

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

**ANDA 77-393**

**Name:** Sterile Water for Injection USP, packaged in 5 mL and 10 mL single-dose plastic ampules.

**Sponsor:** Taro Pharmaceuticals Ireland Ltd.

**Approval Date:** August 11, 2006

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**ANDA 77-393**

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**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**ANDA 77-393**

**APPROVAL LETTER**

ANDA 77-393

AUG 11 2006

Taro Pharmaceuticals U.S.A., Inc.  
U.S. Agent for: Taro Pharmaceuticals Ireland Ltd.  
Attention: Kalpana Rao  
Group Vice President, Regulatory Affairs (Global)  
5 Skyline Drive  
Hawthorne, NY 10532

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated November 19, 2004, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Sterile Water for Injection USP, packaged in 5 mL and 10 mL single-dose plastic ampules.

Reference is also made to your amendments dated February 8, July 21, and September 22, 2005; and January 23, May 24, and June 22, 2006.

We have completed the review of this ANDA and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved. The Division of Bioequivalence has determined your Sterile Water for Injection, USP to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug, Sterile Water for Injection, USP packaged in plastic containers of Hospira, Inc.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications  
5901-B Ammendale Road  
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

  
Gary Buehler  
Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research

8/11/2006

cc: ANDA 77-393  
Division File  
Field Copy  
HFD-610/R. West  
HFD-013  
HFD-610/Orange Book Staff

Endorsements:

HFD-600/N.Nashed/

HFD-623/J.Fan/

HFD-617/R.Adigun/

HFD-613/A.Payne/

HFD-613/J.Grace/

*NW 7/5/06 NW 8/10/06*  
*Q 7/2/06 Q 8/10/06*  
*RA 06/28/06*

*AB  
revised  
9/11/06*

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F/T by

APPROVAL

*Robert West  
8/11/2006*

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*  
**ANDA 77-393**

**LABELING**

APPROVED

AUG 11 2006

DPL 379

ANTIGEN - 20 x 10ml HEPSAL

Scaled at 90%



Sterile Water for Injection, USP

NDC 51672-3018-1

20 single dose x 10 mL ampules

10 mL

NDC 51672-3018-1

20 single dose x 10 mL ampules

10 mL

**Sterile Water for Injection, USP**

FOR DRUG DILUENT USE.  
Preservative Free

**Usual dosage:** See package insert for full prescribing information.  
Do not give intravenously unless rendered nearly isotonic.  
Contains no antimicrobial or other added substance. pH 5.0 to 7.0.  
**Store at 20°-25°C (68°-77°F)** [see USP Controlled Room Temperature]

Rx only

**TARO**

PK-0000-0  
0106-0  
MOO

Mfd. by:  
Taro Pharmaceuticals Ireland, Ltd.  
Roscrea Co, Tipperary, Ireland

Dist. by:  
Taro Pharmaceuticals U.S.A., Inc.  
Hawthorne, NY 10532



NDC 51672-3018-1

20 single dose x 10 mL ampules

10 mL

**Sterile Water for Injection, USP**

FOR DRUG DILUENT USE.  
Preservative Free

**Usual dosage:** See package insert for full prescribing information.  
Do not give intravenously unless rendered nearly isotonic.  
Contains no antimicrobial or other added substance. pH 5.0 to 7.0.  
**Store at 20°-25°C (68°-77°F)** [see USP Controlled Room Temperature]

Rx only

**TARO**

DPL 946  
20 X 5ml  
187 x 34 x 73mm

APPROVED  
AUG 11 2006

# Scaled at 90%



170MM

170MM

# Sterile Water for Injection, USP Rx Only Plastic Ampule

APPROVED

AUG 11 2006

## DESCRIPTION

This preparation is designed solely for parenteral use only after addition of drugs that require dilution or must be dissolved in an aqueous vehicle prior to injection.

Sterile Water for Injection, USP is a sterile, nonpyrogenic preparation of water for injection, which contains no bacteriostat, antimicrobial agent or added buffer and is supplied only in single-dose containers to dilute or dissolve drugs for injection. The blow-fill-sealed twist-off top, plastic ampule is molded from a specially formulated polypropylene. For I.V. injection, add sufficient amount to a solute to make an approximately isotonic solution.

Water for Injection, USP is chemically designated H<sub>2</sub>O. The pH is 5.0 to 7.0.

## CLINICAL PHARMACOLOGY

Water is an essential constituent of all body tissues and accounts for approximately 70% of total body weight. Average normal adult daily requirement ranges from two to three liters (1.0 to 1.5 liters each for insensible water loss by perspiration and urine production).

Water balance is maintained by various regulatory mechanisms. Water distribution depends primarily on the concentration of electrolytes in the body compartments and sodium (Na<sup>+</sup>) plays a major role in maintaining physiologic equilibrium.

The small volume of fluid provided by Sterile Water for Injection, USP when used only as a pharmaceutical aid for diluting or dissolving drugs for parenteral injection, is unlikely to exert a significant effect on fluid balance except possibly in newborns or very small infants.

## INDICATIONS AND USAGE

This preparation is indicated only for diluting or dissolving drugs intended for parenteral injection, according to instructions of the manufacturer of the drug to be administered.

## CONTRAINDICATIONS

Sterile Water for Injection, USP must be made approximately isotonic prior to use.

## WARNINGS

Intravenous administration of Sterile Water for Injection without a solute may result in hemolysis.

Some drugs for injection may be incompatible in a given vehicle, or when combined in the same vehicle. Consult with pharmacist, if available.

The plastic ampule is molded from a specially formulated polypropylene.

When diluting or dissolving drugs, mix thoroughly and use promptly.

Do not store reconstituted solutions of drugs for injection unless otherwise directed by the manufacturer of the solute.

## PRECAUTIONS

Do not use unless the solution is clear and seal intact. Do not reuse single-dose containers, discard unused portion.

Consult the manufacturer's instructions for choice of vehicle, appropriate dilution or volume for dissolving the drugs to be injected, including the route and rate of injection.

Inspect reconstituted (diluted or dissolved) drugs for clarity (if soluble) and freedom from unexpected precipitation or discoloration prior to administration.

*Pregnancy Category C.* Animal reproduction studies have not been conducted with Sterile Water for Injection, USP. It is also not known whether Sterile Water for Injection, USP can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Sterile Water for Injection, USP with additives should be given to a pregnant woman only if clearly needed.

## Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies with solutions in polypropylene ampules have not been performed to evaluate carcinogenic potential, mutagenic potential or effects on fertility.

## Drug Interactions

Some drugs for injection may be incompatible in a given vehicle, or when combined in the same vehicle. Consult with pharmacist, if available.

When diluting or dissolving drugs, mix thoroughly and use promptly.

Do not store reconstituted solutions of drugs for injection unless otherwise directed by the manufacturer of the solute.

Do not use unless the solution is clear and seal intact. Do not reuse single-dose containers. Discard unused portion.

## ADVERSE REACTIONS

Reactions which may occur because of this solution, added drugs or the technique of reconstitution or administration include febrile response, local tenderness, abscess, tissue necrosis or infection at the site of injection, venous thrombosis or phlebitis extending from the site of injection and extravasation.

If an adverse reaction does occur, evaluate the patient, institute appropriate countermeasures, and if possible, retrieve and save the remainder of the unused vehicle for examination.

## OVERDOSAGE

Use only as a diluent or solvent. This parenteral preparation is unlikely to pose a threat of fluid overload except possibly in newborn or very small infants.

## DOSAGE AND ADMINISTRATION

The volume of the preparation to be used for diluting or dissolving any drug for injection, is dependent on the vehicle concentration, dose and route of administration as recommended by the manufacturer of the drug and be administered.

Use aseptic technique for entry and withdrawal from container.

This parenteral should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. See **PRECAUTIONS**.

## HOW SUPPLIED

NDC #	Volume
51672-3018-0	single-dose 5 mL Ampule
51672-3018-1	single-dose 10 mL Ampule

Packaged in a polypropylene ampule. Ampules are packaged 20 per tray.

**Store at 20°-25°C (68°-77°F)** [see USP Controlled Room Temperature].

Mfd. by: Taro Pharmaceuticals Ireland, Ltd., Roscrea Co, Tipperary, Ireland  
Dist. by: **Taro Pharmaceuticals U.S.A., Inc.**, Hawthorne, NY 10532

Revised: January, 2006

175 MM

175 MM

NDC 51672-3018-0      single dose 5 mL  
Sterile Water for Injection, USP  
Rx only, FOR DRUG DILUENT USE.  
Mfd. by: Taro Pharmaceuticals Ireland, Ltd.



