CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

10-515/S031

Trade Name: Isuprel®

Generic Name: isoproterenol hydrochloride

Sponsor: Hospira

Approval Date: 3/21/2013

Indication: Isoproterenol hydrochloride injection is indicated:
• For mild or transient episodes of heart block that do not require electric shock or pacemaker therapy.
• For serious episodes of heart block and Adams-Stokes attacks (except when caused by ventricular tachycardia or fibrillation).
• For use in cardiac arrest until electric shock or pacemaker therapy, the treatments of choice, is available.
• For bronchospasm occurring during anesthesia.
• As an adjunct to fluid and electrolyte replacement therapy and the use of other drugs and procedures in the treatment of hypovolemic and septic shock, low cardiac output (hypoperfusion) states, congestive heart failure, and cardiogenic shock.

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

10-515/S031

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 010515/S-031

APPROVAL LETTER

Hospira, Inc.
Attention: Ms. Karen R. Tubergen
275 North Field Drive
Dept. 0389, Bldg. H2-2
Lake Forest, IL 60045

Dear Ms. Tubergen:

Please refer to your Supplemental New Drug Application (sNDA) originally submitted September 30, 2011, and resubmitted November 20, 2012 under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Isuprel (Isoproterenol HCl) Injection, 0.2 mg/mL.

We acknowledge receipt of your amendments dated November 20, 2012, January 23 and 31, and March 20, 2013.

The November 20, 2012 submission constituted a complete response to our February 3, 2012 action letter.

This "Prior Approval" supplemental new drug application provides for a re-formulation of the drug product and alternate site for the manufacture and release testing of the drug substance.

We have completed our review of this supplemental new drug application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

Content of labeling must be identical to the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

As agreed, submit final printed carton and container labels, identical to the carton and immediate container labels you submitted as a redlined version on March 20, 2013, as soon as they are available, but no more than 30 days after they are printed.

Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 010515/S-031**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Quynh Nguyen, Pharm.D., RAC
Regulatory Health Project Manager
(301) 796-0510

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

STEPHEN M GRANT
03/21/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

10-515/S031

OTHER ACTION LETTER(s)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 10-515/S031 **COMPLETE RESPONSE**

Hospira, Inc.
Attention: Linda Biava
Sr. Regulatory Associate
275 N. Field Dr
Lake Forest, IL 60045

Dear Ms. Biava:

Please refer to your supplemental new drug application (sNDA) dated September 30, 2011 received October 3, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Isuprel (Isoproterenol HCl) Injection.

This "Prior Approval" supplemental new drug application provides for a re-formulation of the drug product and alternate site for the manufacture and release testing of the drug substance.

We have completed the review of your application, and have determined that we cannot approve this application in its present form. We have described below our reason for this action and, where possible, our recommendations to address the issue.

CHEMISTRY, MANUFACTURING AND CONTROL

1. The Drug Master File (DMF) 25,212 has been reviewed and determined to be inadequate to support your NDA. Deficiencies have been communicated to the DMF holder.
2. Indicate whether the source of Drug Substance (described in DMF 25,212) is the same as that approved. If not, provide comparative information on the manufacturing process, starting materials, controls, impurities, and container closure for the approved and proposed sources of the Drug Substance.
3. List other approved suppliers of Drug Substance ((b) (4) DMF (b) (4) is inactive), if any.
4. Set numerical limits for (b) (4) content in API specifications. The data provided is insufficient to omit testing for (b) (4).
5. A shelf life of 18 months for Drug Product is not supported by the stability data. Provide stability data to support the shelf life of 18 months in the proposed formulation or amend the shelf life claim to 12 months. Extension of shelf life based on real time data as they become available can be done via Annual Report.
6. Clarify what the following in Section P.3.3 means. (b) (4) (b) (4) Please state that (b) (4) will not be performed or list specific conditions under which (b) (4) will be performed.

7. Provide comparative impurity profile for approved DS and that manufactured by the proposed process. Indicate if [redacted] (b) (4), [redacted] (b) (4) and [redacted] (b) (4) are new impurities; if yes, indicate if these impurities are genotoxic.
8. Submit data to support the safety of injecting directly into the heart a formulation with two calcium chelators (EDTA and citrate) in the setting of life-threatening myocardial dysfunction.

FACILITY INSPECTIONS

9. During a recent inspection of the Hospira manufacturing facility McPherson, Kansas, our investigator conveyed deficiencies to the representative of the facility. Satisfactory compliance with Current Good Manufacturing Practices for Drugs is required for all manufacturing and testing facilities before this supplement may be approved.

LABELING

10. For all Container Labels and Carton Labeling
    a. Ensure that the lot number and expiration date is placed on all container labels and carton labeling.
    b. Ensure the route of administration statement is included on the principle display panel. This statement should read "Intravenous, subcutaneous, intramuscular, and intracardiac use only"
11. For the 1 mL and 5 mL Ampul Container Label, remove the storage information to save space and reduce the cluttered appearance of the label, per 21 CFR 201.10 (i).
12. For the 1 mL Ampul Container Label and Carton Labeling, move the strength statement so it is inside of the color block that has the proprietary and established names, for increased prominence
13. For all Carton Labeling, revise the net quantity statement to say the following:
    a. 5 mL ampul x 10 ampuls per carton
    b. 1 mL ampul x 25 ampuls per Uni-Amp™ unit dose pak
14. For insert Labeling, include the volume of Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP needed for dilution of Isuprel administered as a bolus intravenous injection in the dosage tables

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have

such a meeting, submit your meeting request as described in the FDA's *Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants*, May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Hasmukh B. Patel, Ph.D.
Branch Chief
Branch III, Division of New Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

HASMUKH B PATEL
02/03/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

10-515/S031

LABELING

Isuprel™ Rx only

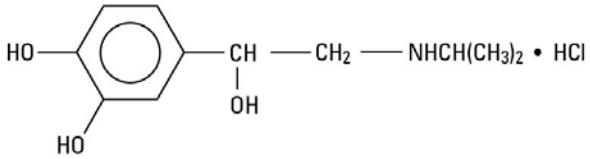
Isoproterenol Hydrochloride Injection, USP

Sterile Injection

DESCRIPTION

Isoproterenol hydrochloride is 3,4-Dihydroxy-α-[(isopropylamino)methyl] benzyl alcohol hydrochloride, a synthetic sympathomimetic amine that is structurally related to epinephrine but acts almost exclusively on beta receptors. The molecular formula is $C_{11}H_{17}NO_3$ • HCl. It has a molecular weight of 247.72 and the following structural formula:

Isoproterenol hydrochloride is a racemic compound.



Each milliliter of the sterile solution contains:

Isoproterenol hydrochloride injection, USP	0.2 mg
Edetate Disodium (EDTA)	0.2 mg
Sodium Chloride	7.0 mg
Sodium Citrate, Dihydrate	2.07 mg
Citric Acid, Anhydrous	2.5 mg
Water for Injection	1.0 mL

The pH is adjusted between 2.5 and 4.5 with hydrochloric acid or sodium hydroxide.

The sterile solution is nonpyrogenic and can be administered by the intravenous, intramuscular, subcutaneous, or intracardiac routes.

CLINICAL PHARMACOLOGY

Isoproterenol is a potent nonselective beta-adrenergic agonist with very low affinity for alpha-adrenergic receptors. Intravenous infusion of isoproterenol in man lowers peripheral vascular resistance, primarily in skeletal muscle but also in renal and mesenteric vascular beds. Diastolic pressure falls. Renal blood flow is decreased in normotensive subjects but is increased markedly in shock. Systolic blood pressure may remain unchanged or rise, although mean arterial pressure typically falls. Cardiac output is increased because of the positive inotropic and chronotropic effects of the drug in the face of diminished peripheral vascular resistance. The cardiac effects of isoproterenol may lead to palpitations, sinus tachycardia, and more serious arrhythmias; large doses of isoproterenol may cause myocardial necrosis in animals.

Isoproterenol relaxes almost all varieties of smooth muscle when the tone is high, but this action is most pronounced on bronchial and gastrointestinal smooth muscle. It prevents or relieves bronchoconstriction, but tolerance to this effect develops with overuse of the drug.

In man, isoproterenol causes less hyperglycemia than does epinephrine. Isoproterenol and epinephrine are equally effective in stimulating the release of free fatty acids and energy production.

Absorption, Fate, and Excretion. Isoproterenol is metabolized primarily in the liver and other tissues by COMT. Isoproterenol is a relatively poor substrate for MAO and is not taken up by sympathetic neurons to the same extent as are epinephrine and norepinephrine. The duration of action of isoproterenol may therefore be longer than that of epinephrine, but is still brief.

INDICATIONS AND USAGE

Isoproterenol hydrochloride injection is indicated:

- For mild or transient episodes of heart block that do not require electric shock or pacemaker therapy.
- For serious episodes of heart block and Adams-Stokes attacks (except when caused by ventricular tachycardia or fibrillation). (See **CONTRAINDICATIONS**.)
- For use in cardiac arrest until electric shock or pacemaker therapy, the treatments of choice, is available. (See **CONTRAINDICATIONS**.)
- For bronchospasm occurring during anesthesia.
- As an adjunct to fluid and electrolyte replacement therapy and the use of other drugs and procedures in the treatment of hypovolemic and septic shock, low cardiac output (hypoperfusion) states, congestive heart failure, and cardiogenic shock. (See **WARNINGS**.)

CONTRAINDICATIONS

Use of isoproterenol hydrochloride injection is contraindicated in patients with tachyarrhythmias; tachycardia or heart block caused by digitalis intoxication; ventricular arrhythmias which require inotropic therapy; and angina pectoris.

WARNINGS

Isoproterenol hydrochloride injection, by increasing myocardial oxygen requirements while decreasing effective coronary perfusion, may have a deleterious effect on the injured or failing heart. Most experts discourage its use as the initial agent in treating cardiogenic shock following myocardial infarction. However, when a low arterial pressure has been elevated by other means, isoproterenol hydrochloride injection may produce beneficial hemodynamic and metabolic effects.

In a few patients, presumably with organic disease of the AV node and its branches, isoproterenol hydrochloride injection has paradoxically been reported to worsen heart block or to precipitate Adams-Stokes attacks during normal sinus rhythm or transient heart block.

PRECAUTIONS

General

Isoproterenol hydrochloride injection should generally be started at the lowest recommended dose. This may be gradually increased if necessary while carefully monitoring the patient. Doses sufficient to increase the heart rate to more than 130 beats per minute may increase the likelihood of inducing ventricular arrhythmias. Such increases in heart rate will also tend to increase cardiac work and oxygen requirements which may adversely affect the failing heart or the heart with a significant degree of arteriosclerosis.

Adequate filling of the intravascular compartment by suitable volume expanders is of primary importance in most cases of shock and should precede the administration of vasoactive drugs. In patients with normal cardiac function, determination of central venous pressure is a reliable guide during volume replacement. If evidence of hypoperfusion persists after adequate volume replacement, isoproterenol hydrochloride injection may be given.

In addition to the routine monitoring of systemic blood pressure, heart rate, urine flow, and the electrocardiograph, monitor the response to therapy by frequent determination of the central venous pressure and blood gases. Closely observe patients in shock during isoproterenol hydrochloride injection administration. If the heart rate exceeds 110 beats per minute, it may be advisable to decrease the infusion rate or temporarily discontinue the infusion. Determinations of cardiac output and circulation time may also be helpful. Take appropriate measures to ensure adequate ventilation. Pay attention to acid-base balance and to the correction of electrolyte disturbances.

Drug Interactions
Isoproterenol hydrochloride injection and epinephrine should not be administered simultaneously because both drugs are direct cardiac stimulants and their combined effects may induce serious arrhythmias. The drugs may, however, be administered alternately provided a proper interval has elapsed between doses.

Avoid ISUPREL when potent inhalational anesthetics such as halothane are employed because of potential to sensitize the myocardium to effects of sympathomimetic amines.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals to evaluate the carcinogenic potential of isoproterenol hydrochloride have not been done. Mutagenic potential and effect on fertility have not been determined. There is no evidence from human experience that isoproterenol hydrochloride injection may be carcinogenic or mutagenic or that it impairs fertility.

Pregnancy Category C
Animal reproduction studies have not been conducted with isoproterenol hydrochloride. It is also not known whether isoproterenol hydrochloride can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Isoproterenol hydrochloride should be given to a pregnant woman only if clearly needed.

Nursing Mothers
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when isoproterenol hydrochloride injection is administered to a nursing woman.

Pediatric Use
Safety and efficacy of isoproterenol in pediatric patients have not been established.

Intravenous infusions of isoproterenol in refractory asthmatic children at rates of 0.05-2.7 mcg/kg/min have caused clinical deterioration, myocardial necrosis, congestive heart failure and death. The risks of cardiac toxicity appear to be increased by some factors [acidosis, hypoxemia, coadministration of corticosteroids, coadministration of methylxanthines (theophylline, theobromine) or aminophylline] that are especially likely to be present in these patients. If I.V. isoproterenol is used in children with refractory asthma, patient monitoring must include continuous assessment of vital signs, frequent electrocardiography, and daily measurements of cardiac enzymes, including CPK-MB.

Geriatric Use
Clinical studies of Isuprel did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects in clinical circumstances. There are, however, some data that suggest that elderly healthy or hypertensive patients are less responsive to beta-adrenergic stimulation than are younger subjects. In general, dose selection for elderly patients should usually start at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant diseases or other drug therapy.

