacy - use of benzyl alcohol does, 4) an ANDA cannot have a warning the RLD does not contain, 5) the ANDA is not BE to the RLD, 6) the ANDA is not

[1] PR online

	TE to the RLD, and 7) exclusivity does not end until 6-19-99. Relevant History for ANDA 75-599 (Original submission of this current submission for propofol injectable emulsion: • On February 12, 1992, Abbott requested an opinion from the DBE as to the need for a BE study based on the uniqueness of the emulsion –based formulation. • On August 25, 1993 the DBE provided the following information: o "The globule size of the proposed drug product will have great influence on the safety and efficacy of the product. Therefore, information should be provided about the globule size distribution and control, including upper globule size limit….. • On March 15, 1999, OGD received the application (ANDA #75-599) for Propofol Injectable Emulsion 10 mg/mL, using alternate inactive ingredients as preservatives, specifically benzyl alcohol 0.15% and sodium benzoate 0.07%. The listed reference drug contains edetate disodium as a preservative. • On July 1, 1999, OGD received a copy of a memorandum from Dr. Rappaport (Deputy Director, DACCADP, HFD-170) requesting preclinical and clinical studies to support this formulation. On July 30, 1999, OGD issued "fatal-flaw" not approvable letter to the firm. • Subsequently, Abbott provided additional data from the literature to support the use of benzyl alcohol in subjects > 3 years of age. • On December 27, 1999, Dr. Rappaport issued a memorandum reversing the previous recommendation. In view of this reversal Abbott's applications was returned to the review queue. In addition, FDA's response to AstraZeneca citizen's petition, Section E.1. page 9, last paragraph states the following "We have reviewed, based on scientific experience, the potential hazardous associated wit benzyl alcohol. A review of all relevant information indicates that a generic

propofol product containing benzyl alcohol presents negligible risk to the indicated patient population".

- The waiver request submitted to ANDA 75-599 on July 30, 1999 and February 03, 2000 was reviewed by the Division of Bioequivalence and the request was denied due to high mean globule size of the test product compared to the RLD (review date 3/17/2000).

    - On March 29, 2000, the firm challenges the decision to deny the waiver request of ANDA #75-599 based on the difference in globule size pattern between the test and RLD product (see attachment in appendix)

The DBE reviewer of the March 29, 2000 submission made the following comments:

- DBE management discussed the issues regarding the globule size pattern of Abbott's propofol injectable emulsion 10 mg/mL (ANDA #75-599) on July 5, 2000. It was noted that Abbott's (b) (4)

- The reviewer of submission dated March 29, 2000 made the following conclusion: "The Division of Bioequivalence agrees that the information submitted by Abbott Laboratories demonstrates that the formulation of Propofol Injectable Emulsion, 10 mg/ml, is acceptable under 21 CFR 314.94(9)(iii). The test product is deemed bioequivalent to the currently approved Zeneca's Diprivan® (propofol) Injectable Emulsion, 10 mg/ml, under 21 CFR 320.24(b)(6) of the Bioavailability/Bioequivalence Regulations" (see attachment on appendix).

<u>Brief history of the ANDA #74-704 (see attachment on appendix for more details)</u>:

- (b) (4)

	(b) (4) • The firm's formulation Propofol Injectable Emulsion 1%, with EDTA was found acceptable to the Division of Bioequivalence (review date 3/26/97). As previously stated, this formulation was tentatively approved by OGD.

C. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	
Single-dose fed	No	
Steady-state	No	
In vitro dissolution	No	
Waiver requests	Yes	1
BCS Waivers	No	
Vasoconstrictor Studies	No	
Clinical Endpoints	No	
Failed Studies	No	
Amendments	No	

D. Pre-Study Bioanalytical Method Validation:

N/A

E. In Vivo Studies:

N/A

F. Formulation

Location in appendix	Section IV, Page 9
Are inactive ingredients within IIG limits?	**Yes**
If NO, list ingredients outside of limits	
If a tablet, is the product scored?	**N/A**
If yes, which strengths are scored?	
Is scoring of RLD the same as test?	
Is the formulation acceptable?	**Yes**
If not acceptable, why?	

G. In Vitro Dissolution

N/A

H. Waiver Request(s)

Strengths for which waivers are requested	10 mg/mL
Regulation cited	21 CFR 320.24 (b) (6)
Proportional to strength tested in vivo?	N/A
Is dissolution acceptable?	N/A
Waivers granted?	Yes
If not then why?	