5ml 22 x 10mm

NDC 51672-3018-1      single dose 10 mL  
Sterile Water for Injection, USP  
Rx only, FOR DRUG DILUENT USE.      Mfd. by: Taro Pharmaceuticals Ireland, Ltd.



10ml 45 x 8mm

APPROVED

AUG 11 2006

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**ANDA 77-393**

**LABELING REVIEWS**

**REVIEW OF PROFESSIONAL LABELING #1  
DIVISION OF LABELING AND PROGRAM SUPPORT  
LABELING REVIEW BRANCH**

*Date 11-29-05*

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ANDA Number: 77-393                      Dates of Submission: Feb. 8, 2005; Nov. 14, 2004 (original)  
Applicant's Name: Taro Pharms Ireland  
Established Name: Sterile Water for Injection USP, 5 mL and 10 mL - ampules

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**Labeling Deficiencies:**

**1. CONTAINER (5 mL and 10 mL):**

- a. Include the drug use "FOR DRUG DILUTENT USE".
- b. Please provide a drawing of your ampules and comment on how one would gain access to the product inside the ampules. The reference listed drug uses glass ampules that must be popped at the designated line.
- c. Please indicate "single dose".

**2. CARTON (20s X 5 mL):**

- a. Place the following in bold print and all caps "FOR DRUG DILUTENT USE".
- b. Revise "ampoules" to read "ampules".
- c. See comments under CONTAINER.
- d. Include the pH range

**3. INSERT:**

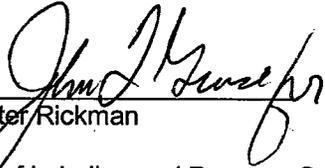
- a. Include the "Rx only" statement so that it follows the title.
- b. Please include a statement about your ampule composition.
- c. CONTRAINDICATIONS - add USP to the established name.
- d. PRECAUTIONS-
  - i. We recommend including a pregnancy subsection. We refer you the CFR for guidance.
  - ii. You cited "plastic syringe" revise to reflect your container specifically "plastic ampule".
  - iii. Drug Interactions subsection- add, "...seal intact. Do not reuse single-dose containers. Discard unused portion".
- e. WARNINGS - you cited plastic syringe revise to comply with your product specifications "plastic ampule".
- f. DOSAGE AND ADMINISTRATION - Add "Use aseptic technique for entry and withdrawal from container".
- g. HOW SUPPLIED - Describe your containers as single-dose containers and delete the container size 5 mL in a 5 mL ampule should read 5 mL ampules. Change the spelling of ampoules.

Please revise your labels and labeling, as instructed above, and submit actual sized final printed labels and labeling. The electronic labeling rule published December 11, 2003, (68.FR 69009) requires

submission of labeling content in electronic format effective June 8, 2004. For additional information, consult the following guidance for industry regarding electronic submissions: Providing Regulatory Submissions in Electronic Format — ANDAs (Issued 6/2002) (<http://www.fda.gov/cder/guidance/5004fnl.htm>). The guidance specifies labeling to be submitted in pdf format. To assist in our review, we request that labeling also be submitted in MS Word format.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - <http://www.fda.gov/cder/cdernew/listserv.html> or <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

  
Wm. Peter Rickman  
Director  
Division of Labeling and Program Support  
Office of Generic Drugs  
Center for Drug Evaluation and Research

~~APPROVAL SUMMARY~~  
**REVIEW OF PROFESSIONAL LABELING**  
**DIVISION OF LABELING AND PROGRAM SUPPORT**  
**LABELING REVIEW BRANCH**

**ANDA Number** 77-393  
**Date of Submission**  
**Applicant** Taro Pharm  
**Drug Name**  
**Strength(s)**

FPL Approval Summary		
<b>Container Labels</b>		<b>Submitted</b>
5 ml and 10 mL	XXXXXXXX	vol XX
<b>Package Insert Labeling</b>	#XXXXRev.	vol XX

**BASIS OF APPROVAL:**

**Patent Data For NDA 18-801**

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	None			PI	

**Exclusivity Data For NDA 18-801**

Code/sup	Expiration	Description	Labeling impact

**Reference Listed Drug**

RLD on the 356(h) form SWFI  
 NDA Number 18-801  
 RLD established name Sterile Water for Injection USP  
 Firm Abbott  
 Currently approved PI S-023  
 AP Date April 7, 2004

Note: RLD insert is combined with several other diluent products that are not the subject of this application. Y-27 submitted in Dec 2004 with a revision date of 1997 has been superceded by April 7, 2004 revision year 2000.

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. <b>USP 24</b>	x		
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?			x
<b>Error Prevention Analysis</b>			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
<b>PACKAGING</b> -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC. [see FTR]		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
<b>LABELING</b>			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			x
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and		X	

labeling? Is "Jointly Manufactured by...", statement needed?			
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			x
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
<b>Scoring:</b> Describe scoring configuration of RLD and applicant (p. #) in the FTR			
Is the scoring configuration different than the RLD?			x
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			x
<b>Inactive Ingredients:</b> (FTR: List p. # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?	X		
Do any of the inactives differ in concentration for this route of administration?			X
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
<b>USP Issues:</b> (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?[see FTR]		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
<b>Bioequivalence Issues:</b> (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
<b>Patent/Exclusivity Issues:</b> FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state. <b>NONE</b>			

**NOTE TO CHEMIST:**

**FOR THE RECORD:**

**1. MODEL LABELING**

This review was based on the labeling for NDA 18-801 diluent products by Abbott now hospira. The insert includes glass ampules, plastic vials, plastic syringes for 9% NA Cl, 5% dextrose and SWFI al for use as a drug diluent

2. **PATENTS/EXCLUSIVITIES: See above.** Originally firm had 88-400 but the correct RLD is 18-801 see attached email from Don Hare dated 1/4/05. Orange Book will make all NDA application into RLD [Vol. A1.1 pg. 10-12]

3. **MANUFACTURING FACILITY OF FINISHED DOSAGE FORM** by taro pharm in Ireland for Taro PhARM USA in Hawthorne, NY [Vol. A1.]

4. **CONTAINER/CLOSURE**

RLD: 5 ml, 10 mL, 20 mL SD glass ampul, 10 mL, 20 mL, 50 mL SD- and 100 mL single -dose plastic floptop vials, and Ansyr Plastic syringes.

ANDA: 5 mL and 10 mL SD plastic ampuls.

[Vol. A1.2 pg.]

5. **INACTIVE INGREDIENTS**

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. No bacteriostatid, antimicrobial agent or added buffer. [Vol. A1.1 pg. 106 and Vol. A1.2 pg. 532.]

6. **PACKAGING CONFIGURATIONS**

RLD: glass vials in cartons of 5s

ANDA: plastic ampules in boxes of 20s

USP: Preserve in single-dose glass or plastic containers, of not larger than 1-L size. Glass containers are preferably of Type I or Type II glass. [Vol. ]

7. **STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON**

USP:

RLD: CRT.15-30C

ANDA: Store at 20-25C

8. **DISPENSING STATEMENTS COMPARISON**

USP: Label it to indicate that no antimicrobial or other substance has been added, and that it is not suitable for intravascular injection without first having been made approximately isotonic by the addition of a suitable solute.

RLD: same

ANDA (*Insert*): Same

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Date of Review: 10/25/05

Date of Submission: Feb. 8, 2005; Nov. 14, 2004 (original)

---

cc:

ANDA: 77-393  
DUP/DIVISION FILE  
HFD-613/APayne/JGrace (no cc)  
V:\FIRMSNZ\TARO\LTRS&REV\77393NA1.lab.doc  
Review digital signature and Date: APayne 10/25/05  
Draft e-dr \CDSESUB1\N77393IN\_000\2005-02-08

*Done 10/25/05*  
*John D...*  
*11/30/05*

**APPROVAL SUMMARY  
 REVIEW OF PROFESSIONAL LABELING  
 DIVISION OF LABELING AND PROGRAM SUPPORT  
 LABELING REVIEW BRANCH**

<b>ANDA Number</b>	77-393
<b>Date of Submission</b>	23 Jan 2006
<b>Applicant</b>	Taro Pharm
<b>Drug Name</b>	Sterile Water for Injection USP
<b>Strength(s)</b>	5 mL and 10 mL - ampules

**FPL Approval Summary - only paper copies -**

Container Labels	Submitted	
5 ml and 10 mL	23 Jan 2006,	vol 5.1A
Cartons -20s	23 Jan 2006	vol 5.1A
Package Insert Labeling	23 Jan 2006	vol 5.1A

**BASIS OF APPROVAL:**

**Patent Data For NDA 18-801**

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	None			PI	

**Exclusivity Data For NDA 18-801**

Code/sup	Expiration	Description	Labeling impact

**Reference Listed Drug**

RLD on the 356(h) form	SWFI
NDA Number	18-801
RLD established name	Sterile Water for Injection USP
Firm	Abbott
Currently approved PI	S-023
AP Date	April 7, 2004

Note: RLD insert is combined with several other diluent products that are not the subject of this application. Y-27 submitted in Dec 2004 with a revision date of 1997 has been superceded by April 7, 2004 revision year 2000.