ADVERSE REACTIONS

The following reactions to isoproterenol hydrochloride injection have been reported:

CNS: Nervousness, headache, dizziness, nausea, visual blurring.

Cardiovascular: Tachycardia, palpitations, angina, Adams-Stokes attacks, pulmonary edema, hypertension, hypotension, ventricular arrhythmias, tachyarrhythmias.

In a few patients, presumably with organic disease of the AV node and its branches, isoproterenol hydrochloride injection has been reported to precipitate Adams-Stokes seizures during normal sinus rhythm or transient heart block.

Respiratory: Dyspnea.

Other: Flushing of the skin, sweating, mild tremors, weakness, pallor.

OVERDOSAGE

The acute toxicity of isoproterenol hydrochloride in animals is much less than that of epinephrine. Excessive doses in animals or man can cause a striking drop in blood pressure, and repeated large doses in animals may result in cardiac enlargement and focal myocarditis.

In case of accidental overdosage as evidenced mainly by tachycardia or other arrhythmias, palpitations, angina, hypotension, or hypertension, reduce rate of administration or discontinue isoproterenol hydrochloride injection until patient's condition stabilizes. Blood pressure, pulse, respiration, and ECG should be monitored.

It is not known whether isoproterenol hydrochloride is dialyzable.

The oral LD_{50} of isoproterenol hydrochloride in mice is 3,850 mg/kg ± 1,190 mg/kg of pure drug in solution.

DOSAGE AND ADMINISTRATION

Start ISUPREL injection at the lowest recommended dose and increase the rate of administration gradually if necessary while carefully monitoring the patient. The usual route of administration is by intravenous infusion or bolus intravenous injection. In dire emergencies, the drug may be administered by intracardiac injection. If time is not of the utmost importance, initial therapy by intramuscular or subcutaneous injection is preferred.

Recommended dosage for adults with heart block, Adams-Stokes attacks, and cardiac arrest:

Route of Administration	Preparation of Dilution	Initial Dose	Subsequent Dose Range*
Bolus intravenous injection	Dilute 1 mL (0.2 mg) in 9 mL of Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP	0.02 mg to 0.06 mg (1 mL to 3 mL of diluted solution)	0.01 mg to 0.2 mg (0.5 mL to 10 mL of diluted solution)
Intravenous infusion	Dilute 10 mL (2 mg) in 500 mL of 5% Dextrose Injection, USP	5 mcg/min. (1.25 mL of diluted solution per minute)	
Intramuscular	Use Solution undiluted	0.2 mg (1 mL)	0.02 mg to 1 mg (0.1 mL to 5 mL)
Subcutaneous	Use Solution undiluted	0.2 mg (1 mL)	0.15 mg to 0.2 mg (0.75 mL to 1 mL)
Intracardiac	Use Solution undiluted	0.02 mg (0.1 mL)	

* Subsequent dosage and method of administration depend on the ventricular rate and the rapidity with which the cardiac pacemaker can take over when the drug is gradually withdrawn.

There are no well-controlled studies in children to establish appropriate dosing; however, the American Heart Association recommends an initial infusion rate of 0.1 mcg/kg/min, with the usual range being 0.1 mcg/kg/min to 1 mcg/kg/min.

Recommended dosage for adults with shock and hypoperfusion states:

Route of Administration	Preparation of Dilution†	Infusion Rate††
Intravenous infusion	Dilute 5 mL (1 mg) in 500 mL of 5% Dextrose Injection, USP	0.5 mcg to 5 mcg per minute (0.25 mL to 2.5 mL of diluted solution)

† Concentrations up to 10 times greater have been used when limitation of volume is essential.

†† Rates over 30 mcg per minute have been used in advanced stages of shock. The rate of infusion should be adjusted on the basis of heart rate, central venous pressure, systemic blood pressure, and urine flow. If the heart rate exceeds 110 beats per minute, it may be advisable to decrease or temporarily discontinue the infusion.

Recommended dosage for adults with bronchospasm occurring during anesthesia:

Route of Administration	Preparation of Dilution	Initial Dose	Subsequent Dose
Bolus intravenous injection	Dilute 1 mL (0.2 mg) in 9 mL of Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP	0.01 mg to 0.02 mg (0.5 mL to 1 mL of diluted solution)	The initial dose may be repeated when necessary

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Such solution should not be used.

HOW SUPPLIED

NDC	Container	Concentration	Fill	Quantity
0409-1442-02	Ampul	0.2 mg/mL	1 mL	UNI-AMP™ pak of 25
0409-1442-03	Ampul	1 mg/5 mL (0.2 mg/mL)	5 mL	10 ampuls per carton

Protect from light. Keep in opaque container until used.

Store at 20º to 25ºC (68º to 77ºF). [See USP Controlled Room Temperature.]

Do not use if the injection is pinkish or darker than slightly yellow or contains a precipitate.

Revised: 03/2013

EN-3173

Hospira, Inc., Lake Forest, IL 60045 USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

10-515/S031

MEDICAL REVIEW(S)

CLINICAL REVIEW

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: March 8, 2012
From: Martin Rose, MD, JD, Medical Officer
To: NDA File
Subject: Isuprel (Isoproterenol injection) – NDA 01015, S-31: CMC supplement for formulation change
Submission Dates: 10/3/2012, 2/3/2102, 11/20/2012, 1/2/2013, 1/31/2012
Review Date: 2/14/2013
Materials Reviewed: Above submissions; Nonclinical review (2/14/2013), notes provided by nonclinical review (Dr. Willard)

Background:

The Sponsor, Hospira, submitted this supplement to remove lactic acid, sodium lactate, and sodium metabisulfite from the Isuprel formulation and replace them with EDTA 0.2 mg, sodium citrate dihydrate 2.0708 mg, and citric acid, anhydrous 2.4897 mg (all in 1 mg water for injection). Both citrate ion and EDTA are calcium binders. We noted that Isuprel is indicated for intracardiac injection in patients in cardiac arrest. We were concerned that the direct injection of calcium binders into the ventricle might lower calcium levels in the myocardium and possibly depress myocardial function, with potentially lethal consequences. The Sponsor did not address this issue in its submission.

We asked the sponsor to provide information to support the safety of the new formulation. The Sponsor responded by proposing to (b) (4) No new safety information was submitted with this proposal.

We were not prepared to allow the Sponsor to take this course. (b) (4) It also seemed possible that the hypocalcemic effects of the new excipients might be inconsequential; if so, there would be no need to change labeling.

FDA's Assessment of Risk of Hypocalcemia and Myocardial Depression:

Accordingly, Dr. James Willard, the nonclinical reviewer for this NDA, performed modeling of the potential effects of the formulation change on calcium levels in the

heart and myocardial tissue. Notes regarding his modeling assumptions and calculations are appended to this review. Briefly, he assumed that the recommended intracardiac dose of 0.1 mL of Isuprel was injected as a bolus into the right ventricle of a 79 pound person with an RV volume of 77.5 mL, with a plasma content rounded to 50 mL. He also assumed that the citrate and EDTA concentrations and resulting calcium levels in the ventricle and myocardial extracellular fluid would be identical, which is an extreme, worst-case assumption, and that binding of calcium to citrate or EDTA would be on a 1:1 molar basis. If total plasma calcium was 10 mg/dL (2.5 mmol/L), prior to injection, the resulting reduction of total plasma calcium concentration would be 0.2%, assuming that the % reduction was similar in bound and ionic calcium. If the reduction in calcium was limited to ionic calcium and was not buffered by bound calcium stores, the reduction would be about 0.4%. These changes, which represent worst-case analyses, are trivial and would not be expected to affect myocardial contractility.

Recommendation:

There is no clinical reason to be concerned about effects of the proposed formulation change on myocardial calcium levels. (b) (4)

Appendix – see next page

Appendix: Notes regarding modeling provided by Dr. Willard:

Calcium binding of EDTA, Sodium Citrate and Citric acid in Isuprel's new formulation:

Isuprel contains:

EDTA @ 0.42 mg/mL which is equal to 1.1 mmol/L

Na Citrate @ 2.0708 mg/mL which is equal to 8 mmol/L

Citric Acid @ 2.4897 mg/mL which is equal to 13 mmol/L

Original suggestion was a 100 lb child

Modified to a 79.2 lb child (37 kg)

Body Surface Area: 1.38 m^2

Ventricular Volume: 77.5 mL

Plasma Volume (60%): ~50 mL

Plasma [Ca++]: 10 mg/dL so 5 mg in 50 mL or 2.5 mM

Isuprel is indicated for a 0.1 mL injection for intracardiac injection

EDTA and Citrate bind Ca++ in a 1:1 stoichiometry

Final concentration of Ca++ is 2.5 mmol/L, in 50 mL =0.125 mmol

Final concentration of EDTA is 0.0008 mmol/L in 50 mL = 0.00004 mmol

Final concentration of Citrate is 0.00021 mmol

Therefore 0.00025 mmol Ca++ chelator

That would reduce the Ca++ to 0.12475 mmol from 0.125 mmol

Karen Hicks cites a reference that right ventricular volume ranges from 100-160 mL, at 100 mL the plasma volume would be 60 mL, and would only differ slightly from this estimate, with less Ca++ being chelated. (Eur J Echocardiogr 2006 mar; 7(2) 79-108.).

Information for example from: Buechel, E.V., Kaiser, T., Jackson, C., Schmitz, A., and C.J. Kellenberger. Normal right- and left ventricular volumds and myocardial mass in children measured by steady state free precession cardiovascular magnetic resonance. J Cardiovasc Magn Reson. 2009; 11(1): 19.

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/s/

MARTIN ROSE
03/08/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

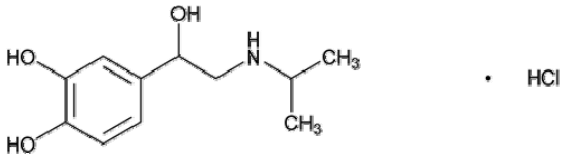
APPLICATION NUMBER:

10-515/S031

CHEMISTRY REVIEW(S)

Chemistry Review: # 1	**1. Division:** **DHP**	**2. NDA Number: 10-515**
3. Name and Address of Applicant: Hospira Inc. 275 North Field Dr. Dept, 0389, Bldg. H2-2 Lake Forest, IL 60045	**4. Supplement(s): S** **Number: 031 Resubmission** **Date(s): 11/21/2012**	
5. Name of Drug: Isuprel	**6. Nonproprietary name: Isoproterenol Hydrochloride Injection, USP**	
7. Supplement Provides for: Applicant's complete response to Agency CR letter dated 2/3/2012.		**8. Amendment(s):**
9. Pharmacological Category: **Bronchodilator**	**10. How Dispensed:** R_x	**11. Related Documents:** DMF 25,212
12. Dosage Form: Injectable	**13. Potency:** 1:5000	

14. Chemical Name and Structure: 3,4-Dihydroxy-α-[(isopropylamino)methyl]benzyl alcohol hydrochloride.



15. Comments: 15. Comments: The original submission proposed a new formulation of DP, Isuprel, and a new DS manufacturer, DMF holder 25,212. Numerous CMC, Clinical, and Labeling issues were identified. The application was not approved (CR letter dated 2/3/2012). DMF 25,212 was found inadequate to support the proposed change in S-031.

This Resubmission is the applicant's Response to the Agency CR letter dated 2/3/2012. The applicant has addressed the Agency concerns in this resubmission. Clinical, Pharm/Tox, Miccrobiology, and DMEPA reviewers recommend approval for their respective disciplines. The OC gave an overall recommendation of Acceptable based on district recommendation for the sites proposed in the associated DMF 25,212 on 3/12/2013. DMF 25,212 was found Adequate by Kavita A. Vyas (review dated 3/12/13). No CMC issues are pending for this supplement.

The applicant proposed to (b) (4) in response to Agency's request that they support the safety of the new formulation, which contains two Ca chelators (EDTA and citrate) in an intracardiac setting. The review team concluded that (b) (4) from the label raises the following issues

- (b) (4)
- (b) (4)

(b) (4)

To evaluate the safety concern, the Pharm/Tox and Medical reviewers made theoretical calculation of the Ca ion sequestration by the new formulation based on the dose of DP in intracardiac setting, plasma volume of ventricle, and the amount of Ca chelators (EDTA and citrate) in the proposed formulation. The review team concluded that "there was no clinical reason to be concerned about the effects of the proposed formulation change on myocardial Ca levels. (b) (4) (see review by Medical Officer, Dr. Martin Rose dated 3/8/2013).

The issue of the safety of ca chelators in the new formulation is thus resolved based on recommendation by Medical and Pharm/Tox reviewers.

16. Conclusion: Recommend Approval for NDA 10-515 S-031 from a CMC point of view.

17. Name: **Signature:** **Date: 3/12/13**
Kavita A. Vyas, Ph.D., Chemist

18. Concurrence: **Signature:** **Date:**
Hasmukh Patel., Branch Chief, Div., III, ONDQA

The original submission proposed a new formulation of DP, Isuprel, and a new DS manufacturer, DMF holder 25,212. Numerous CMC, Clinical, and Labeling issues were identified. The application was not approved (CR letter dated 2/3/2012). DMF 25,212 was found inadequate to support the proposed change in S-031.