I. Discussion

The subject application is a resubmission of ANDA 75-599, which was originally submitted on March 8, 1999 by Abbott Labs. Hospira (then Abbot Laboratories) requested withdrawal of the application on April 21, 2003. At the time of withdrawal of the application, all deficiencies, with the exception of the microbial performance deficiency had been addressed. The Test formulation submitted under ANDA 75-599 contained the same active and inactive ingredients as the RLD product, Diprivan® 1% (propofol injectable emulsion, 10 mg/mL) manufactured by AztraZeneca except that the Test formulation contained the benzyl alcohol/sodium benzoate preservative system. The FDA reviewed all relevant information pertaining the inclusion of benzyl alcohol and concluded that a generic propofol product containing benzyl alcohol presented negligible risk to the indicated patient population. Other information relevant to the DBE (including globule size) to support the approval of ANDA 77-908, has been submitted and reviewed under ANDA 75-599. Under ANDA 75-599, the propofol 1% injectable emulsion, 10 mg/ml, was acceptable as per 21 CFR 314.94(9)(iii) and was deemed bioequivalent to the currently approved Zeneca's Diprivan® (propofol) Injectable Emulsion, 10 mg/ml, under 21 CFR 320.24(b)(6). Since then, there have been no changes to the qualitative or quantitative formulation (including globule size) of propofol 1% injectable emulsion. Therefore, as stated above, the test product in the current application is acceptable per 21 CFR 320.24 (b)(6). The application is acceptable with no DBE deficiencies.

J. Recommendations

The Division of Bioequivalence agrees that the information submitted by Hospira, Inc. demonstrates that its Propofol 1% Injectable Emulsion 10 mg/mL falls under 21 CFR 314.94(9)(iii). The application is acceptable per 21 CFR 320.24 (b)(6). The test product, Propofol 1% Injectable Emulsion 10 mg/mL, is deemed bioequivalent to the currently approved Diprivan® 1% (Propofol 1% Injectable Emulsion 10 mg/mL) manufactured by AztraZeneca.

12/07/05

Sandra Suarez-Sharp, Ph.D.
Reviewer, Team III
Division of Bioequivalence

Date

12/7/2005

Yih-Chain Huang, Ph.D.
Team Leader, Team III
Division of Bioequivalence

Date

12/9/05

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

Date

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IV. Appendix

A. Formulation Data

Table 1. Description and Composition of Drug Product Propofol 1% Injectable Emulsion 10 mg/mL

Ingredient (mg/mL)	Hospira's proposed Formulation (mg/mL)	Zeneca's Diprivan® Formulation (mg/mL)[1]
Propofol	10	10
Soybean Oil, USP	100	100
Glycerin, USP	22.5	22.5
Egg Lecithin (b) (4)	12	12
Edetate Disodium (EDTA)	--	0.05
Benzyl Alcohol	1.5	--
Sodium Benzoate	0.70	--
Sodium Hydroxide, NF	To adjust pH	To adjust pH
Water for Injection	qs	qs
(b) (4)	(b) (4)	(b) (4)

[1]Confirmed from the FDA's COMIS database, PDR® and the DBE reviews.

B. Additional Attachments

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BIOEQUIVALENCE COMMENTS

ANDA: 77-908 APPLICANT: Hospira, Inc.

DRUG PRODUCT: Propofol 1% Injectable Emulsion 10 mg/mL

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Barbara M. Davit

for Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 77-908
ANDA DUPLICATE
DIVISION FILE
HFD-650/ Bio Secretary - Bio Drug File
HFD-650/ Suarez

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Endorsements: (Final with Dates)
HFD-650/ Suarez-Sharp SSS 12/07/05
HFD-650/ YC. Huang YH 12/7/2005
HFD-650/ D. Conner BRD 12/9/05

BIOEQUIVALENCE - **ACCEPTABLE**

Submission dates:
09/~~20~~30/2005.

1. WAIVER (WAI) OK

Strength: 10 mg/mL
Outcome: AC

Outcome Decision: AC - Acceptable

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #:	77-908
SPONSOR:	Hospira, Inc.
DRUG AND DOSAGE FORM:	Propofol 1% Injectable Emulsion 10 mg/mL Solution
STRENGTH(S):	10 mg/mL
TYPES OF STUDIES:	N/A
CINICAL STUDY SITE(S):	N/A
ANALYTICAL SITE(S):	N/A

STUDY SUMMARY:	N/A
DISSOLUTION:	N/A.
WAIVER REQUEST:	Acceptable

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic No New facility _____ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER: Sandra Suarez-Sharp, Ph.D. BRANCH: III

INITIAL : SSS DATE : 12/07/05

TEAM LEADER: Yih-Chain Huang, Ph.D BRANCH: III

INITIAL : YCH DATE : 12/7/2005

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : BPC DATE : 12/9/05