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. <b>USP 24</b>	x		
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?			x
<b>Error Prevention Analysis</b>			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
<b>PACKAGING</b> -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC. [see FTR]		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
<b>LABELING</b>			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			x
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and		X	

labeling? Is "Jointly Manufactured by...", statement needed?			
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			x
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
<b>Scoring:</b> Describe scoring configuration of RLD and applicant (p. #) in the FTR			
Is the scoring configuration different than the RLD?			x
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			x
<b>Inactive Ingredients:</b> (FTR: List p. # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?	X		
Do any of the inactives differ in concentration for this route of administration?			X
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
<b>USP Issues:</b> (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?[see FTR]		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
<b>Bioequivalence Issues:</b> (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
<b>Patent/Exclusivity Issues:</b> FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state. <b>NONE</b>			

**NOTE TO CHEMIST:**

**FOR THE RECORD:**

1. MODEL LABELING

This review was based on the labeling for NDA 18-801 diluent products by Abbott now hospira. The insert includes glass ampules, plastic vials, plastic syringes for 9% NA Cl, 5% dextrose and SWFI al for use as a drug diluent

2. **PATENTS/EXCLUSIVITIES:** See above. Originally firm had 88-400 but the correct RLD is 18-801, see attached email from Don Hare dated 1/4/05. Orange Book will make all NDA application into RLD [Vol. A1.1 pg. 10-12]

3. **MANUFACTURING FACILITY OF FINISHED DOSAGE FORM** by taro pharm in Ireland for Taro PhARM USA in Hawthorne, NY [Vol. A1.]

4. **CONTAINER/CLOSURE**

RLD: 5 ml, 10 mL, 20 mL SD glass ampul, 10 mL, 20 mL, 50 mL SD- and 100 mL single -dose plastic fliptop vials, and Ansy Plastic syringes.

ANDA: 5 mL and 10 mL SD plastic ampuls.

[Vol. A1.2 pg.]

5. **INACTIVE INGREDIENTS**

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. No bacteriostatid, antimicrobial agent or added buffer. [Vol. A1.1 pg. 106 and Vol. A1.2 pg. 532.]

6. **PACKAGING CONFIGURATIONS**

RLD: glass vials in cartons of 5s

ANDA: plastic ampules in boxes of 20s

USP: Preserve in single-dose glass or plastic containers, of not larger than 1-L size. Glass containers are preferably of Type I or Type II glass. [Vol. ]

7. **STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON**

USP:

RLD: CRT.15-30C

ANDA: Store at 20-25C

8. **DISPENSING STATEMENTS COMPARISON**

USP: Label it to indicate that no antimicrobial or other substance has been added, and that it is not suitable for intravascular injection without first having been made approximately isotonic by the addition of a suitable solute.

RLD: same

ANDA (Insert): Same

---

Date of Review: 2/01/06

Date of Submission: 23 JAN 2006

---

cc:

ANDA: 77-393  
DUP/DIVISION FILE  
HFD-613/APayne/JGrace (no cc)  
V:\FIRMSNZ\TARO\LTRS&REV\77393AP1.lab.doc  
Review digital signature and Date: APayne 2/01/06  
Fpl NO edr

*APayne 2/1/06*  
*John M. 2.10.2006*

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*  
**ANDA 77-393**

**CHEMISTRY REVIEWS**

#1

**CHEMISTRY REVIEW**

**ANDA 77-393**

**Sterile Water for Injection USP, in Plastic Container**

**Taro Pharmaceuticals Ireland Ltd.**

**Nashed E. Nashed, Ph.D.**

**Chemistry Division 1**

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# Chemistry Review Data Sheet

1. ANDA: 77-393 (First Generic)
2. REVIEW #: 1
3. REVIEW DATE: 3/9/05
4. REVIEWER: Nashed E. Nashed, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

N/A

Document Date

N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original Submission

Acceptable for filling

New Correspondence

Telephone Amendment

Document Date

11/19/04

11/22/04

1/5/05

1/21/05

7. NAME & ADDRESS OF APPLICANT:

Name: Taro Pharmaceuticals Ireland Ltd.

U.S. Agent: Taro Pharmaceuticals U.S.A., Inc.

Address: 5 Skyline Drive, Hawthorne, NY 10532

Representative: Kalpana Rao

Telephone: 914-345-9001

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A

b) Non-Proprietary Name (USAN): Sterile Water for Injection, USP

9. LEGAL BASIS FOR SUBMISSION:

The firm has provided Paragraph I Certification.  
 The firm certifies, in its opinion and to the best of its knowledge, that there are no patents listed, for Sterile Water for Injection, USP in Plastic Container.  
 The Reference Listed Drug is Sterile Water for Injection, USP in Plastic Vials manufactured by Hospira, Inc., the NDA 18-801holder.  
 The firm certifies that in its opinion and to the best of its knowledge, there are no unexpired exclusivities for Sterile Water for Injection, USP.

10. PHARMACOL CATEGORY:

Diluents

11. DOSAGE FORM:

Liquid

12. STRENGTH/POTENCY:

100%

13. ROUTE OF ADMINISTRATION:

Injectable; injection

14. Rx/OTC DISPENSED:      xx   Rx             OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

     SPOTS product – Form Completed

  xx   Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

H<sub>2</sub>O        M.W. 18

17. RELATED/SUPPORTING DOCUMENTS:

# CHEMISTRY REVIEW

## Chemistry Review Data Sheet

### A. DMFs:

b(4)

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
5	III	[ ]	[ ]	4			

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

### B. Other Documents: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

### 18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Pending		
EES	Pending		
Methods Validation	Not required.		
Labeling	Pending		
Bioequivalence	Acceptable	3/17/05	L. Sanchez
EA	Acceptable.		
Radiopharmaceutical	N/A		

**CHEMISTRY REVIEW**

Chemistry Review Data Sheet

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt.  Yes  No If no, explain reason(s) below:

# The Chemistry Review for ANDA 77-393

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

This application is not approvable due to minor deficiencies.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

The Sterile Water for Injection USP will be packaged in 5 mL and 10 mL ampoule.

b(4)

Water for injection, USP used in the manufacture Sterile Water for Injection, USP complies with USP specifications for Water for Injection intended for use in the preparation of parenteral products. The water used for the preparation of Sterile Water for Injection, USP is

b(4)

The water used in the manufacture of Sterile Water for Injection, USP is  and

The firm has provided blank copy of the master batch record (MBR) for the intended maximum product batch size of   (both 5 mL and 10 mL ampoules) in Module 3, Section 3.2.P.3.3.A.

b(4)

The firm has submitted copies of the exhibit batch records Lot #TP41 (Batch size:   for the 5 mL Ampoule and Lot #TP45 (Batch size:   for the 10 mL Ampoule in section 3.2.R.1

#### B. Description of How the Drug Product is Intended to be Used

This parenteral preparation is indicated only for diluting or dissolving drugs for intravenous, intramuscular or subcutaneous injection, according to instructions of the manufacturer of the drug to be administered.

## CHEMISTRY REVIEW

### Executive Summary Section

The volume of the preparation to be used for diluting or dissolving any drug for injection, is dependent on the vehicle concentration, dose and route of administration as recommended by the manufacturer.

Use aseptic technique for single entry and withdrawal from all containers. Single dose vials should be entered just once.

When diluting or dissolving drugs, mix thoroughly and use promptly.

Do not store reconstituted solutions of drugs for injection unless directed by the manufacturer of the solute.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

The recommended storage condition is 20° – 25°C (68° – 77°F)

The product is supplied in 5 mL in a 5 mL Ampoule, and 10 mL in a 10 mL Ampoule. Packaged in a polypropylene ampoule. Ampoules are packaged 20 vials per tray.

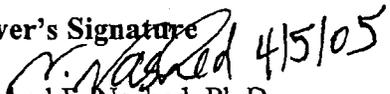
Single dose use. No preservative added. Unused portion of ampoule should be discarded. Use only if solution is clear and seal intact.

#### C. Basis for Approvability or Not-Approval Recommendation

The application is not approvable due to minor deficiencies.

### III. Administrative

#### A. Reviewer's Signature

  
Nashed E. Nashed, Ph.D.