This Resubmission is the applicant's Response to the Agency CR letter dated 2/3/2012. The applicant has addressed the Agency concerns in this resubmission, and responses are summarized below. Clinical, Pharm/Tox, Miccrobiology, and DMEPA reviewers recommend approval for their respective disciplines. The OC gave an overall recommendation of Acceptable based on district recommendation for the sites proposed in the associated DMF 25,212 on 3/12/2013. DMF 25,212 was found Adequate by Kavita A. Vyas (review dated 3/12/13). No CMC issues are pending for this supplement.

Agency Question 1.

The Drug Master File (DMF) 25,212 has been reviewed and determined to be inadequate to support your NDA. Deficiencies have been communicated to the DMF holder.

Applicant's response to Agency Question 1.

The applicant stated that the holder of DMF 25,212 has amended the DMF to adequately address deficiencies identified by the agency.

Reviewer's Evaluation: Adequate.

Agency Question 2.

Indicate whether the source of Drug Substance (described in DMF 25,212) is the same as that approved. If not, provide comparative information on the manufacturing process, starting materials, controls, impurities, and container closure for the approved and proposed sources of the Drug Substance.

Applicant's Response to Agency Question 2.

The applicant reiterated that the currently approved DS supplier is (b) (4), DMF (b) (4), and that the proposed DS supplier, is Hospira, Boulder, DMF 25,212. The requested information for the currently approved supplier is not available because DMF (b) (4) is no longer active. The applicant provided information regarding approved specifications, quantitative and qualitative comparative analysis to the proposed Boulder material, as well as a complete qualification package for the proposed supplier Hospira, Boulder DS material.

Reviewer's Evaluation: Adequate. *Comparison of DS manufactured by the proposed and proposed manufacturing process should be provided for a supplement so that a side by side comparison of the quality of the 2 products can be made (as discussed with the applicant in a T-con dated 11/14/2012). However, because (as the applicant claims) information about the old DP is not available, the DS made by the proposed process is treated as a new product. Detailed evaluation of the process and impurities was made in the first cycle. Impurities formed in the new process are treated as new impurities and ICH guidelines were applied. Pharm/Tox reviewer was consulted for comment on the genotoxic impurities (see question 7, and limits of (b) (4) (question 4)).*

Agency Question 3.

List other approved suppliers of the Drug Substance ((b) (4) DMF (b) (4) is inactive), if any.

Applicant's Response to Agency Question 3.

The applicant stated that there are no other approved suppliers of the drug substance.

Reviewer's Evaluation: Adequate.

Agency Question 4.

Set numerical limits for (b) (4) content in API specification. The data provided is insufficient to omit testing for (b) (4).

Applicant's Response to Agency Question 4.

The applicant is proposing a limit for (b) (4) of (b) (4) Revised DS specifications are listed at the end of the review for completeness. This limit was found acceptable by the Pharm/Tox reviewer, Dr. James Willard (see review dated 2/14/2013).

Reviewer's Evaluation: Adequate. *This limit was found acceptable by the Pharm/Tox reviewer, Dr. James Willard (see review dated 2/14/2013).*

Agency Question 5.

A shelf life of 18 months for Drug Product is not supported by the stability data. Provide stability data to support the shelf life of 18 months in the proposed formulation or amend the shelf life claim to 12 months. Extension of shelf life based on real time data as they become available can be done via Annual Report.

Applicant's Response to Agency Question 5.

The applicant provided long term stability data (25 °C, 60% RH, 18 month) for 3 lots of 1 mL ampoule, and 3 lots of 5 mL ampoule. They also provided accelerated stability data (40 °C, 75% RH, upto 6 months), and intermediate stability conditions (30 °C, 65% RH, 18 months) for 3 lots each of 1 mL and 5 mL ampoules. No mention of changes in the stability protocol is made. Typical data are shown in table 1 below.

Table 1. Stability Results for Isoproterenol Hydrochloride Injection, USP 1 mL Ampul (Lot PD0-175)

			25C/60% RH (Long Term)				
Test	Spec.	Initial T0	3 Months	6 Months	9 Months	12 Months	18 Months
Description	(b) (4)	colorless liquid	colorless liquid	colorless liquid	colorless liquid	colorless liquid	colorless liquid
pH <791>		3.9	3.9	3.9	3.9	3.9	3.9
EDTA Content		199 µg/mL	197 µg/mL	202 µg/mL	192 µg/mL	194 µg/mL	195 µg/mL
Isoproterenol HCl (% Label)		203 µg/mL 101.5%	200 µg/mL 100.0%	201 µg/mL 100.5%	201 µg/mL 100.5%	201 µg/mL 100.5%	198 µg/mL 99.0%
Specified Imp. Impurity (b		ND	ND	<0.1%	0.1%	0.3%	0.4%
Unspecified Impurities		<0.1% (0.47) <0.1% (1.85)	<0.1% (0.48) <0.1% (1.82)	<0.1% (0.39) <0.1% (0.45)	<0.1% (0.46) <0.1% (1.84)	<0.1% (0.47) <0.1% (1.68) <0.1% (1.82)	<0.1% (0.35) <0.1% (0.43) <0.1% (0.46) <0.1% (0.90) <0.1% (1.70) <0.1% (1.85) <0.1% (3.60)
Total Impurities		0.0% (<0.1%)	0.0% (<0.1%)	0.0% (<0.1%)	0.1%	0.3%	0.4%
Color and Clarity		Clear and colorless	Clear and colorless	Clear and colorless	Clear and colorless	Clear and colorless	Clear and colorless
Sterility <71>		Complies	NR	NR	NR	Complies	Complies
Bacterial Endotoxins <85>		<7.46 EU/mg	NR	NR	NR	<7.46 EU/mg	<7.46 EU/mg
Particulate Matter <788>		223 7	NR	NR	NR	239 15	146 5

ND=None Detected, NMT = Not More Than

Based on the real time stability data generated for the registration batches, the applicant proposes to set DP expiration date of 18 months, when stored at controlled room temperature (20– 25°C; 68 – 77°F).

Reviewer's Evaluation: Adequate. *The updated stability data summarized in table above indicate that the DP continues to meet product specifications through 18 months at 25 °C, 60% RH. All samples remained within specifications for all tests including Description, Color and Clarity, pH, EDTA, Sterility, BET, and particulates. No significant trends were observed. The product exhibited some color after 6 months accelerated stability and 18 month intermediate conditions; however the results were still within the specifications. Additionally, they noted that the particulates, while all within USP specifications, demonstrated some variability. An internal evaluation indicated that glass particles are generated when the neck of the ampul is broken for the test possibly resulting in higher counts of particulates that are not indicative of the product formulation. The applicant removed the test Clarity of Solution from D Pstability testing. This is acceptable because there is a test for Description and particlulates.*
The issue of stability data for the proposed shelf life is resolved.

Agency Question 6.

Clarify what the following in Section P.3.3 means. (b) (4) " Please state that (b) (4) will not be performed or list specific conditions under which (b) (4) will be performed.

Applicant's Response to Agency Question 6.

The applicant revised the wording in Section 3.2.P.3.3 Description of Manufacturing Process and Process Controls as follows. " (b) (4) (b) (4)

Reviewer's Evaluation: Adequate.

Agency Question 7.

Provide comparative impurity profile for approved DS and that manufactured by the proposed process. Indicate if (b) (4), (b) (4) and (b) (4) are new impurities; if yes, indicate if these impurities are genotoxic.

This question is related to the following Agency request made on 11/28/2012 made by email following a T-con between the applicant t and the CMC team.

In reference to the telecom on November 14, 2012 concerning Question 7 of the complete Response Letter of February 3, 2012 we determined that the requested comparative impurity profile should be provided to carry out a complete evaluation of the proposed changes to the drug substance manufacturing site and the analytical methods. These data can be submitted as an amendment to the November 20, 2012 submission.

Applicant's Response to Agency Question 7 and Amendment dated 1/23/2013.

As clarified above, the applicant reiterated that a comparative impurity profile for the Ds manufactured by the approved and proposed processes is not available. The DMF for the approved DS is inactive and therefore further identification and characterization of impurities by that supplier is not feasible. Therefore, the impurities listed above are treated as new impurities.

The applicant provided a comparison of BI DS and the proposed DS (see chromatograms below). They also summarized the Peak Imurities in the 2 DS samples (see table II below). Impurity (b) (4) and is equivalent in both DS samples. Unspecified unknown impurity with RRT of (b) (4) was identified as (b) (4), a synthetic process impurity, and is at equivalent level of (b) (4) in both DS samples. The number of unspecified unknown impurities and relative retention times are similar for both DS with the exception of the peak at RRT (b) (4). This unknown impurity is not detectable in proposed material. Total Impurities are greater for the approved DS (b) (4) relative to proposed DS (b) (4) Much of this increase arises from the single unknown peak at RRT (b) (4).

FIGURE 1. HPLC Chromatogram for Hospira Boulder DS (Lot A3510-09-03 Reg)

FIGURE 2. HPLC Chromatogram for (b) (4) DS (Lot 271109)

TABLE II. Peak Impurity Comparison for Isoproterenol Hydrochloride

Reviewer's Evaluation: Adequate. *The impurity profiles of Ds made using the proposed and approved methods are comparable as seen in the chromatograms. Other impurities are present at comparable levels. Total impurities are lower in DS made using the proposed process. The limits for these impurities are set as for new impurities, using ICH guidelines. Two of these impurities are potential genotoxic* (b) (4) *Pharm/Tox reviewer, Dr. James Willard, found the applicant's limits for these acceptable (see review dated 2/14/2013).*
The issue of impurities is thus resolved.

Agency Question 8.

Submit data to support the safety of injecting directly into the heart a formulation with two calcium chelators (EDTA and citrate) in the setting of life-threatening myocardial dysfunction.

Applicant's Response to Agency Question 8.

The applicant proposed to (b) (4) from the label thereby (b) (4)

However, the review team concluded that (b) (4) (b) (4) was not acceptable. (b) (4)

Reviewer's Evaluation: Adequate. *The review team concluded that* (b) (4)

- (b) (4)
- (b) (4)

To evaluate the safety concern, the Pharm/Tox and Medical reviewers made theoretical calculation of the Ca ion sequestration by the new formulation based on the dose of DP in intracardiac setting, plasma volume of ventricle, and the amount of Ca chelators (EDTA and citrate) in the proposed formulation. The review team concluded that "there was no clinical reason to be concerned about the effects of the proposed formulation change on myocardial Ca levels. (b) (4) *(see review by Medical Officer, Dr. Martin Rose dated 3/8/2013).*

The issue of the safety of Ca chelators in the new formulation is thus resolved based on recommendation by Medical and Pharm/Tox reviewers.

Agency Question 9.

During a recent inspection of the Hospira manufacturing facility McPherson, Kansas, our investigator conveyed deficiencies to the representative of the facility. Satisfactory compliance with Current Good Manufacturing Practices for Drugs is required for all manufacturing and testing facilities before this supplement may be approved.

FACILITY INSPECTIONS

Applicant's Response to Agency Question 9.

The applicant stated that manufacturing facility in McPherson, Kansas has responded to all conveyed deficiencies and provided a revised cGMP statement from McPherson. OC gave an overall recommendation of acceptable based on District recommendation (on 2/13/2013) for the proposed facility. Report is attached at the end of the review.

Reviewer's Evaluation: Adequate. *Adequate based on the overall recommendation by OC.*

Agency Question 10.

For all Container Labels and Carton Labeling LABELING

a. Ensure that the lot number and expiration date is placed on all container labels and carton labeling.

b. Ensure the route of administration statement is included on the principle display panel. This statement should read "Intravenous, subcutaneous, intramuscular, and intracardiac use only"

Applicant's Response to Agency Question 10.

Refer to review by DMEPA.

Agency Question 11. For the 1 mL and 5 mL Ampul Container Label, remove the storage information to save space and reduce the cluttered appearance of the label, per 21 CFR 201.10 (i).

Applicant's Response to Agency Question 11.

Refer to review by DMEPA.

Agency Question 12.

For the 1 mL Ampul Container Label and Carton Labeling, move the strength statement so it is inside of the color block that has the proprietary and established names, for increased prominence.

Applicant's Response to Agency Question 12.

Refer to review by DMEPA.

Agency Question 13.

For all Carton Labeling, revise the net quantity statement to say the following:

a. 5 mL ampul x 10 ampuls per carton

b. 1 ml ampul x 25 ampuls per Uni-Amp™ unit dose pak

Applicant's Response to Agency Question 13.

Refer to review by DMEPA.

Agency Question 14.

For insert Labeling, include the volume of Sodium Chloride Injection, USP or 5% Dextrose Injection USP needed for dilution of Isuprel administered as a bolus intravenous injection in the dosage tables.

a. The strength statement for the 1 mL Container and Carton labels has been revised to read "0.2 mg/mL" removing the additional reference to 0.2 mg to comply with USP formatting.

b. The ratio, 1:5000, after the Sterile Injection was removed on all labeling to minimize confusion.

Applicant's Response to Agency Question 14.

Refer to review by DMEPA.

GRATUITOUS AMENDMENT

DRUG SUBSTANCE

In addition to the changes made in this Complete Response (Q4), Hospira submits the following changes to the API specifications in alignment with a recent revision to DMF 25,212:

The applicant revised DS specifications to remove (b) (6)

Reviewer's Evaluation: Adequate. *The applicant's rationale summarized above is acceptable. Furthermore, 3 batches of DS release data submitted in the original submission S-031 indicated that* (b) (4) *was present at "not detectable" levels. The method for detection was validated and found adequate for its use in the first cycle of review.*

DRUG PRODUCT

pH: The applicant initially proposed a pH release specification of 2.5 -4.5 in accordance with USP standards. They now propose to (b) (4) because they observe no change in pH for the registration batches over time (18 months).

Reviewer's Evaluation: Adequate. (b) (4) *is acceptable.*

Specifications

(b) (4)

Reviewer's Evaluation: Adequate. *Addition of an ID test is acceptable.*

Sterility Test Method Validation: The applicant submited *Section 3.2 P.5.3.4 Validation of Analytical Procedures –Sterility* for Isuprel® (Isoprotererenol Hydrochloride Injection, USP). The original submission inadvertently contained incorrect drug product information.

Reviewer's Evaluation: Adequate. *Microbiology reviewer, Dr. Jessica Cole, recommends approval from a Microbiology point of view (see review dated 1/14/2013).*

Supplementary Materials

DS Specifications

Table 1. Drug Substance Specification

Test	Regulatory Method	Alternate Method [c]	Limit
(b) (4)			

NMT = Not more than; NLT = Not less than, HPLC = High pressure liquid chromatography; GC = Gas chromatography

[a] In-house (non-USP) analytical procedures are provided in Section 3.2.S.4.2.

[b] The validation data for the analytical procedures are provided in Section 3.2.S.4.3.

[c] It is acknowledged that in the event of dispute, only the results obtained by the USP monograph will be considered conclusive.

[d] Aerobic microbial count and bacterial endotoxin tests are additional tests conducted beyond the requirements of the monograph

Note about Section 3.2.S.3. Manufacturers

Several sites included in the DS DMF were not requested for inspection during review cycle 1. All proposed sites were requested to EES in this cycle. The OC gave an overall recommendation of Acceptable for all proposed sites. A complete list of the DS and DP manufacturing sites mentioned in NDA (in review cycle 1) is listed below for completeness (Table 1 for DS and Table 2 for DP). The sites related to DMF 25,212 are listed in Review 2 for DMF 25,212 (found adequate by Kavita A. Vyas on 3/12/13). A summary EER is attached at the end of the review.

Table 1. Site Establishment Information

Manufacturer's Name & Address	Contact Details	Function
Hospira Boulder, Inc. 4876 Sterling Drive Boulder, CO 80301 Registration: 3005231248	Tel: 303-245-6200 Fax: 303-938-1255 Contact: Brian McCudden Email: brian.mccudden@hospira.com	Drug substance: manufacturing, Analytical release testing, Stability testing
Hospira S.p.A Via Fosse Ardeatine, 2, Liscate 20060, Italy Registration: 3004640070	Tel: (+39) 02 954541 Fax: (+39) 02 9587771 Contact: Nevio Panzeri Email: nevio.panzeri@hospira.com	Analytical release testing
Hospira, Inc. 1776 Centennial Drive McPherson, KS 67460 Registration: 1925262	Tel: 620-241-6200 Fax: 620-241-6248 Contact: Bob Williford Email: Robert.williford@hospira.com	Biological and analytical drug substance release testing
(b) (4)		Biological and analytical drug substance release testing
		Biological and analytical drug substance release testing

Table 2 DP Manufacturing sites with responsibilities

Company Name and Address	Contact Name	Responsibilities
Hospira Boulder, Inc. 4876 Sterling Drive Boulder, CO 80301 Registration: 3005231248	Tel: 303-245-6200 Fax: 303-938-1255 Contact: Brian McCudden Email: brian.mccudden@hospira.com	Drug substance release testing,
Hospira, Inc. 1776 N. Centennial Drive McPherson, KS 67460 Registration No. 1925262	Robert Williford Manager, Plant Quality Assurance Tel. (620) 241-6200 Ext. 6198 Fax (620) 241-6284 Email: robert.williford@hospira.com	Drug Substance testing Excipient testing Component testing Manufacture of drug product In-process control testing Release testing of drug product Packaging and labeling of drug product Stability testing site for drug product
Hospira, Inc. 375 North Field Drive Lake Forest, IL 60045 Registration No. 3004591926	Gary Moulton Manager, Quality Tel. (224) 212-4631 Fax (224) 212-5205 Email: gary.moulton@hospira.com	Stability testing for registration and commercial stability batches

EER Report

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 10515/031	**Sponsor:**	HOSPIRA
Org. Code:	110		275 NORTH FIELD DR BLDG H2
Priority:	3P		LAKE FOREST, IL 600455046
Stamp Date:	03-OCT-2011	**Brand Name:**	ISUPREL
PDUFA Date:	21-MAR-2013	**Estab. Name:**	
Action Goal:		**Generic Name:**	ISOPROTERENOL HYDROCHLORIDE
District Goal:	14-FEB-2013	**Product Number; Dosage Form; Ingredient; Strengths**	
		001; SOLUTION, INJECTION; ISOPROTERENOL HYDROCHLORIDE; 0.2MG/ML	

FDA Contacts:	T. BOUIE	Project Manager	3017961649
	K. VYAS	Review Chemist	3017964787
	N. CHIDAMBARAM	Team Leader	3017961339

Overall Recommendation:	ACCEPTABLE	on 12-MAR-2013	by T. SHARP	()	3017963208
	PENDING	on 11-MAR-2013	by EES_PROD		
	PENDING	on 11-MAR-2013	by EES_PROD		
	ACCEPTABLE	on 13-FEB-2013	by R. PRABHAKARA	()	3017964668
	PENDING	on 01-AUG-2012	by EES_PROD		
	PENDING	on 02-MAR-2012	by EES_PROD		
	WITHHOLD	on 02-MAR-2012	by EES_PROD		
	WITHHOLD	on 02-FEB-2012	by EES_PROD		
	WITHHOLD	on 25-JAN-2012	by EES_PROD		
	ACCEPTABLE	on 18-OCT-2011	by EES_PROD		
	PENDING	on 05-OCT-2011	by EES_PROD		

Establishment:	**CFN:**	**FEI:** 3005231248	
	HOSPIRA BOULDER INC		
	BOULDER, , UNITED STATES 803012350		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
	DRUG SUBSTANCE RELEASE TESTER		
Profile:	NON-STERILE API BY CHEMICAL SYNTHESIS	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	17-JAN-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	**CFN:** **FEI:** 3004640070		
	HOSPIRA SPA VIA FOSSE ARDEATINE 2 LISCATE, , ITALY		
DMF No:	25212	**AADA:**	
Responsibilities:	DRUG SUBSTANCE RELEASE TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	12-MAR-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	**CFN:** 1925262 **FEI:** 1925262		
	HOSPIRA WORLDWIDE, INC MCPHERSON, , UNITED STATES 674609301		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE OTHER TESTER FINISHED DOSAGE MANUFACTURER		
Profile:	(b) (4)	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	13-FEB-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	(b) (4)		
DMF No:	25212	**AADA:**	
Responsibilities:	DRUG SUBSTANCE RELEASE TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	11-MAR-2013		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	(b) (4)		
DMF No:	25212	**AADA:**	
Responsibilities:	DRUG SUBSTANCE RELEASE TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	11-MAR-2013		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	(b) (4)		
DMF No:	25212	**AADA:**	
Responsibilities:	DRUG SUBSTANCE RELEASE TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	11-MAR-2013		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

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

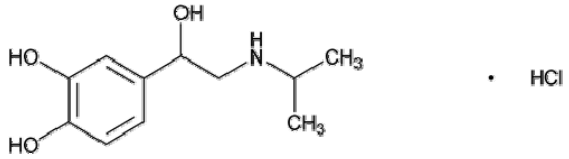
/s/

KAVITA A VYAS
03/12/2013

HASMUKH B PATEL
03/12/2013

Chemistry Review: # 1	**1. Division:** **DHP**	**2. NDA Number: 10-515**
3. Name and Address of Applicant: Hospira Inc. 275 North Field Dr. Dept, 0389, Bldg. H2-2 Lake Forest, IL 60045	**4. Supplement(s): S** **Number: 031** **Date(s): 9/30/2011**	
5. Name of Drug: Isuprel	**6. Nonproprietary name: Isoproterenol Hydrochloride Injection, USP**	
7. Supplement Provides for: (1) New supplier of DS, and associated changes, and (2) Reformulation of DP.		**8. Amendment(s):**
9. Pharmacological Category: **Bronchodilator**	**10. How Dispensed:** R_x	**11. Related Documents:**
12. Dosage Form: Injectable	**13. Potency:** 1:5000	

14. Chemical Name and Structure: 3,4-Dihydroxy-α-[(isopropylamino)methyl]benzyl alcohol hydrochloride.



15. Comments: This PAS proposes (i) Alternate Drug Substance (DS) supplier and related changes to the API methods and specifications. In support, the applicant provided LOA to DMF 25,212 a new DMF describing the API. (ii) Reformulation of Drug Product. In support, the applicant provided comparison data for assay and impurities upon storage for the approved and reformulated DP, and provided batch analyses and stability data. These data indicate that the impurity profile is cleaner to that in approved formulation, and (iii) The corresponding labeling changes to include new information on inactive ingredients. Also, both (approved and proposed) formulations could be available in the market for about 18 months (following approval of this supplement). Therefore, they assigned new NDC numbers to differentiate the two products.

Several CMC issues are identified, chiefly that the differences between the approved and proposed manufacturing process are unclear, and the applicant was asked to clarify this (IR sent on 1/11/2011).

The Microbiology reviewer recommends Approval (Jessica Cole 11/28/2011) and DMEPA Labeling review (Morgan Walker 12/30/2011) finds the proposed label unacceptable (IR sent on 1/11/2012). Biopharm reviewer recommeds approval for the biowaiver of new formulation (Elsbeth Chikhale, 1/27/2012). The OC made an overall recommendation of Withold for the proposed sites (2/2/2012). Pharmacology/Toxicology reviewers need more information about whether the proposed impurities are genotoxic (if these are new impurities). Clinical reviewer needs more information on the safety of the new formulation in intra-cardiac use (Martin Rose).

16. Conclusion: Recommend Complete Response for NDA 10-515 S-031 from a CMC point of view.

17. Name: **Signature:** **Date: 1//12/12**
Kavita A. Vyas, Ph.D., Chemist

18. Concurrence: **Signature:**
Date:
Hiten Patel., Branch Chief, Div., III, ONDQA

APPEARS THIS WAY ON ORIGINAL

APPEARS THIS WAY ON ORIGINAL

Background Information, Proposed Change, and Supporting Documents:

Isuprel, NDA 10-515, was approved in 1956 as a beta-2-agonist, and is indicated for cardiac arrest and mild or transient episodes of heart block, among other things.

In this PA supplement, the applicant proposes:

1. An alternate supplier of the Drug Substance (DS) and related changes to the API methods and specifications. Specifically:
   - ♦ Change in specifications, including (i) addition of residual solvents limits, methods and validation, (ii) addition of alternate related compounds limits, method and validation, (iii) addition of limits for bacterial endotoxins testing, addition of antimicrobial testing, and (iv) removal of test for odor
   - ♦ Minor manufacturing process changes due to new supplier of DS
   - ♦ Proposed specifications are more extensive than USP monograph for Isoproterenol, and those approved with respect to residual solvents and impurities.

In support, the applicant provided
- ♦ LOA to a new Type II DMF 25,212 for DS
- ♦ Certification that the proposed API manufacturing site is cGMP compliant; OC gave an overall recommendation of Acceptable based on 10/18/2011 on district recommendation.
- ♦ Batch Analyses for 3 batches of DS manufactured by the Applicant (Hospira Boulder), release to and tested by the Applicant (Hospira Inc.). These batches meet all Compendial and the proposed specifications.

2. To reformulate DP as follows (b) (4)

- ♦ Removal of the (b) (4)
- ♦ Removal of sodium metabisulfite as an antioxidant
- ♦ Replace lactic acid buffer with citric acid buffer
- ♦ Add EDTA as formulation stabilizer and chelating agent

They revised the DP specifications for
- ♦ Addition of limits for Residual Solvents according to (b) (4)
- ♦ Addition of limits for Related Compounds and validation
- ♦ Lowered Bacterial Endotoxin limit
- ♦ Added limits for EDTA and provided method and validation

In support, the applicant provided comparison data for Assay and Impurities upon storage for the approved and reformulated DP, and provided batch analyses and stability data. These data indicate that the impurity profile is superior to that in approved formulation.

3. The corresponding labeling changes. The applicant will discontinue the currently approved formulation upon approval of this revised formulation, but they note that both (approved and proposed) formulations could be available in the market for about 18 months (following approval). Therefore, they assigned new NDC numbers to differentiate the two products. They updated the label to indicate:
   - ♦ Change in formulation, and
   - ♦ Change in NDC Numbers.

4. They submitted the NDA in eCTD format for the first time.

Analysis of Proposed Changes:

1. DS Supply: [redacted] the approved supplier of API, has discontinued supply of Isoproterenol. The corresponding DMF [redacted] is discontinued since 2001. Therefore, it is unclear who was supplying the API since 2001.