#### B. Endorsement Block

James M. Fan

 4/5/05

Withheld 11 page(s)  
of trade secret and/or  
confidential commercial  
information from

\_\_\_\_\_ Chemistry Review #1 \_\_\_\_\_

(b) (4)

**CHEMISTRY REVIEW**

Chemistry Assessment Section

**36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT**

ANDA: 77-393

APPLICANT: Taro Pharmaceuticals Ireland Ltd.

DRUG PRODUCT: Sterile Water for Injection USP, in Plastic Container

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. ✓

2.

3.

**b(4)**

4. L

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The firms referenced in your application should be in compliance with cGMP at the time of approval.
2. Please provide all available drug product room temperature stability data.

**CHEMISTRY REVIEW**

Chemistry Assessment Section

3. Labeling and microbiology information you have provided is pending review. After the reviews are completed, any deficiencies found will be communicated to you under a separate cover.

Sincerely yours,



Rasmikant M. Patel, Ph.D.

Director

Division of Chemistry I

Office of Generic Drugs

Center for Drug Evaluation and Research

CHEMISTRY REVIEW

Chemistry Assessment Section

cc: ANDA 77-393  
ANANDA DUP  
Division File  
Field Copy

Endorsements:

HFD-627/N.Nashed /3/11/05 *NN 4/5/05*  
HFD-627/J.Fan/4/1/05  
HFD-617/A.Vu/4/4/05 *4/5/05*

F/T:ard/4/4/05

*Initials for  
4/5/05*

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#2



**CHEMISTRY REVIEW**



**ANDA 77-393**

**Sterile Water for Injection USP, in Plastic Container**

**Taro Pharmaceuticals Ireland Ltd.**

**Nashed E. Nashed, Ph.D.**

**Chemistry Division 1**

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<b>C. Basis for Approvability or Not-Approval Recommendation</b> .....	<b>8</b>
<b>Chemistry Assessment</b> .....	<b>9</b>



# Chemistry Review Data Sheet

1. ANDA: 77-393 (First Generic)

2. REVIEW #: 2

3. REVIEW DATE: 9/15/05

Revised: 11/21/05

Revised: 6/30/06

4. REVIEWER: Nashed E. Nashed, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	N/A

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission	11/19/04
Acceptable for filling	11/22/04
New Correspondence	1/5/05
Telephone Amendment	1/21/05
Minor Amendment	7/21/05
Gratuitous Amendment	9/22/05
Labeling Amendment	1/23/06
Minor Amendment (Micro Amendment)	5/24/06
Telephone Amendment	6/22/06

7. NAME & ADDRESS OF APPLICANT:

Name: Taro Pharmaceuticals Ireland Ltd.  
U.S. Agent: Taro Pharmaceuticals U.S.A., Inc.

Address: 5 Skyline Drive, Hawthorne, NY 10532

Representative: Kalpana Rao

Telephone: 914-345-9001



8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: N/A
- b) Non-Proprietary Name (USAN): Sterile Water for Injection, USP

9. LEGAL BASIS FOR SUBMISSION:

Taro has provided Paragraph I Certification.

In the opinion and to the best of knowledge of Taro Pharmaceuticals, there are no patents that claim the listed drug, Sterile Water for Injection USP, referred to in this application.

Taro certified that the reference listed drug is not entitled to a period of marketing exclusivities.

The Reference Listed Drug is Sterile Water for Injection in plastic container; NDA 18-801 is hold by Hospira, Inc.

10. PHARMACOL CATEGORY:

Diluents

11. DOSAGE FORM:

Liquid

12. STRENGTH/POTENCY:

100% (5 mL and 10 mL - ampules)

13. ROUTE OF ADMINISTRATION:

Injectable; injection

14. Rx/OTC DISPENSED:   xx   Rx        OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

       SPOTS product – Form Completed

  xx   Not a SPOTS product



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

**H<sub>2</sub>O**

**M.W. 18**

### 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
[ ]	III	[ ]	[ ]	4			

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

#### B. Other Documents: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

### 18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Acceptable	6/23/06	Marla Stevens-Riley
EES	Acceptable	7/7/06	
Methods Validation	Not required.		
Labeling	Acceptable	2/10/06	A. Payne
Bioequivalence	Acceptable	3/17/05	A. Sigler
EA	Not required		
Radiopharmaceutical	N/A		



19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. \_\_\_ Yes \_\_xx\_\_ No If no, explain reason(s) below:

The application is Minor

# The Chemistry Review for ANDA 77- 393

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

Application is approvable.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

The drug product is supplied as 5 mL and in a 5 mL ampoule, and 10 mL in a 10 mL ampoule. The ampoules are made of polypropylene, and packaged 20 per tray.

b(4)

Water for injection, USP used in the manufacture Sterile Water for Injection, USP complies with USP specifications for Water for Injection intended for use in the preparation of parenteral products. The water used for the preparation of Sterile Water for Injection, USP is

b(4)

The water used in the manufacture of Sterile Water for Injection, USP is   and

b(4)

Taro has provided blank copy of the master batch record (MBR) for the intended maximum product batch size will be   (both 5 mL and 10 mL ampoules) in Section 3.2.P.3.3.A, pages 1 to 144.

b(4)

The firm has submitted copies of the exhibit batch records Lot #TP41 (Batch size:  ) for the 5 mL ampoule with a yield of   in Section 3.2.R.1 on page 57 and Lot #TP45 (Batch size:  ) for the 10 mL ampoule with a yield of   in Section 3.2.R.1 on page 219.

#### B. Description of How the Drug Product is Intended to be Used

Sterile Water for Injection, USP is a diluent indicated for parenteral use after the addition to drugs that require dilution or constitution in an aqueous vehicle prior

**Executive Summary Section**

to intravenous, intramuscular or subcutaneous injection, according to instructions of the manufacturer of the drug to be administered.

The volume of the preparation to be used for diluting or dissolving any drug for injection, is dependent on the vehicle concentration, dose and route of administration as recommended by the manufacturer.

Use aseptic technique for single entry and withdrawal from all containers. Single dose vials should be entered just once.

When diluting or dissolving drugs, mix thoroughly and use promptly.

Do not store reconstituted solutions of drugs for injection unless directed by the manufacturer of the solute.

This Parenteral drug product should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

The recommended storage condition is 20° – 25°C (68° – 77°F)

**C. Basis for Approvability or Not-Approval Recommendation**

Application is approvable.

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of trade secret and/or  
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information from

\_\_\_\_\_ Chemistry Review #2 \_\_\_\_\_

(b) (4)



**30. MICROBIOLOGY**

Micro is acceptable on 6/23/06 by Marla Stevens-Riley.

**31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS**

Not required

**32. LABELING**

Labeling is acceptable on 2/10/06 by A. Payne.

**33. ESTABLISHMENT INSPECTION**

EER is acceptable on 7/7/06.

**34. BIOEQUIVALENCE**

Bio is acceptable on 3/17/05 by A. Sigler.

**35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL  
EXCLUSION: Satisfactory**

Taro Pharmaceuticals Ireland Ltd, hereby requests a categorical exclusion under 21 CFR 25.30 and 25.31(a).

Taro Pharmaceuticals Ireland Ltd, certifies that, to the best of its knowledge and belief that its in compliance with all local environmental laws.

**APPEARS THIS WAY  
ON ORIGINAL**



# CHEMISTRY REVIEW



## Chemistry Assessment Section

cc: ANDA 77-393  
ANDA DUP  
Division File  
Field Copy

Endorsements:

HFD-627/N.Nashed /7/5/06  
HFD-627/J.Fan /7/2/06  
HFD-617/R. Adigun/7/5/06

*W 8/10/06*  
*R 8/10/06*

F/T:ard/8/9/06

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**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**ANDA 77-393**

**MICROBIOLOGY REVIEWS**

# Product Quality Microbiology Review

## Review for HFD-640

28 October 2005

**ANDA: 77-393**

### Drug Product Name

**Proprietary:** none

**Non-proprietary:** Sterile Water for Injection USP

**Drug Product Priority Classification:** N/A

**Review Number:** 1

### Dates of Submission(s) Covered by this Review

Letter	Stamp	Consult Sent	Assigned to Reviewer
11-19-04	11-22-04	N/A	10-14-05

### Submission History (for amendments only)

Submission Date(s)	Microbiology Review #	Review Date(s)
N/A		

### Applicant/Sponsor

**Name:** Taro Pharmaceuticals Ireland Ltd.

**Address:** Lourdes Road

Roscrea, Co. Tipperary Ireland

USA AGENT: Taro Pharmaceuticals USA Inc.