Also, the applicant claims to have made "minor manufacturing process changes due to new supplier of DS", but did not clarify what these are. It is unclear what changes are made to the API synthesis, manufacturing process, and packaging. They supplied LOA to the new DMF 25,212, which describes the manufacturing process in detail but it is unclear how this process differs from the approved process. Specifically, the following issues are unclear:

- If the starting materials are the same for the proposed and approved syntheses.
- If the residual solvents are different from the approved supplier. All residual solvent limits are controlled at the [redacted] and [redacted] limits, so it is not an issue but this indicates that the synthetic process is different.
- If in-process steps are similar in the proposed and approved processes.
- At what stage are the impurities removed in the two processes.
- If new impurities are identified in the proposed method. The applicant submitted a rationale for the control of potential impurities in this supplement, [redacted] The [redacted] lacks these impurities testing altogether. The applicant's proposal is acceptable because it meets the [redacted], and exceeds [redacted] specifications, provided the impurities are not genotoxic (see Other Discipline recommendations below).

The primary container for the DS proposed here is PE bags. It is unclear what the approved CCS was, but DS being a solid, this is not considered an issue here. The applicant provided quality documents for the PE bags [redacted].

This change is acceptable as a stand-alone application (notwithstanding the above) if they cannot reveal details of the previously approved process, provided they answer the deficiency comments (at the end of review). While exceeding the [redacted] requirement raises questions for generics, this is not considered an issue here because the impurity profile and DS here appears to be cleaner than USP.

2. DP Reformulation: The proposed [redacted].

The applicant compared the two formulations by testing assay and impurities (the major critical quality attributes) for 6 lots of expired DP at 25 °C/60%RH, and 6 lots of DP stored at 40°C/75%RH for three months. They reason that 3 months at 40°C/75%RH simulates stress/degradation that is observed at 25°C/60% RH at 18 months. Therefore the 3 month accelerated data is used for comparison. [redacted]

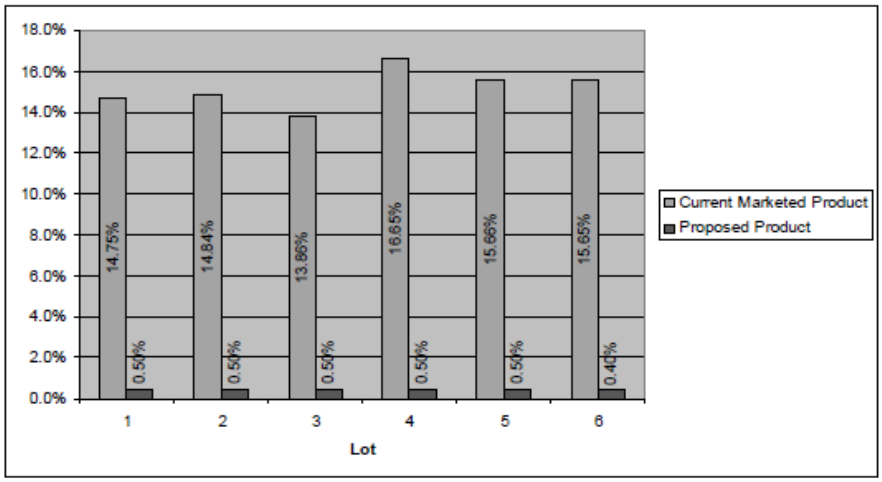
Comparative results of the impurity testing approved DP formulation show significantly higher individual and total impurities (see Fig. 2 below) relative to that in proposed formulation. The impurity profile difference in the two formulations is striking in Figure 2 below (although there is a caveat:

comparison of 3 month accelerated with 18 month long term is inappropriate, and comparative data is only provided for these time points).

Figure 1. Label Claim

(b) (4)

Figure 2. Total Impurities



3. Other Discipline Recommendations: The applicant submitted a waiver for *in vivo* bioavailability studies on the grounds that DP is an injection. Biopharm reviewer recommends approval (see review by Elsbeth Chikhale (1/27/2012). Micro reviewer (Jessica Cole 11/28/2011) recommends approval.

Other issues were identified with the proposed reformulation. Clinical Reviewer (Martin Rose; email dated 2/2/2012) recommended "that the applicant should submit data to support the safety of injecting directly into the heart a formulation with these two calcium chelators in the setting of life-threatening myocardial dysfunction". Pharm/Tox (Thomas Papoian and Abert Defelice) agreed that the risk of general organ toxicity due to the proposed impurity is low (email dated 1/27/2012), but recommended determining if impurities are genotoxic. The OC made an overall recommendation of withhold based on district recommendation (2/2/2012).

Review Notes

All Changes and Justifications are summarized below

Description of Proposed Change	Justification
Related to Alternate API: Added new residual solvents method Added related compound/impurities methods Added supporting method validations	New API supplier had specific residual solvents different from the existing supplier. As such a new method was needed. Added an Impurities method to meet current regulatory requirements.
Removed odor test for API Added AMC test Added BET Test	Revised API specifications to meet current USP and to reflect new API supplier
Method of Manufacture: Allows for use of either (b) (4) (b) (4) for pH adjustment, instead of (b) (4) only.	To ensure that correct target pH is achieved during manufacturing and to ensure lot to lot consistency in product pH.
Removed method/spec for Sodium Metabisulfite	No longer utilized in formulation
Added new method for EDTA Added related compound/impurities methods Added supporting method validations	Added EDTA to formulation, method needed to monitor correct formulation and ensure EDTA is present through shelf life at levels sufficient to stabilize product. Related compounds method added to meet current USP/ICH and FDA requirements for monitoring of related compounds.
Lowered BET specification, justification and/new method (kinetic) validation	The limit for BET in the product was lowered significant from USP limit based on the maximum daily dose calculation. See Section 32P56-Justification of Spec for details of MDD calculation.
Manufacturing Process validation to limit Oxygen in the headspace	(b) (4)
Assigned new NDC Number to reformulated product	Per discussions with FDA and review of guidance, Hospira determined that to clearly differentiate the currently approved product from the proposed reformulated product, a new List number and NDC number would be assigned. While Hospira intends to cease product of the currently approved formulation and convert over to the proposed formulation upon Agency approval, both products could potentially be distributed in the field during the first 18 months.
Updated labeling, package insert, roll labels and outer carton with proposed ingredients. Alternate formulation identified by use of new List number/NDC Number	The labeling has been updated to reflect the new NDC number assigned to the proposed formulation.

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data

The applicant presented the NDA in eCTD format for the first time. Differences are summarized below.

S DRUG SUBSTANCE [Isoproterenol Hydrochoride, Hospira Boulder, Inc.]

(b) (4)

47 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

[redacted]

A.1	**Facilities and Equipment (biotech only)**	**Not applicable**
A.2	**Adventitious Agents Safety Evaluation**	**Not applicable**
A.3	**Novel Excipients Not applicable**	
R	**REGIONAL INFORMATION**	
R1	**Executed Batch Records**	
R2	**Comparability Protocols**	**Not applicable**

A. Labeling & Package Insert

1.14.1 Draft Labeling

1.14.1.1 Draft Carton and Container Labels

The applicant provided annotated side by side comparisons of proposed container and carton labels (see below). For details see labeling review by Morgan A. Walker (12/20/2011).The proposed and approved container labeling is the same except (i) the product list number, 1410, is revised to NDC number, and the proposed formulation is assigned new NDC numbers (0409-1442-02 and 0409-1442-03); (ii) updated document internal ID number; and (iii) DP formulation is updated to replace Sodium Metabisulfite, Lactic Acid and Sodium Lactate with EDTA, Sodium Citrate and Citric Acid. Sodium Hydroxide has been added as a pH adjuster.

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

1.14.1.3 Draft Labeling Text

The applicant modified Sections on Description (see below), to add quantitative information on the new formulation in Structured Product Labeling (SPL).

Each milliliter of the sterile 1:5000 solution contains:

ISUPREL™, brand of isoproterenol hydrochloride injection, USP		0.2 mg
Edetate Disodium (EDTA)		0.2 mg
Sodium Chloride		7.0 mg
Sodium Citrate, Dihydrate		(b) (4)
Citric Acid, Anhydrous		(b) (4)
Water for Injection	qs ad	1.0 mL

The pH is adjusted between 2.5 and 4.5 with hydrochloric acid or sodium hydroxide.

Changes are also made to the How supplied Sction to indicate the new NDS numbers.

NDC	Container	Concentration	Fill Quantity
0409-1442-02	Ampul	0.2 mg (0.2 mg/mL)	1 mL UNI-AMPTM pak of 25
0409-1442-03	Ampul	1 mg/5 mL (0.2 mg/mL)	5 mL 10 ampuls per carton

Protect from light. Keep in opaque container until used.
Store at 20º to 25ºC (68º to 77ºF). [See USP Controlled Room Temperature.]

Do not use if the injection is pinkish or darker than slightly yellow or contains a precipitate.

Reviewer's Evaluation: Adequate. *The labeling changes are made to add quantitative information about new inactive ingredients added in the new formulation. As discussed above, the approved and proposed formulations will be available simultaneously for a short time, so, new NDC numbers are assigned to the proposed formulation to distinguish the two. No CMC issues are identified in the container, carton labels, or product labeling. See review by Morgan Walker (12/30/2011) for details of labeling.*

Overall Conclusion.

CMC issues of clarification of API source and the similarity of the approved and proposed manufacturing processes are pending, leading to unresolved issues about impurities. DMF 25,212 referenced in support of this supplement was found inadequate (Kavita A. Vyas, 2/3/2012). The

Microbiology reviewer recommends Approval (Jessica Cole 11/28/2011) and DMEPA Labeling review (Morgan Walker 12/30/2011) finds the proposed label unacceptable (IR sent on 1/11/2012; no response). The OC made an overall recommendation of Withold for the proposed manufacturing sites (2/2/2012) based on district recommendation. Clinical Reviewer (Martin Rose; email dated 2/2/2012) recommended "that the applicant should submit data to support the safety of injecting directly into the heart a formulation with these two calcium chelators in the setting of life-threatening myocardial dysfunction". Pharm/Tox (Thomas Papoian and Abert Defelice) agreed that the risk of general organ toxicity due to the proposed impurity is low (email dated 1/27/2012), but recommended determining if impurities are genotoxic.

Overall, **recommend Complete Response for NDA 10-515 S-031 from a CMC point of view because the supporting DMF is inadequate.**

III. List Of Deficiencies To Be Communicated

1. Indicate whether the source of Drug Substance (described in DMF 25,212) is the same as that approved. If not, provide comparative information on the manufacturing process, starting materials, controls, impurities, and container closure for the approved and proposed sources of the Drug Substance.

2. List other approved suppliers of Drug Substance (Boehringer Ingelheim DMF (b) (4) is inactive), if any.

3. Set numerical limits for (b) (4) content in API specifications. The data provided is insufficient to omit testing for (b) (4).

4. A shelf life of 18 months for Drug Product is not supported by the stability data. Provide stability data to support the shelf life of 18 months in the proposed formulation or amend the shelf life claim to 12 months. Extension of shelf life based on real time data as they become available can be automatically done via Annual Reports.

5. Clarify what the following in Section P.3.3 means. (b) (4) Please state that (b) (4) will not be performed or list specific conditions under which (b) (4) will be performed.

6. Provide comparative impurity profile for approved DS and that manufactured by the proposed process. Indicate if (b) (4) and (b) (4) are new impurities; if yes, indicate if these impurities are genotoxic.

7. (b) (4)

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 10515/031	**Sponsor:**	HOSPIRA
Org. Code:	110		275 NORTH FIELD DR BLDG H2
Priority:	3P		LAKE FOREST, IL 600455046
Stamp Date:	03-OCT-2011	**Brand Name:**	ISUPREL
PDUFA Date:	03-FEB-2012	**Estab. Name:**	
Action Goal:		**Generic Name:**	ISOPROTERENOL HYDROCHLORIDE
District Goal:	30-DEC-2011	**Product Number; Dosage Form; Ingredient; Strengths**	001; SOLUTION, INJECTION; ISOPROTERENOL HYDROCHLORIDE; 0.2MG/ML

FDA Contacts:	D. HENRY	Project Manager	301-796-4227
	N. CHIDAMBARAM	Team Leader	301-796-1339

Overall Recommendation:	WITHHOLD	on 02-FEB-2012	by D. SMITH	()
	WITHHOLD	on 25-JAN-2012	by EES_PROD	
	ACCEPTABLE	on 18-OCT-2011	by EES_PROD	
	PENDING	on 05-OCT-2011	by EES_PROD	

Establishment:	**CFN:**	**FEI:** 3005231248	
	HOSPIRA BOULDER, INC. 4876 STERLING DR BOULDER, CO 803012350		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER DRUG SUBSTANCE RELEASE TESTER		
Profile:	NON-STERILE API BY CHEMICAL SYNTHESIS	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	18-OCT-2011		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	**CFN:** 1925262	**FEI:** 1925262	
	HOSPIRA WORLDWIDE, INC 1776 CENTENNIAL DR MCPHERSON, KS 674609301		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE OTHER TESTER FINISHED DOSAGE MANUFACTURER		
Profile:	(b) (4) PARENTERAL DRUG	**OAI Status:**	POTENTIAL OAI
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	02-FEB-2012		
Decision:	WITHHOLD		
Reason:	DISTRICT RECOMMENDATION		

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/s/

KAVITA A VYAS
02/03/2012

HASMUKH B PATEL
02/03/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

10-515/S031

PHARMACOLOGY REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation I
Division of Cardiovascular and Renal Products

Memo

To: Albert De Felice, Ph.D. Team Leader Pharmacologist
Quynh Nguyen, RPM

From: James M. Willard, Ph.D. Pharm/Tox Reviewer

CC:

Date: May 10, 2013

Re: NDA 010515 – change of supplier

The present submission began as a CMC consult about a change in supplier for Isuprel (Isoproterenol Hydrochloride). Due to a change in excipients (EDTA and citric acid for sodium metabisulfate), (b) (4) thus requiring a review from the Division of Cardiovascular and Renal Products. This reviewer was requested to review Questions 4 and 7 from the sponsor's response to questions from the FDA to the sponsor. The question came up as to how much calcium would be bound by the EDTA and Citrate present in the formulation. Calculation of calcium binding in the proposed dose (0.1 mL) in an anticipated ventricular space was done to examine the potential for disruption of cardiac calcium homeostasis.

Calcium binding of EDTA, Sodium Citrate and Citric acid in Isuprel's new formulation:

Isuprel contains:

EDTA @ 0.42 mg/mL which is equal to 1.1 mmol/L

Na Citrate @ 2.0708 mg/mL which is equal to 8 mmol/L

Citric Acid @ 2.4897 mg/mL which is equal to 13 mmol/L

Original suggestion was a 100 lb child

Modified to a 79.2 lb child (37 kg)

Body Surface Area: 1.38 m^2

Ventricular Volume: 77.5 mL

Plasma Volume (60%): ~50 mL

Plasma [Ca++]: 10 mg/dL so 5 mg in 50 mL or 2.5 mM

Isuprel is indicated for a 0.1 mL injection for intracardiac injection

EDTA and Citrate bind Ca++ in a 1:1 stoichiometry

Final concentration of Ca++ is 2.5 mmol/L, in 50 mL =0.125 mmol

Final concentration of EDTA is 0.0008 mmol/L in 50 mL = 0.00004 mmol

Final concentration of Citrate is 0.00021 mmol

Therefore 0.00025 mmol Ca++ chelator

That would reduce the Ca++ to 0.12475 mmol from 0.125 mmol

Karen Hicks cites a reference that right ventricular volume ranges from 100-160 mL, at 100 mL the plasma volume would be 60 mL, and would only differ slightly from this estimate, with less Ca++ being chelated. (Eur J Echocardiogr 2006 mar; 7(2) 79-108.).

Info for example from: Buechel, E.V., Kaiser, T., Jackson, C., Schmitz, A., and C.J. Kellenberger. Normal right- and left ventricular volumds and myocardial mass in children measured by steady state free precession cardiovascular magnetic resonance. J Cardiovasc Magn Reson. 2009; 11(1): 19.

The conclusion is that minimal quantities of calcium would be removed from the plasma, having little or no effect on cardiac function. (b) (4)

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/s/

JAMES M WILLARD
05/10/2013
this one should be cleaner and leaner!

ALBERT F DEFELICE
05/10/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation I
Division of Cardiovascular and Renal Products

Memo

To: Albert De Felice, Ph.D. Team Leader Pharmacologist
Quynh Nguyen, RPM

From: James M. Willard, Ph.D. Pharm/Tox Reviewer

CC:

Date: January 30, 2013

Re: NDA 010515 – change of supplier

The present submission began as a CMC consult about a change in supplier for Isuprel (Isoproterenol Hydrochloride). Due to a change in excipients (EDTA and citric acid for sodium metabisulfate), (b) (4) , thus requiring a review from the Division of Cardiovascular and Renal Products. This reviewer was requested to review Questions 4 and 7 from the sponsor's response to questions from the FDA to the sponsor. The complete document with the questions and responses is attached as an addendum.

4. Set numerical limits for (b) (4) content in API specification. The data provided is insufficient to omit testing for (b) (4).

Hospira is proposing a limit for (b) (4) of (b) (4). The revised drug substance specification is presented in *Section 3.2.S.4.1 Specifications*, and the test method and method validation for determination of (b) (4) are presented in revised *Section 3.2.S.4.2.4 Analytical Procedures* and Section 3.2.S.4.3.4 *Validation of Analytical Procedures*, respectively.

Question 4 was whether a limit for (b) (4) in the drug product of (b) (4) is acceptable. This amount is acceptable for several reasons.

1. Product is for a single use, thus minimizing exposure
2. The Drug Product is reconstituted to 0.2 mg/ml, which makes the level in the reconstituted Drug Substance to be (b) (4)
3. The Drug Substance is further diluted by 10- or 50-fold depending on the application, further reducing the level to (b) (4).

4. The sponsor reported a limit of quantitation to be (b) (4) for (b) (4), therefore with a (b) (4) limit in the Drug Product, (b) (4) should not be detectable in any of the applications approved for its usage.

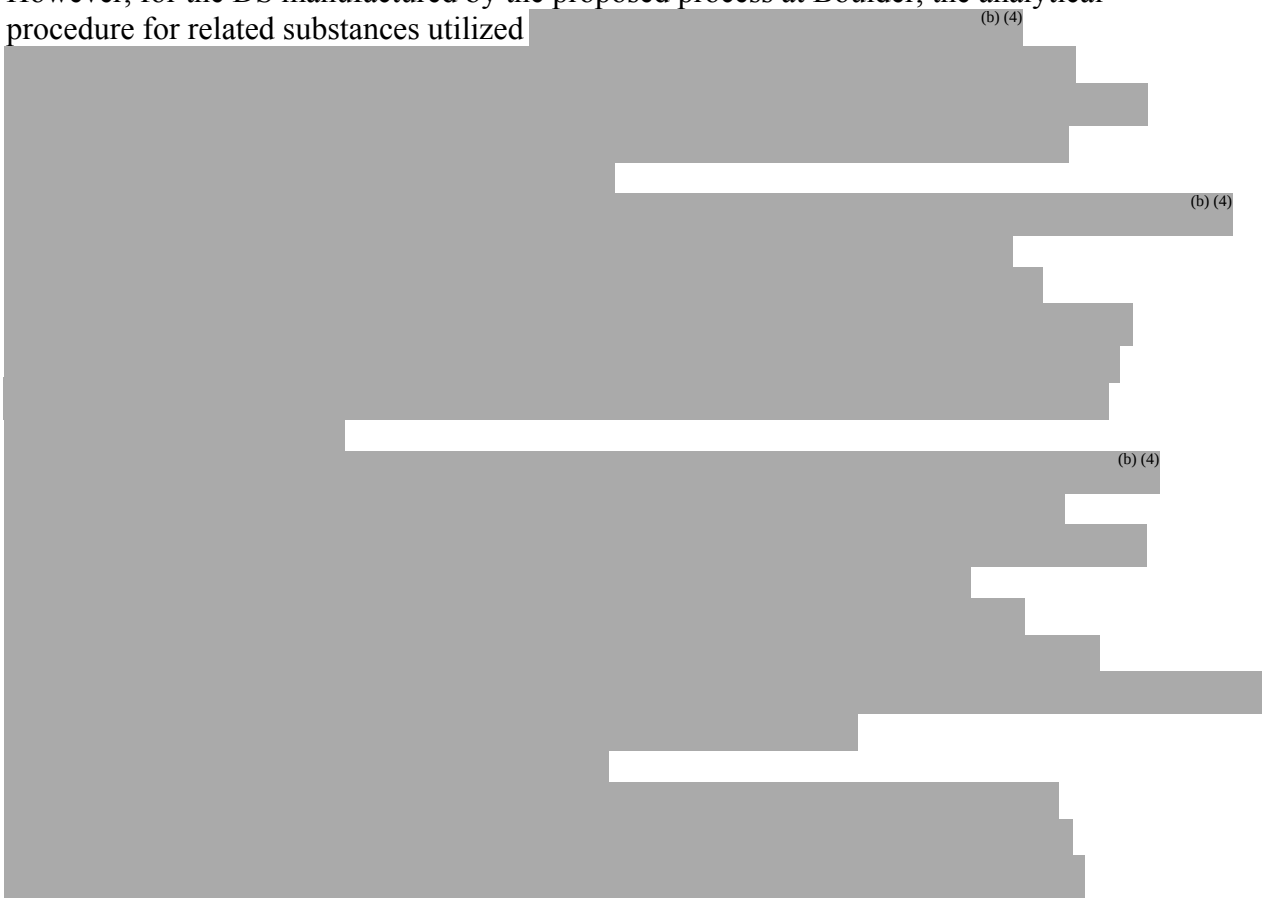
5. No (b) (4) was detected in any of the batches that were analyzed.

6. (b) (4) exposure from the worst case example of (b) (4) in the Drug Product, would not provide sufficient exposure to cause toxicity. In rats and rabbits, (b) (4) in the drug product, however, as pointed out in #3, with the dilution factors, and then factoring in the dilution factor of a (b) (4) provides a dosing of (b) (4), thus providing a safety margin of approximately (b) (4). With the maximum daily recommended dose of 1.8 mg of Isuprel, the maximum dose of (b) (4) would be (b) (4). Since (b) (4) would be the Human Equivalent dose of (b) (4) on a mg/m^2 basis, that provides an over (b) (4) fold safety margin.

7. Provide comparative impurity profile for approved DS and that manufactured by the proposed process. Indicate if (b) (4) and (b) (4) are new impurities; if yes, indicate if these impurities are genotoxic.

A comparative impurity profile for the approved drug substance ((b) (4)) and that manufactured by the proposed process (Boulder) is not available. The DMF for the approved DS is inactive and therefore further identification and characterization of impurities by that supplier is not feasible.

However, for the DS manufactured by the proposed process at Boulder, the analytical procedure for related substances utilized (b) (4)



Question 7 dealt with several impurities that were potentially found in the Drug Product. Isuprel was originally approved in 1956, prior to many of the regulations presently in effect. There were 3 compounds found that were positive for genotoxicity in a DEREK for Windows QSAR study.

(b) (4)

Summary and Conclusions:

Isuprel's safety has not been compromised by a change in manufacturer, and the product is very similar to that previously marketed. The sponsor did (b) (4) of EDTA and citric acid, two calcium chelators. There is no concern about the levels of (b) (4) in the Drug Product, levels are so low that it would be impractical through Isuprel to achieve significant exposure levels. In addition, the qualifying batches showed no detectable levels of (b) (4). There is a low level of concern about the potential, as determined by DEREK for Windows, genotoxicity of (b) (4), (b) (4) It would be optimal if they were tested for genotoxicity, minimally in an Ame's Assay, especially (b) (4) which is found in the drug product. However, exposure levels to (b) (4) would be low, and the other potential impurities were not detected in the test batches. I can see no reason to not approve the change in manufacturer, (b) (4).

Addendum 1 - pages 5-17 - CMC response from Hospira from Feb. 3, 2012
Addendum 2 - pages 18+ - Comparative chromatograms (b) (4) and Hospira Isoproterenol HCl.

CHEMISTRY, MANUFACTURING AND CONTROLS

1. **The Drug Master File (DMF) 25,212 has been reviewed and determined to be inadequate to support your NDA. Deficiencies have been communicated to the DMF holder.**

   The DMF holder has informed Hospira that the DMF 25,212 has been amended to adequately address deficiencies. For your convenience, Hospira is providing a copy of the cover letter for the submitted DMF 25,212.

2. **Indicate whether the source of Drug Substance (described in DMF 25,212) is the same as that approved. If not, provide comparative information on the manufacturing process, starting materials, controls, impurities, and container closure for the approved and proposed sources of the Drug Substance.**

   As specified in the original submission, the currently approved drug substance supplier is (b) (4), DMF (b) (4). The proposed drug substance supplier requested within this supplement is Hospira, Boulder, DMF 25,212. The requested information for the currently approved supplier is not available as the DMF is no longer active. Hospira has provided information where available regarding approved specifications, quantitative and qualitative comparative analysis to the proposed Boulder material, as well as a complete qualification package for the proposed supplier Hospira, Boulder DS material.

3. **List other approved suppliers of the Drug Substance ((b) (4) DMF (b) (4) is inactive), if any.**

   Currently, there are no other approved suppliers of the drug substance.

4. **Set numerical limits for (b) (4) content in API specification. The data provided is insufficient to omit testing for (b) (4).**

   Hospira is proposing a limit for (b) (4) of (b) (4) The revised drug substance specification is presented in *Section 3.2.S.4.1 Specifications*, and the test method and method validation for determination of (b) (4) are presented in revised *Section 3.2.S.4.2.4 Analytical Procedures* and Section 3.2.S.4.3.4 *Validation of Analytical Procedures*, respectively.

5. **A shelf life of 18 months for Drug Product is not supported by the stability data. Provide stability data to support the shelf life of 18 months in the proposed formulation or amend the shelf life claim to 12 months. Extension of shelf life based on real time data as they become available can be done via Annual Report.**

   Hospira is providing 18 month stability data at room temperature (25°C, 60% RH) for each of the exhibit batches. The updated stability data, included in *Section 3.2.P.8.3 Stability Data*, indicates that the product continues to meet product specifications through

18 months at 25°C, 60% RH. Based on the stability data generated for the registration batches, Hospira proposes that the expiration dating be set at eighteen (18) months for all presentations of the subject drug product, when stored at controlled room temperature (20 – 25°C; 68 – 77°F).

6. **Clarify what the following in Section P.3.3 means. (b) (4) Please state that (b) (4) will not be performed or list specific conditions under which (b) (4) will be performed.**

Hospira has revised the wording in *Section 3.2.P.3.3 Description of Manufacturing Process and Process Controls* accordingly.