5 Skyline Drive

Hawthorne, NY 10532

**Representative:** Kalpana Rao, Vice President Regulatory Affairs

**Telephone:** 914-345-9001

**Name of Reviewer:** Marla Stevens-Riley, Ph.D.

**Conclusion:** Not recommended for approval based on sterility assurance

## Product Quality Microbiology Data Sheet

- A. 1. **TYPE OF SUBMISSION:** Original submission
- 2. **SUBMISSION PROVIDES FOR:** Initial marketing of sterile drug product
- 3. **MANUFACTURING SITE:** Taro Pharmaceuticals Ireland Limited  
 Lourdes Road  
 Roscrea, Co. Tipperary  
 Ireland
- 4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** sterile, solution, intravenous, intramuscular, or subcutaneous injection
- 5. **METHOD(S) OF STERILIZATION:**    
7
- 6. **PHARMACOLOGICAL CATEGORY:** Diluent. Only for diluting or dissolving drugs according to instructions of the manufacturer of the drug to be administered
- B. **SUPPORTING/RELATED DOCUMENTS:** none
- C. **REMARKS:** none

b(4)

filename: 77-393.doc

**Executive Summary**

**I. Recommendations**

- A. **Recommendation on Approvability - Not Recommended** for approval based on sterility assurance. Specific comments regarding the manufacture of sterile drug products are provided in "H. List of Microbiology Deficiencies and Comments" sections.
- B. **Recommendations on Phase 4 Commitments and/or Agreements, if Approvable - N/A**

**II. Summary of Microbiology Assessments**

b(4)

- A. **Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology - Filling of product into polypropylene ampoules in an unknown room**

b(4)

- B. **Brief Description of Microbiology Deficiencies-Incomplete and unclear information for validation of the**  incomplete environmental monitoring information, and incomplete container closure integrity information.
- C. **Assessment of Risk Due to Microbiology Deficiencies - The public health risk associated with these deficiencies is moderate.**

**III. Administrative**

- A. **Reviewer's Signature** Marla Stevens-Riley
- B. **Endorsement Block**  
 Microbiology Reviewer: Marla Stevens-Riley, Ph.D. 4/24/06  
 Microbiology Team Leader: Neal J. Sweeney, Ph.D.
- C. **CC Block**  
 cc:  
 Original ANDA 77-393  
 HFD- 600  
 Field Copy

*Neal J. Sweeney*  
4-25-06

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of trade secret and/or

confidential commercial

information from

Microbiology Review #1

(b) (4)

# Product Quality Microbiology Review

## Review for HFD-640

14 June 2006

**ANDA: 77-393**

**Drug Product Name**

**Proprietary:** none

**Non-proprietary:** Sterile Water for Injection USP

**Drug Product Priority Classification:** N/A

**Review Number:** 2

**Dates of Submission(s) Covered by this Review**

Letter	Stamp	Consult Sent	Assigned to Reviewer
5-24-06	5-25-06	N/A	6-6-06
6-22-06	6-23-06	N/A	6-23-06

**Submission History (for amendments only)**

Submission Date(s)	Microbiology Review #	Review Date(s)
11-19-04	1	10-28-05

**Applicant/Sponsor**

**Name:** Taro Pharmaceuticals Ireland Ltd.

**Address:** Lourdes Road

Roscrea, Co. Tipperary Ireland

USA AGENT: Taro Pharmaceuticals USA Inc.

5 Skyline Drive

Hawthorne, NY 10532

**Representative:** Kalpana Rao, Vice President Regulatory Affairs

**Telephone:** 914-345-9001

**Name of Reviewer:** Marla Stevens-Riley, Ph.D.

**Conclusion:** Recommended for approval based on sterility assurance

## Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUBMISSION:** amendment
  2. **SUBMISSION PROVIDES FOR:** response to deficiencies
  3. **MANUFACTURING SITE:** Taro Pharmaceuticals Ireland Limited  
 Lourdes Road  
 Roscrea, Co. Tipperary  
 Ireland
  4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** sterile, solution, intravenous, intramuscular, or subcutaneous injection, single-use
  5. **METHOD(S) OF STERILIZATION:**    
 7
  6. **PHARMACOLOGICAL CATEGORY:** Diluent. Only for diluting or dissolving drugs according to instructions of the manufacturer of the drug to be administered

b(4)

B. **SUPPORTING/RELATED DOCUMENTS:** none

C. **REMARKS:** The May 24, 2006 amendment is in response to the deficiency letter dated April 26, 2006. Teleconferences were held on June 9 and June 21, 2006 with Kalpana Rao for clarification of information related to the sterilization validation and related to container closure integrity. The specific information is noted in the relevant sections. The June 22, 2006 telephone amendment provides the locations in the original submission that correspond to the data in Appendix 2 of the May 24, 2006 amendment.

filename: 77-393a1.doc

**APPEARS THIS WAY  
ON ORIGINAL**

**Executive Summary**

**I. Recommendations**

- A. Recommendation on Approvability - Not Recommended** for approval based on sterility assurance. Specific comments regarding the manufacture of sterile drug products are provided in "H. List of Microbiology Deficiencies and Comments" sections.
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable - N/A**

**II. Summary of Microbiology Assessments**

b(4)

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology - Filling of product into polypropylene ampoules**
- B. Brief Description of Microbiology Deficiencies - none.**
- C. Assessment of Risk Due to Microbiology Deficiencies - The public health risk associated with this product is minimal.**

**III. Administrative**

**A. Reviewer's Signature**

*Marla Stevens-Riley*

**B. Endorsement Block**

Microbiology Reviewer: Marla Stevens-Riley, Ph.D. 6/23/06  
 Microbiology Team Leader: Neal J. Sweeney, Ph.D.

**C. CC Block**

cc:  
 Original ANDA 77-393  
 HFD- 600  
 Field Copy

*Neal J. Sweeney*  
 6-23-06

Withheld 13 page(s)  
of trade secret and/or  
confidential commercial  
information from

Microbiology Review #2

(b) (4)

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*  
**ANDA 77-393**

**BIOEQUIVALENCE REVIEW**

1.1/2-1

**DIVISION OF BIOEQUIVALENCE REVIEW**

---

**ANDA No.** 77-393  
**Drug Product Name** Sterile Water for Injection, USP  
**Strength** 5 mL and 10 mL vials  
**Applicant Name** Taro Pharmaceuticals U.S.A., Inc.  
**Address** Five Skyline Drive, Hawthorne, NY 10532  
**Submission Date(s)** November 19, 2004  
**Amendment Date(s)**  
**Reviewer** Aaron Sigler, Pharm.D.  
**First Generic** No  
**File Location** V:\firmsnz\taro\ltrs&rev\77393W1104.doc

---

**I. Submission Summary**

**A. Drug Product Information**

**Test Product** Sterile Water for Injection, 5 and 10 mL vials  
**Reference Product** Sterile Water for Injection , 10, 20, and 50 mL vials  
**RLD Manufacturer** None, but using American Pharm. Partner's product  
**NDA No.** 88400  
**RLD Approval Date** January 16, 1984  
**Indication** Diluting or dissolving drugs for intravenous, intramuscular, or subcutaneous injection.

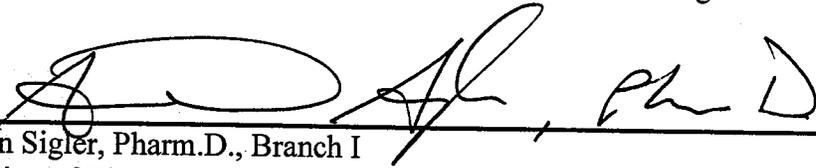
**B. Formulation**

Ingredient	Test (mL)	Reference (mL)
Sterile Water for Injection, USP	100% in 5 and 10 mL vials	100% in 10, 20 and 50 mL vials

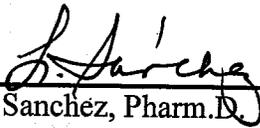
48

**Recommendations**

The Division of Bioequivalence agrees that the information submitted by Taro Pharmaceuticals U.S.A., Inc. demonstrates that its test product, Sterile Water for Injection, USP falls under the criteria set forth in 21 CFR 320.22(b)(1) of the Bioavailability/ Bioequivalence Regulations. The waiver is granted.



Aaron Sigler, Pharm.D., Branch I  
Division of Bioequivalence



Lizzie Sanchez, Pharm.D.  
Special Assistant to the Director  
Division of Bioequivalence



3/17/05

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

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77-393

APPLICANT: Taro Pharmaceuticals U.S.A., Inc.

DRUG PRODUCT: Sterile Water for Injection, USP, 5 mL and 10 mL vials

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,



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

CC: ANDA 77-393  
ANDA DUPLICATE  
DIVISION FILE

Printed in final on 17MAR05

Endorsements: (Final with Dates)

HFD-655/ A. Sigler *B*

HFD-655/ L. Sanchez

HFD-650/ D. Conner

*SM 3/17/05*

BIOEQUIVALENCE - ACCEPTABLE Submission date: 19NOV04

1. **WAIVER** (WAI)

Strengths:

**Outcome: AC**

**Outcome: AC- Acceptable**

MAR 17 2005

OFFICE OF GENERIC DRUGS  
DIVISION OF BIOEQUIVALENCE

ANDA # : 77-393

SPONSOR : Taro Pharmaceuticals U.S.A., Inc.

DRUG AND DOSAGE FORM : Sterile Water for Injection, USP

STRENGTH(S) : 5 mL and 10 mL vials

STUDY SUMMARY : The test drug product is a parental solution intended solely for administration by injection and contains the same active and inactive ingredients in the same concentration as the approved reference listed product. A waiver of the in-vivo bioavailability/bioequivalence study requirements is granted [21 CFR 320.22(b)(1)]

DSI INSPECTION STATUS

Inspection needed: No	Inspection status:	Inspection results:
First Generic <u>No</u>	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause _____		
Other _____		

PROJECT MANAGER: Aaron Sigler, Pharm.D.

BRANCH: I

INITIAL : AS

DATE : 17 MAR 05

SPECIAL ASSISTANT TO THE DIRECTOR: Lizzie Sanchez, Pharm.D.

INITIAL : LS

DATE : 3/17/05

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

INITIAL : DC

DATE : 3/17/05

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*  
**ANDA 77-393**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**



Taro Pharmaceuticals U.S.A., Inc.

505 (16) (K)  
NOTED  
21 MAR 2005  
77 393

November 19, 2004

Office of Generic Drugs  
Food and Drug Administration, CDER  
Document Control Room  
Metro Park North II  
7500 Standish Place  
Room 150  
Rockville, MD 20855-2773

**RE: Abbreviated New Drug Application  
Sterile Water for Injection, USP**

Dear Sir/ Madam:

Taro Pharmaceuticals Ireland Ltd. (Taro) submits, today, an original, abbreviated new drug application (ANDA) seeking approval to market Sterile Water for Injection, USP, a product that has no reference listed drug in the "Approved Drug Products with Therapeutic Equivalence Evaluations", commonly known as the "Orange Book". As there is no reference listed drug, Taro has based its product upon a representative drug product, Sterile Water for Injection, USP manufactured by American Pharmaceutical Partners.

This ANDA is prepared in the ICH-CTD format, following the recommendations of the following guidance documents:

*Submitting Marketing Applications According to the ICH-CTD Format – General Considerations*

*M4: Organization of the CTD*

*M4E: The CTD – Efficacy*

*M4Q: The CTD – Quality*

*M4S: The CTD – Safety*

This ANDA is comprised of 5 volumes. The volumes are distributed as follows:

- Module 1 – Administrative and Prescribing Information (1 volume)
- Module 2 – Common Technical Document Summaries (1 volume)
- Module 3 – Quality (3 volumes)
- Module 4 – Non-clinical Study Reports (Not Applicable)
- Module 5 – Clinical Study Reports (Not Applicable)

RECEIVED  
NOV 22 2004  
OGD / CDER

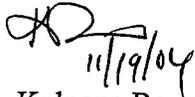
Taro Pharmaceuticals U.S.A., Inc., the U. S. Agent for Taro Pharmaceuticals Ireland Ltd., is filing archival, review and field copies as follows:

Archival copy (5 volumes)	Blue Jackets: Modules 1, 2 and 3
Review Copy (5 volumes)	Red Jackets Modules 1, 2 and 3
<b>Field Copy</b> (5 volume)	Maroon Jacket: Module 1, 2 and 3
Pharmacokinetic Copy (1 volume)	Orange Jacket Module 1

Taro hereby certifies that the "field copy" is a true copy of the technical sections of the ANDA (copy: this letter, 356h form, "true copy certification). This "field copy" is contained in Maroon folders.

If you have any questions regarding this application, please contact the undersigned (the U. S. Agent) at 914-345-9001, ext. 6298.

Sincerely,



11/19/04

Kalpana Rao (U.S. Agent)  
Vice President, Regulatory Affairs (Global, CMC)



Taro Pharmaceuticals U.S.A., Inc.

January 5, 2005

Office of Generic Drugs  
Food and Drug Administration, CDER  
Document Control Room  
Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773  
Attn: Jeen Min

77-393

**RE: Abbreviated New Drug Application  
Sterile Water for Injection, USP**

**NEW CORRESP**  
*N/MC*

Dear Mr. Min:

Thank you for your telephone call yesterday, January 4, 2005. As per your request, Taro Pharmaceuticals Ireland Ltd. (Taro) submits, today, a "Reprocessing Statement" inadvertently omitted from the original Abbreviated New Drug Application made on November 19, 2004. This submission is made as an amendment to the original ANDA.

If you have any questions regarding this application, please contact Ms. Kalpana Rao, the US. Agent, at 914-345-9001, ext. 6298.

Sincerely,

Barbara Lynn Cantor  
Director, Regulatory Affairs (International)

*NAI Jm 1/26/05*

**RECEIVED**  
JAN 12 2005  
OGD / CDER



Taro Pharmaceuticals U.S.A., Inc.

January 21, 2005

Office of Generic Drugs  
Food and Drug Administration, CDER  
Document Control Room  
Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773  
Attn: Jeen Min

ORIG AMENDMENT

N/MC

**RE: ANDA 77-393**  
**Sterile Water for Injection, USP**  
**Telephone Amendment**

Dear Mr. Min:

Thank you for your many telephone calls and the information regarding the proposed Reference Listed Drug (Hospira NDA 18-801), soon to be made official in the "Orange Book".

As per your request, Taro Pharmaceuticals Ireland Ltd. (Taro) hereby submits the following:

- Form FDA 356h
- Basis for Submission [21 CFR 314.94(a)(3)]
- Patent Certification (Paragraph I Certification) with Orange Book listing
- Exclusivity Statement

Taro hereby commits to provide comparison labeling (using Reference Listed Drug, Sterile Water for Injection, USP, NDA 18-801, manufactured by Hospira, labeled for Abbott Laboratories).

If you have any questions regarding this application, please contact the undersigned (the U. S. Agent) at 914-345-9001, ext. 6298.

Sincerely,

*KR*  
1/21/04

Kalpana Rao (U.S. Agent)  
Vice President, Regulatory Affairs (Global, CMC)

RECEIVED

JAN 24 2005

OGD / CDER

ANDA 77-393

JAN 24 2005

Taro Pharmaceuticals U.S.A., Inc.  
US Agent for Taro Pharmaceuticals Ireland Ltd.  
Attention: Kalpana Rao  
5 Skyline Drive  
Hawthorne, NY 10532

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to the telephone conversations dated January 4 and 14, 2005 and your correspondence dated January 5 and 21, 2005.

NAME OF DRUG: Sterile Water for Injection USP, in Plastic Container

DATE OF APPLICATION: November 19, 2004

DATE (RECEIVED) ACCEPTABLE FOR FILING: November 22, 2004

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Peter Chen  
Project Manager  
301-827-5848

Sincerely yours,

  
Wm Peter Rickman  
Director

Division of Labeling and Program Support  
Office of Generic Drugs  
Center for Drug Evaluation and Research

ANDA 77-393

cc: DUP/Jackets  
HFD-600/Division File  
Field Copy  
HFD-610/  
HFD-143/OIM/DRM

Endorsement:

HFD-615/M. Shimer, Chief, RSB

HFD-615/J. Min, CSO J. Min 1/24/05 date

M. Shimer date 24 Jan 2005

V:\FIRMSNZ\TARO\LTRS&REV\77393.ACK.DOC

F/T

ANDA Acknowledgment Letter!

February 8, 2005



Taro Pharmaceuticals U.S.A., Inc.

Attn: Jeen Min  
Office of Generic Drugs  
Food and Drug Administration, CDER  
Document Control Room, MPN II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

N/AF

**Re: ANDA 77-393**  
**Sterile Water for Injection, USP**  
**Telephone Amendment**

Dear Mr. Min:

Reference is made to our Abbreviated New Drug Application (ANDA) for Sterile Water for Injection, USP submitted November 19, 2004 and Taro's letter dated January 21, 2005.

At this time, based upon the commitment made in our above referenced letter, we are submitting a revised labeling section, Module 1.4 Prescribing Information. As indicated, we have revised our labels and labeling using Sterile Water for Injection, USP as manufactured by Hospira under NDA 18-801. In addition, we are providing electronic files for the labeling as submitted in this Telephone Amendment.

This concludes our response. Should you require any additional information, please do not hesitate to contact the undersigned at (914) 345-9001 x6298.

Sincerely,

A handwritten signature in black ink, appearing to read "Kalpana Rao", written in a cursive style.