7. **Provide comparative impurity profile for approved DS and that manufactured by the proposed process. Indicate if (b) (4) and (b) (4) are new impurities; if yes, indicate if these impurities are genotoxic.**

A comparative impurity profile for the approved drug substance (Boehringer Ingleheim) and that manufactured by the proposed process (Boulder) is not available. The DMF for the approved DS is inactive and therefore further identification and characterization of impurities by that supplier is not feasible.

However, for the DS manufactured by the proposed process at Boulder, the analytical procedure for related substances utilized (b) (4)

(b) (4)

[redacted]

8. Submit data to support the safety of injecting directly into the heart a formulation with two calcium chelators (EDTA and citrate) in the setting of life-threatening myocardial dysfunction.

(b) (4)

[redacted] The revised labeling is included in QCA-3048V1, QCA-3049V1, QEN-3013V1, QIM-2217V1, QRL-3904V1, and QRL-3905V1.

FACILITY INSPECTIONS

9. During a recent inspection of the Hospira manufacturing facility McPherson, Kansas, our investigator conveyed deficiencies to the representative of the facility. Satisfactory compliance with Current Good Manufacturing Practices for Drugs is required for all manufacturing and testing facilities before this supplement may be approved.

The Hospira manufacturing facility in McPherson, Kansas has responded to all conveyed deficiencies. Hospira believes that this facility has met Agency expectations to acquire satisfactory compliance with Current Good Manufacturing Practices. A revised cGMP statement from McPherson is included.

LABELING

10. For all Container Labels and Carton Labeling

a. **Ensure that the lot number and expiration date is placed on all container labels and carton labeling.**

The lot number and expiration is stamped on each container and carton labeling at the time of manufacture. Please see QCA-3048V1, QCA-3049V1, QIM-2217V1, QRL-3904V1, and QRL-3905V1 indicating the placement and location of the lot number and expiration date for each.

b. **Ensure the route of administration statement is included on the principle display panel. This statement should read "Intravenous, subcutaneous, intramuscular, and intracardiac use only"**

(b) (4)

Please see updated labeling in QCA-3048V1, QCA-3049V1, QIM-2217V1, QRL-3904V1, and QRL-3905V1.

11. For the 1 mL and 5 mL Ampul Container Label, remove the storage information to save space and reduce the cluttered appearance of the label, per 21 CFR 201.10 (i).

The storage information has been removed from the 1 mL and 5 mL Ampul Container Label as requested. Please see updated labeling in QRL-3904V1 and QRL-3905V1.

12. For the 1 mL Ampul Container Label and Carton Labeling, move the strength statement so it is inside of the color block that has the proprietary and established names, for increased prominence.

The strength statement for the 1 mL Ampul container label has been moved to within the color block as suggested. Please see updated labeling in QRL-3904V1. [redacted] (b) (4)

13. For all Carton Labeling, revise the net quantity statement to say the following:

a. **5 mL ampul x 10 ampuls per carton**

The requested changes to carton labeling were incorporated as specified. Please see updated labeling in QCA-3048V1.

b. **1 ml ampul x 25 ampuls per Uni-Amp™ unit dose pak**

The requested changes to carton labeling were incorporated as specified. Please see updated labeling in QCA-3049V1.

14. For insert Labeling, include the volume of Sodium Chloride Injection, USP or 5% Dextrose Injection USP needed for dilution of Isuprel administered as a bolus intravenous injection in the dosage tables.

The volume of Sodium Chloride Injection, USP or the volume of 5% Dextrose Injection USP required for dilution has been incorporated in the insert labeling. Please see updated labeling in QEN-3013V1.

Additionally, per e-mail communication with Don Henry on 02/22/2012 the following changes were also made to the labeling with agreement from the Agency:

a. The strength statement for the 1 mL Container and Carton labels has been revised to read "0.2 mg/mL" removing the additional reference to 0.2 mg to comply with USP formatting. Please refer to QCA-3049V1 and QRL-3904V1.

b. The ratio, 1:5000, after the Sterile Injection was removed on all labeling to minimize confusion. Please refer to QCA-3048V1 and QCA-3049V1.

GRATUITOUS AMENDMENT

In addition to the requested additional information, Hospira respectfully requests the following changes be accepted to ensure accuracy and consistency of the application.

DRUG SUBSTANCE
In addition to the changes made in this Complete Response (Q4), Hospira submits the following changes to the API specifications in alignment with a recent revision to DMF 25,212:

Specifications
The Drug Substance specifications have been revised to [redacted] (b) (4)

DRUG PRODUCT

Specifications
pH: Hospira originally submitted the pH release specification as 2.5 -4.5 in accordance with USP standards. As there has been no change in pH for the registration batches over time (18 months), [redacted] (b) (4) Please refer to the revised *Section 3.2.P.5.1 Specifications* and *Section 3.2.P.8.3 Stability Data.*

Identification: Hospira requests the addition a of second identification test for Isoproterenol Hyrdrochloride Injection, USP. For identity of Isoproterenol by [redacted] (b) (4) (b) (4) Please refer to revised Sections *3.2.P.5.1 Specifications, 3.2.P.5.2.1 Analytical Procedures*, and *3.2.P.5.3.1 Validation of Analytical Procedures*.

Sterility Test Method Validation

Hospira respectfully submits *Section 3.2 P.5.3.4 Validation of Analytical Procedures – Sterility* for Isuprel® (Isoprotererenol Hydrochloride Injection, USP). The original submission inadvertently contained incorrect drug product information.

June 6, 2012

Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room (CDR)
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: Isuprel (Isoproterenol Hydrochloride), Drug Substance Master File 25212

Response to Isuprel Drug Substance DMF Deficiency Issued on February 3, 2012

Hospira, Inc. hereby amends the DMF for Isuprel, Drug Substance Master File: 25212, in response to the Agency's Notification of Deficiency issued on February 3, 2012. Hospira's response to the request is provided.

The response document is authored in compliance with CTD format. Per the Agency's instruction, Hospira provides two hard copies of the response package herein. In addition, a CD is enclosed to contain the submission files in CTD format with hyperlinks. The files have been scanned for viruses using the current version of McAfee VirusScan Enterprise 8.5.0 virus scanning software.

Hospira Boulder Inc.
4876 Sterling Drive
Boulder, CO 80301

Hospira

We trust that this submission is complete. If you require any clarification or further information, please feel free to contact me.

Sincerely,
HOSPIRA, INC.

Wendy Tian
Associate Director, Global Regulatory Affairs
Hospira Boulder, Inc.
Phone: 224-212-6163
Fax: 224-212-5401
E-mail: wentong.tian@hospira.com

Hospira

cGMP CERTIFICATE – McPHERSON, KANSAS

1. The buildings and equipment in which the drug is manufactured, held, controlled, packaged, and labeled are of suitable design, size, construction, and location to facilitate maintenance and operation for their intended purposes in an orderly and clean manner.
2. The key personnel involved in the manufacture and control of this drug have backgrounds of education and experience appropriate for assuming responsibility to ensure that the drug has the safety, identity, strength, quality, and purity we purport it to possess.
3. The raw materials used in the preparation and processing of this drug conform to appropriate standards of identity, strength, quality, and purity.
4. Adequate batch and control records are kept for each batch of drug produced.
5. The production and control procedures include reasonable precautions to ensure that the drug produced has the identity, strength, quality, and purity we purport it to possess.
6. Suitable specifications, test methods, cleaning procedures, and when indicated, sterilization procedures are used to ensure that containers, closures, and other component parts of packages are suitable for their intended use.
7. Packaging and labeling operations are adequately controlled to prevent mix-ups between drugs; to ensure that correct labeling is employed for the drug; and to identify finished products with lot or control numbers that permit determination of the history of the manufacture and control of the batch of drug.
8. Laboratory controls include adequate specifications and test procedures to ensure that raw materials, drug preparations in the course of processing, and finished products conform to appropriate standards of identity, strength, quality, and purity.
9. Complete records are maintained as to the distribution of each batch of drug in a manner which will facilitate its recall if necessary.
10. Adequate provision is made for testing the stability of raw materials, drug preparations in the course of processing when needed, and finished drugs.

Hospira, Inc. hereby certifies that the methods used in, and the facilities and controls used for the manufacture, processing, packaging, and holding of the drug are in conformity with current good manufacturing practice in accordance with parts 210 and 211 (21 CFR) of the regulations.

Robert E. Williford
Quality Director
Hospira, Inc.
1776 N. Centennial Drive
McPherson, Kansas 67460-1247

24 AUG 2012
Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NDA 10-515/S031

COMPLETE RESPONSE

Hospira, Inc.
Attention: Linda Biava
Sr. Regulatory Associate
275 N. Field Dr
Lake Forest, IL 60045

Dear Ms. Biava:

Please refer to your supplemental new drug application (sNDA) dated September 30, 2011 received October 3, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Isuprel (Isoproterenol HCl) Injection.

This "Prior Approval" supplemental new drug application provides for a re-formulation of the drug product and alternate site for the manufacture and release testing of the drug substance.

We have completed the review of your application, and have determined that we cannot approve this application in its present form. We have described below our reason for this action and, where possible, our recommendations to address the issue.

CHEMISTRY, MANUFACTURING AND CONTROL

1. The Drug Master File (DMF) 25,212 has been reviewed and determined to be inadequate to support your NDA. Deficiencies have been communicated to the DMF holder.
2. Indicate whether the source of Drug Substance (described in DMF 25,212) is the same as that approved. If not, provide comparative information on the manufacturing process, starting materials, controls, impurities, and container closure for the approved and proposed sources of the Drug Substance.
3. List other approved suppliers of Drug Substance ((b) (4) DMF (b) (4) is inactive), if any.
4. Set numerical limits for (b) (4) content in API specifications. The data provided is insufficient to omit testing for (b) (4)
5. A shelf life of 18 months for Drug Product is not supported by the stability data. Provide stability data to support the shelf life of 18 months in the proposed formulation or amend the shelf life claim to 12 months. Extension of shelf life based on real time data as they become available can be done via Annual Report.
6. Clarify what the following in Section P.3.3 means. (b) (4) (b) (4) Please state that (b) (4) will not be performed or list specific conditions under which (b) (4) will be performed.

7. Provide comparative impurity profile for approved DS and that manufactured by the proposed process. Indicate if [redacted] (b) (4) and Impurity [redacted] (b) are new impurities; if yes, indicate if these impurities are genotoxic.
8. Submit data to support the safety of injecting directly into the heart a formulation with two calcium chelators (EDTA and citrate) in the setting of life-threatening myocardial dysfunction.

FACILITY INSPECTIONS

9. During a recent inspection of the Hospira manufacturing facility McPherson, Kansas, our investigator conveyed deficiencies to the representative of the facility. Satisfactory compliance with Current Good Manufacturing Practices for Drugs is required for all manufacturing and testing facilities before this supplement may be approved.

LABELING

10. For all Container Labels and Carton Labeling
    a. Ensure that the lot number and expiration date is placed on all container labels and carton labeling.
    b. Ensure the route of administration statement is included on the principle display panel. This statement should read "Intravenous, subcutaneous, intramuscular, and intracardiac use only"
11. For the 1 mL and 5 mL Ampul Container Label, remove the storage information to save space and reduce the cluttered appearance of the label, per 21 CFR 201.10 (i).
12. For the 1 mL Ampul Container Label and Carton Labeling, move the strength statement so it is inside of the color block that has the proprietary and established names, for increased prominence
13. For all Carton Labeling, revise the net quantity statement to say the following:
    a. 5 mL ampul x 10 ampuls per carton
    b. 1 mL ampul x 25 ampuls per Uni-Amp™ unit dose pak
14. For insert Labeling, include the volume of Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP needed for dilution of Isuprel administered as a bolus intravenous injection in the dosage tables

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have

such a meeting, submit your meeting request as described in the FDA's *Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants*, May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Hasmukh B. Patel, Ph.D.
Branch Chief
Branch III, Division of New Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

HASMUKH B PATEL
02/03/2012

Agency Information Request (e-mail November 28, 2012, T.Bouie)

In reference to the telecom on November 14, 2012 concerning Question 7 of the complete Response Letter of February 3, 2012 we determined that the requested comparative impurity profile should be provided to carry out a complete evaluation of the proposed changes to the drug substance manufacturing site and the analytical methods. These data can be submitted as an amendment to the November 20, 2012 submission.

Hospira Response:

An impurity chromatographic profile comparison (LIS-127-R-002-12) for the drug substance (DS), Isoproterenol Hydrochloride, manufactured at (b) (4) and Hospira Boulder is summarized herein. The HPLC method utilized for the impurity profile comparison is outlined in Table I.

TABLE I: HPLC Method for Impurity Comparison of Isoproterenol Hydrochloride

(b) (4)

(b) (4)

FIGURE 1. HPLC Chromatogram for Hospira Boulder DS (Lot A3510-09-03 Reg)

FIGURE 2. HPLC Chromatogram for (b) (4) DS (Lot 271109)

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From: Griffith, Nicole M.
To: (b) (6) Tubergen, Karen R.; Zutkis, Judith
Subject: FW: NDA 10515/S-031
Date: Wednesday, November 28, 2012 6:34:29 PM

FYI…

_____
From: Bouie, Teshara [Teshara.Bouie@fda.hhs.gov]
Sent: Wednesday, November 28, 2012 10:05 AM
To: Griffith, Nicole M.
Subject: NDA 10515/S-031

Hi Nicole,

In reference to the telecon on November 14, 2012 concerning Question 7 of the Complete Response Letter of February 3, 2012 we determined that the requested comparative impurity profile should be provided to carry out a complete evaluation of the proposed changes to the drug substance manufacturing site and the analytical methods. These data can be submitted as an amendment to the November 20, 2012 submission.