~~For~~ Kalpana Rao (U.S. Agent)  
Vice President, Regulatory Affairs (Global)

RECEIVED  
FEB 09 2005  
OGD / CDER

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

APR 18 2005

ANDA: 77-393

APPLICANT: Taro Pharmaceuticals Ireland Ltd.

DRUG PRODUCT: Sterile Water for Injection USP, in Plastic Container

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1.

T

7

2.

3.

b(4)

4.

L

J

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1.

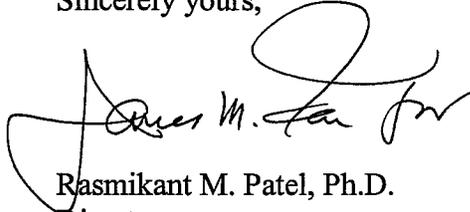
The firms referenced in your application should be in compliance with cGMP at the time of approval.

2.

Please provide all available drug product room temperature stability data.

3. Labeling and microbiology information you have provided is pending review. After the reviews are completed, any deficiencies found will be communicated to you under a separate cover.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Rasmikant M. Patel". The signature is fluid and cursive, with a large loop at the end.

Rasmikant M. Patel, Ph.D.

Director

Division of Chemistry I

Office of Generic Drugs

Center for Drug Evaluation and Research

July 21, 2005



Taro Pharmaceuticals U.S.A., Inc.

Peter Chen, Project Manager  
Office of Generic Drugs  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Document Control Room, Metro Park North II  
7500 Standish Place, Room 150  
Rockville MD 20855

**ORIG AMENDMENT**

N/AM

**MINOR AMENDMENT**

Re: **ANDA 77-393**  
**Sterile Water for Injection USP, 5 mL and 10 mL in plastic containers**

Dear Sir/Madam:

Reference is made to Taro Pharmaceutical Ireland Ltd.'s Abbreviated New Drug Application (ANDA) submitted, on November 19, 2004, under section 505(j) of the Federal Food, Drug and Cosmetic Act, for Sterile Water for Injection USP, 5 mL and 10 mL in plastic containers. Reference is also made to the Agency letter dated April 18, 2005, in which the following deficiencies were communicated:

**A. Deficiencies**

L

7

b(4)

L

J

Withheld 2 page(s)

of trade secret and/or

confidential commercial

information from

\_\_\_\_\_ TARO amendment letter dated 7/21/05 \_\_\_\_\_

(b) (4)



Taro Pharmaceuticals U.S.A., Inc.

**ORIG AMENDMENT**

N/A

September 22, 2005

Ms. Thuyanh (Ann) Vu  
Project Manager  
Office of Generic Drugs, Food and Drug Administration, CDER  
Document Control Room, Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

*Remy Dreyfus*

**GRATUITOUS AMENDMENT**

**RE: ANDA 77-393  
Sterile Water for Injection, USP**

Dear Ms. Vu:

Reference is made to Taro Pharmaceutical Ireland Ltd.'s Abbreviated New Drug application (ANDA) 77-393, submitted on November 19, 2004 under section 505(j) of the Federal Food, Drug and Cosmetic Act, for Sterile Water for Injection USP, in 5 mL and 10 mL plastic containers.

Enclosed, please find a gratuitous amendment to the ANDA. This amendment is to include Taro Pharmaceutical Industries Ltd., 14 Hakitor Street, Haifa Bay, 26110, Israel as an alternative site for USP particulate testing of the finished product and stability samples, inadvertently omitted from our previous submissions. The revised Module 3, section 3.2.P.3.1 is provided.

In addition, drug product stability data for TP41 (5 mL ampoule) and TP45 (10 mL ampoule) to 12 months, at room temperature (25° C ± 2° C/40% ± 5% RH) are provided in revised Module 3, section 3.2.P.8.

If you have any questions regarding this application, please contact Ms. Kalpana Rao at 914-345 9001, ext. 6298.

Sincerely,

*Kalpana Rao*  
9/24/05

Kalpana Rao  
GVP, Regulatory Affairs (Global)

RECEIVED

SEP 23 2005

OGD/CDER

January 23, 2006



Taro Pharmaceuticals U.S.A., Inc.

Attention: Angela Payne  
Office of Generic Drugs  
CDER, FDA  
Document Control Room, Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855

ORIG AMENDMENT

N/AF

**Re:        ANDA #77-393**  
**Sterile Water for Injection, USP**  
**Labeling Amendment**

Dear Ms. Payne:

Reference is made to our Abbreviated New Drug Application (ANDA) for Sterile Water for Injection, USP submitted November 19, 2004, and to the labeling deficiency letter received on November 29, 2005 in which the following was requested:

***Labeling Deficiencies:***

***1. CONTAINER (5 mL and 10 mL)***

*Comment 1*

*Include the drug use "FOR DRUG DILUENT USE"*

**Response**

**Taro has revised the container label as requested.**

*Comment 2*

*Please provide a drawing of your ampules and comment on how one would gain access to the product inside the ampules. The reference listed drug uses glass ampules that must be popped at the designated line.*

**Response**

**A drawing of the 5 mL and 10 mL ampule is attached (attachment 1). This drawing was included in our original submission, under Module 3, section 3.2.P.7 Drug Product Container Closure System.**

**The ampule has a tab at the top that is twisted to gain access to the product.**

*Comment 3*

*Please indicate "single dose".*

**Response**

**Taro has revised the container label as requested.**

RECEIVED

JAN 24 2006

OGD / CDER

## 2. CARTON (20s x 5 mL)

### Comment 1

Place the following in bold print and all caps "FOR DRUG DILUENT USE"

### Response

Taro has revised the carton as requested.

### Comment 2

Revise "ampoules" to read "ampules"

### Response

Taro has revised the carton as requested.

### Comment 3

See comments under CONTAINER

### Response

Taro notes the comments and has revised the carton as requested.

### Comment 4

Include the pH range.

### Response

Taro has revised the carton as requested.

## 3. INSERT

### Comment 1

Include the "Rx only" statement so that it follows the title.

### Response

Taro has revised the insert as requested.

### Comment 2

Please include a statement about your ampule composition.

### Response

Taro has revised the insert as requested.

### Comment 3

CONTRAINDICATIONS - add USP to the established name

### Response

Taro has revised the insert as requested.

### Comment 4

PRECAUTIONS -

i. We recommend including a pregnancy subsection. We refer you to the CFR for guidance.

- ii. *ii. You cited "Plastic syringe: revise to reflect your container specifically "Plastic ampule".*
- iii. *iii. Drug Interactions subsection - add, "seal intact. Do not reuse single-dose containers. Discard unused portion".*

**Response**

**Taro has revised the insert as requested.**

**Comment 5**

*WARNINGS - you cited plastic syringe revise to comply with your product specifications "plastic ampule".*

**Response**

**Taro has revised the insert as requested.**

**Comment 6**

*DOSAGE AND ADMINISTRATION - Add "Use aseptic technique for entry and withdrawal from container".*

**Response**

**Taro has revised the insert as requested.**

**Comment 7**

*HOW SUPPLIED - Describe your containers as single-dose containers and delete the container size 5 mL in a 5 mL ampule should read 5 mL ampules. Change the spelling of ampoules.*

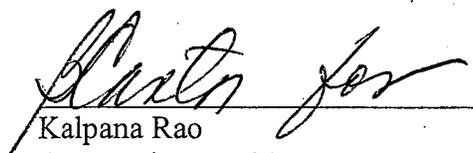
**Response**

**Taro has revised the insert as requested.**

**Taro is including a CD with the PDF files of the labels and labeling as well as a Word document for the Package Insert. In addition, and in accordance with 21 CFR 314.94(a)(8)(iv) we have also provided a side-by-side comparison of our proposed labeling with our previously submitted package insert.**

This completes our response to the deficiency letter of November 29, 2005. If there are any questions regarding this amendment, or if additional information is required, please contact the undersigned.

Sincerely,

  
\_\_\_\_\_  
Kalpana Rao  
Group Vice President , Regulatory Affairs (Global)  
Taro Pharmaceuticals U.S.A., Inc.

May 24, 2006



Taro Pharmaceuticals U.S.A., Inc.

Ms. Bonnie McNeal  
Microbiology Project Manager  
Office of Generic Drugs, CDER, FDA  
Document Control Room, Metro Park North II  
7500 Standish Place, Room 150  
Rockville MD 20855-2773

ORIG AMENDMENT

N/AS

Re: **ANDA 77-393**  
**Sterile Water for Injection, USP**  
**MINOR AMENDMENT - RESPONSE TO MICROBIOLOGY DEFICIENCIES**

Dear Ms. McNeal:

Reference is made to our Abbreviated New Drug Application (ANDA) for Sterile Water for Injection, USP submitted November 19, 2004, and to the microbiology deficiency letter received on April 26, 2006 in which the following was requested:

A. *Microbiology Deficiencies*

I. T

7

b(4)

b(4)

- Manufacturer: [
- Model Number: [
- Equipment Name: [
- Location: [

Building

] in operation). Please see Attachment 1, Equipment Drawing.

RECEIVED

MAY 25 2006

Withheld 10 page(s)  
of trade secret and/or  
confidential commercial  
information from

\_\_\_\_\_ TARO letter dated 5/24/06 \_\_\_\_\_

(b) (4)

b(4)

B. *In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:*

Comment 1

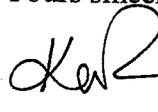
*For future submissions, please refer to the Agency's 1994 "Guidance for Industry for the submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products" for guidance on the kinds of information to submit for review.*

Response 1

**Taro notes and acknowledges the comment to refer to the Agency's 1994 "Guidance for Industry for the submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products" for guidance on the kinds of information to submit for review.**

This completes our response to the deficiency letter of April 26, 2006. If there are any questions regarding this amendment, or if additional information is required, please contact the undersigned.

Yours sincerely

 5/24/06

Kalpana Rao (US Agent)  
Group Vice President, Regulatory Affairs (Global)  
Taro Pharmaceuticals U.S.A., Inc.

June 22, 2006

Ms. Bonnie McNeal  
Microbiology Project Manager  
Office of Generic Drugs, CDER, FDA  
Document Control Room, Metro Park North II  
7500 Standish Place, Room 150  
Rockville MD 20855-2773



Taro Pharmaceuticals U.S.A., Inc.

ORIG AMENDMENT

N/AS

Re: **ANDA 77-393**  
**Sterile Water for Injection, USP**  
**TELEPHONE AMENDMENT**

Dear Ms. McNeal:

Reference is made to our Abbreviated New Drug Application (ANDA) for Sterile Water for Injection, USP submitted November 19, 2004, and the microbiology deficiency letter response, dated May 24, 2006. Reference is also made to the telephone conversation between Ms. Kalpana Rao and Ms. Marla Stevens-Riley on June 20 and 21, 2006, in which additional information, regarding data for the pages located in Appendix 2 of the May 24, 2006 submission, was requested.

Taro hereby replaces page 1 of 5, found in Appendix 2 of the May 24, 2006 submission. The original page incorrectly identified the Program as P3 when, in actuality, it was P2. The replacement page identifies the Program (correctly) as P3.

The following table identifies the location, in Taro's original submission dated November 19, 2004, where supporting data (to the summary charts) may be found:

<u>Appendix 2 page reference</u> (submission dated 5/24/06)	<u>Data Location</u> (submission dated 11/19/04)
page 1 of 5: $\Gamma$	Module 3, Sec. 3.2.P.3.5.A, pp.162-169
page 2 of 5:	Module 3, sec. 3.2.P.3.5.A, pp. 223-237
page 3 of 5: <b>b(4)</b>	Module 3, Sec. 3.2.P.3.5.C, pp. 27, 28, 42, 43
page 4 of 5:	Module 3, Sec. 3.2.P.3.5.A, pp. 181-198
page 5 of 5: $\perp$	Module 3, Sec.3.2.9.3.5.C, pp. 28, 44, 45

Study 7  
Study 9  
Study 12  
Study 8  
Study 1

This completes our response to the deficiency letter of April 26, 2006. If there are any questions regarding this amendment, or if additional information is required, please contact the undersigned.

Yours sincerely

*Kalpana Rao*  
Kalpana Rao (US Agent)  
Group Vice President, Regulatory Affairs (Global)  
Taro Pharmaceuticals U.S.A., Inc

RECEIVED

JUN 23 2006

OGD / CDER

OGD APPROVAL ROUTING SUMMARY

ANDA # 77-393 Applicant Taro Pharmaceuticals Ireland, Ltd.  
 Drug sterile water for injection USP, in ~~injection~~ Strength(s) N/A

APPROVAL TENTATIVE APPROVAL SUPPLEMENTAL APPROVAL (NEW STRENGTH) OTHER

REVIEWER:

DRAFT Package FINAL Package

1. Martin Shimer Chief, Reg. Support Branch  
 Date 28 June 06 Date 8/1/06  
 Initials MS Initials MS/for

Contains GDEA certification:  Yes  No Determ. of Involvement? Yes  No  
 (required if sub after 6/1/92) Pediatric Exclusivity System

Patent/Exclusivity Certification:  Yes  No RLD = N/A  
 If Para. IV Certification did applicant Date Checked N/A

Notify patent holder/NDA holder Yes  No Nothing Submitted  
 Was applicant sued w/in 45 days: Yes  No Written request issued

Has case been settled: Yes  No Date settled:  
 Is applicant eligible for 180 day Study Submitted

Generic Drugs Exclusivity for each strength: Yes  No  
 Date of latest Labeling Review/Approval Summary 1/30/05

Any filing status changes requiring addition Labeling Review Yes  No

Type of Letter:  
 Comments: no patents / applications : eligible for Full AP

2. Project Manager, Rosalyn A. Team 3 Date 06/28/06 Date \_\_\_\_\_  
 Review Support Branch Initials RA Initials \_\_\_\_\_

Original Rec'd date 11/19/04 EER Status Pending  Acceptable OAI  
 Date Acceptable for Filing 11/22/04 1 Date of EER Status 4/13/06

Patent Certification (type) L Date of Office Bio Review 3/17/05  
 Date Patent/Exclus. expires N/A Date of Labeling Approv. Sum 02/10/06

Citizens' Petition/Legal Case Yes  No Labeling Acceptable Email Rec'd  Yes  No  
 (If YES, attach email from PM to CP coord) Labeling Acceptable Email filed  Yes  No

First Generic Yes  No Date of Sterility Assur. App. 06/23/06  
 Methods Val. Samples Pending Yes  No

MV Commitment Rcd. from Firm Yes  No

Acceptable Bio reviews tabbed  Yes  No Modified-release dosage form: Yes  No  
 Suitability Petition/Pediatric Waiver Interim Dissol. Specs in AP Ltr: Yes  No

Pediatric Waiver Request Accepted  Rejected  Pending

Previously reviewed and tentatively approved Date N/A  
 Previously reviewed and CGMP def. /NA Minor issued Date N/A

Comments:

3. David Read (PP IVs Only) Pre-MMA Language included Date \_\_\_\_\_  
 OGD Regulatory Counsel, Post-MMA Language Included Initials \_\_\_\_\_

N/A

4. Div. Dir. / ~~Deputy Dir.~~ Date 8/1/06  
 Chemistry Div. I ~~II OR III~~ Initials RA  
 Comments:

The cmc section is satisfactory.

REVIEWER:

FINAL ACTION

5. Frank Holcombe First Generics Only  
Assoc. Dir. For Chemistry  
Comments: (First generic drug review)

Date \_\_\_\_\_  
Initials \_\_\_\_\_

N/A. American Pharmaceutical Partners (APP)'s ANDA 88-400 for this drug product was approved on 1/16/84.

6. Vacant Deputy Dir., DLPS

RLD = Sterile Water for Injection (Plastic Container)  
NDA 18-801  
Hospira Inc.

Date \_\_\_\_\_  
Initials \_\_\_\_\_

7. Peter Rickman  
Director, DLPS

Date 8/10/06  
Initials [Signature]

Para. IV Patent Cert: Yes No ; Pending Legal Action: Yes No ; Petition: Yes No

Comments: Acceptable EES dated 7/7/06 (Verified 8/1/06). NO O.A.I. Alerts noted. Bioprecursor waiver granted under 21 CFR 320.22(b)(1). Drug product is "Q+Q" to the RPD office-level per endorsed 3/1/05. Microbiology/Sterility assurance found acceptable for approval 6/23/06. PPL found acceptable for approval 2/10/06 as endorsed 6/28/06. CMC found acceptable for approval 8/10/06.

8. Robert L. West  
Deputy Director, OGD

Date 8/10/06  
Initials [Signature]

Para. IV Patent Cert: Yes  No; Pending Legal Action: Yes  No; Petition: Yes  No

Comments: There are no unexpired patents or exclusivity listed in the current "Orange Book" for this drug product. This ANDA is recommended for approval.

9. Gary Buehler  
Director, OGD  
Comments:

Date 8/10/06  
Initials [Signature]

First Generic Approval PD or Clinical for BE Special Scientific or Reg. Issue

10. Project Manager, Team Rosalyn  
Review Support Branch

Date [Signature]  
Initials [Signature]

Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification: 13: Time notified of approval by phone 1:45 Time approval letter faxed

FDA Notification: 8/10/06 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list. 8/11/06 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.