Regards,

Teshara G. Bouie
Regulatory Health Project Manager

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/s/

JAMES M WILLARD
02/11/2013

ALBERT F DEFELICE
02/14/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

10-515/S031

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

11 JAN 2013

NDA: 10-515/S-031

Drug Product Name
Proprietary: Isuprel
Non-proprietary: Isoproterenol Hydrochloride Injection, USP

Review Number: 2

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
20 NOV 2012	21 NOV 2012	14 DEC 2012	21 DEC 2012

Submission History (for amendments only)

Submit Date(s)	Microbiology Review #	Review Date(s)
30 SEP 2011	1	23 NOV 2011

Applicant/Sponsor
Name: Hospira, Inc.
Address: 275 North Field Dr.
Dept 0389, Bldg H2-2
Lake Forest, IL 60045
Representative: Karen R. Tubergen
Telephone: 224-212-4638

Name of Reviewer: Jessica G. Cole, PhD

Conclusion: Recommend approval.

Product Quality Microbiology Data Sheet

A. **1.** **TYPE OF SUBMISSION:** Response to a complete response letter for a prior approval CMC supplement

2. **SUBMISSION PROVIDES FOR:** Alternate drug substance supplier and reformulation of the drug product.

3. **MANUFACTURING SITE:** Hospira McPherson, Kansas

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**

- Sterile 1:5000 solution for injection or infusion (intravenous, intramuscular, subcutaneous, or intracardiac)
- 0.2 mg/mL in 1 mL or 5 mL glass ampule

5. **METHOD(S) OF STERILIZATION:** (b) (4)

6. **PHARMACOLOGICAL CATEGORY:** Cardiac stimulant.

B. **SUPPORTING/RELATED DOCUMENTS:** Product quality microbiology review #1 dated 23 November 2011.

C. **REMARKS:** This submission was in the eCTD format. There were no microbiology deficiencies identified in Review #1. However, Hospira's complete response letter indicated that information submitted previously for the sterility test method was inaccurate.

filename: N010515S031R2.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – This application is recommended for approval on the basis of product quality microbiology.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – Not applicable.

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology - This is an (b) (4) processed sterile injectable that is (b) (4) sterilized (b) (4) .

B. Brief Description of Microbiology Deficiencies – Not applicable.

C. Assessment of Risk Due to Microbiology Deficiencies – Not applicable.

III. Administrative

A. Reviewer's Signature _____
Jessica G. Cole, PhD

B. Endorsement Block _____
John Metcalfe, PhD
Senior Microbiology Reviewer

C. CC Block
N/A

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/s/

JESSICA COLE
01/14/2013

JOHN W METCALFE
01/14/2013
I concur.

Product Quality Microbiology Review

23 NOV 2011

NDA: 10-515/S-031

Drug Product Name
Proprietary: Isuprel
Non-proprietary: Isoproterenol Hydrochloride Injection, USP

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
30 SEPT 2011	30 SEPT 2011	05 OCT 2011	06 OCT 2011

Applicant/Sponsor
Name: Hospira, Inc.
Address: 275 North Field Dr.
Dept 0389, Bldg H2-2
Lake Forest, IL 60045
Representative: Linda Biava
Telephone: 224-212-5322

Name of Reviewer: Jessica G. Cole, Ph.D.

Conclusion: Recommended for approval.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Prior Approval CMC supplement

2. SUBMISSION PROVIDES FOR: Alternate drug substance supplier and reformulation of the drug product.

3. MANUFACTURING SITE: Hospira McPherson, Kansas

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:

- Sterile 1:5000 solution for injection or infusion (intravenous, intramuscular, subcutaneous, or intracardiac)
- 0.2 mg/mL in 1 mL or 5 mL glass ampule

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Cardiac stimulant.

B. SUPPORTING/RELATED DOCUMENTS: Product quality microbiology review dated 27 July 2007.

C. REMARKS: This submission was in the eCTD format.

filename: N010515S031R1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – This application is recommended for approval.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – Not applicable.

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – This is an aseptically processed sterile injectable that is (b) (4)

B. Brief Description of Microbiology Deficiencies – Not applicable.

C. Assessment of Risk Due to Microbiology Deficiencies – Not applicable.

III. Administrative

A. Reviewer's Signature _____
Jessica G. Cole, Ph.D.

B. Endorsement Block _____
Stephen Langille, Ph.D.
Senior Microbiology Reviewer

C. CC Block
N/A

Product Quality Microbiology Assessment

1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA

S DRUG SUBSTANCE

(b) (4)

P DRUG PRODUCT

(b) (4)

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P.7 Container Closure System See P.1 above.

P.8 Stability

P.8.1 Stability Summary and Conclusion

MAINTENANCE OF MICROBIOLOGICAL CONTROL AND QUALITY: STABILITY CONSIDERATIONS

Stability conditions include long term (25°C/60% RH), intermediate (30 °C/65% RH), and accelerated (40 °C/75% RH). Sterility and endotoxins are assessed at release and annually during the long term stability program, at release and 12 months for intermediate, and at release, 3, and 6 months for accelerated conditions.

P.8.2 Post-Approval Stability Protocol and Stability Commitment

The first commercial batch of each configuration will be placed on stability and the exhibit batches will be monitored through shelf life. At least one batch from each configuration will be placed into the stability program annually.

- **Container Closure Integrity** – (b) (4) .
- **Endotoxin** – (b) (4)
- **Microbial Limits** – (b) (4)

P.8.3 Stability Data

Six months of acceptable stability data are available for the three batches in each configuration.

A APPENDICES Not applicable.

R REGIONAL INFORMATION

R.1 Executed Batch Record – The executed batch records were provided for all 6 registration batches.

2. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1

A. PACKAGE INSERT Not applicable.

3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

Not applicable.

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/s/

JESSICA COLE
11/28/2011

STEPHEN E LANGILLE
11/28/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

10-515/S031

OTHER REVIEW(S)

RHPM Overview – AP action
NDA 10-515/S-031
Isuprel (Isoproterenol HCl) Injection, 0.2 mg/mL

Sponsor:	Hospira, Inc.
Letter Date:	September 30, 2011
Receipt Date:	October 3, 2011
Complete Response Action:	February 3, 2012
Resubmission Letter Date:	November 20, 2012
Resubmission Receipt Date:	November 21, 2012
User Fee Goal Date:	March 21, 2013

Background
This "Prior Approval" CMC supplemental new drug application for Isuprel (Isoproterenol HCl) Injection provides for a re-formulation of the drug product and alternate site for the manufacture and release testing of the drug substance. A Complete Response (CR) Letter was issued by ONDQA on February 3, 2012, which included a list of deficiencies for CMC, facility inspections, and carton and container labeling.

Hospira, Inc. resubmitted the CMC supplement on November 21, 2012. ONDQA had initially planned on "consulting" the Division of Cardiovascular and Renal Products on the following two Hospira responses to the CR Letter:

- Question 7 regarding impurities and whether they were genotoxic
- Question 8 regarding the safety of injecting a formulation with 2 calcium chelators directly into the heart

The sponsor's response to Question 8 was that they proposed (b) (4)

(b) (4)

To evaluate the safety concern, the pharmacology reviewer, Dr. Willard, performed modeling calculations of the potential effects of the formulation change on myocardial calcium levels. Based on the calculations, the clinical reviewer, Dr. Rose, concluded that "There is no clinical reason to be concerned about effects of the proposed formulation change on myocardial calcium levels. (b) (4) " See Dr. Rose's March 8, 2013 clinical review in DAARTS.

The following reviews were completed (see DAARTS for complete reviews):

Clinical Review
See above for Dr. Rose's recommendation.

Pharmacology Review
In his February 11, 201 review, Dr. Willard wrote:

> Summary and Conclusions:
> Isuprel's safety has not been compromised by a change in manufacturer, and the product is very similar to that previously marketed. The sponsor did drop one of the indications

due to a change in excipients and questions about direct injection into the heart of EDTA and citric acid, two calcium chelators. There is no concern about the levels of (b) (4) in the Drug Product, levels are so low that it would be impractical through Isuprel to achieve significant exposure levels. In addition, the qualifying batches showed no detectable levels of (b) (4). There is a low level of concern about the potential, as determined by DEREK for Windows, genotoxicity of (b) (4) (b) (4) . It would be optimal if they were tested for genotoxicity, minimally in an Ame's Assay, especially (b) (4) which is found in the drug product. However, exposure levels to (b) (4) would be low, and the other potential impurities were not detected in the test batches. I can see no reason to not approve the change in manufacturer, nor do I object to dropping the intracardiac injection indication.

CMC Review
In her March 12, 2013 review, Dr. Vyas recommended approval.

Product Quality Microbiology Review
In her January 14, 2013 review, Dr. Cole recommended approval.

DMEPA Review
DMEPA completed a review of the label, labeling and packaging dated March 14, 2013. See review in DAARTS.

EER Report
The Office of Compliance issued an Overall Recommendation of "Acceptable" on March 12, 2013; see CMC review.

Labeling
Labeling comments on the PI and carton and container were sent to the sponsor via email on March 18, 2013. In a March 18, 2013 email response, the sponsor stated that they could only submit at this time the revised labeling "in a red-lined format. The final art work would take several weeks to complete within [their] systems." The sponsor also stated the following:

> Specifically, with respect to items B.3, C.2, and D.2 (decrease the prominence of label codes), Hospira will not be able to make these changes as requested. The reason is that during the manufacturing/packaging process, the labels are read in-line by a digital camera, so the placement, font size and font type are critical to the manufacturing process and verification of the labels. Currently, the font size is at the minimal setting so as to allow for effective reading by the camera.

DMEPA stated in an email dated March 19, 2013 that the sponsor's proposal not to make the changes as requested in items B.3, C.2, and D.2 (decrease the prominence of label codes) was acceptable.

The sponsor submitted redlined versions of the carton and container labeling on March 20, 2013. Per an email dated March 21, 2013, DMEPA reviewed the redlined versions and found them acceptable, noting that the applicant intended to implement all their comments.

[Note: In the package insert, we had requested that under **DESCRIPTION**, the amounts for Sodium Citrate, Dihydrate was rounded from (b) (4) to 2.1 mg" and for Citric Acid, Anhydrous from (b) (4) to "2.5 mg." For consistency, these amounts were also rounded and changed accordingly in the carton labeling by the sponsor in their redlined submission. Per an email dated 3-21-13, ONDQA agreed with the sponsor making the corresponding changes to the carton labeling. ONDQA also requested an additional change that the amount of Sodium Citrate, Dihydrate be rounded from "2.1 mg" to "2.07 mg." I emailed the sponsor on 3-21-13 and the sponsor agreed per a telephone conversation on 3-2-13 to this additional change, and they will make the corresponding change to their carton labeling.]

I reviewed the PI submitted on March 20, 2013 and found the changes identical to those requested by the Division on March 18, 2013, except for the following change, which is acceptable:

Under **DESCRIPTION**, in the last sentence, the text "[redacted] (b) (4)

[redacted] (b) (4)

In addition, the following minor formatting correction should be made:

The section header "**Drug Interactions**" should be re-located to the next line. It is currently located at the end of the last paragraph under the "**PRECAUTIONS**" section.

[Note: Per an email dated March 21, 2013, the sponsor agreed with this formatting change.]

RPM Summary
An Approval (AP) Letter based on the agreed-upon draft labeling (PI and carton and container) will be drafted for Dr. Stockbridge's signature.

Quynh Nguyen, Pharm.D., RAC
Regulatory Health Project Manager
3-21-13

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/s/

QUYNH M NGUYEN
03/21/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Review

Date:	March 14, 2013
Reviewer:	Kimberly DeFronzo, R.Ph, M.S., M.B.A. Division of Medication Error Prevention and Analysis
Team Leader	Irene Z. Chan, Pharm.D, BCPS Division of Medication Error Prevention and Analysis
Associate Director:	Scott Dallas, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Isuprel (Isoproterenol HCl Injection, USP) 0.2 mg/mL and 1 mg/5 mL (0.2 mg/mL)
Application Type/Number:	NDA 010515/S-031
Applicant/sponsor:	Hospira
OSE RCM #:	2013-62

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1 INTRODUCTION

This review evaluates the revised labels and labeling for Isuprel (Isoproterenol HCl Injection, USP) 0.2 mg/mL and 1 mg/5 mL Solution, submitted on November 21, 2012 under Prior Approval Supplement 031. DMEPA previously reviewed the proposed labels and labeling in OSE Review #2011-3824 dated December 30, 2011. However, the supplement received a Complete Response (CR) on February 3, 2012. This resubmission after the CR contains additional changes to the insert labeling regarding the (b) (4) that were not previously reviewed by DMEPA. Additionally, the Applicant submitted a tray carton labeling that was not previously submitted for review.

1.1 BACKGROUND AND REGULATORY HISTORY

Isuprel (Isoproterenol HCl Injection, USP) 0.2 mg/mL was approved on May 25, 1956 under NDA # 010515 and is currently marketed in the United States solely by Hospira. Isuprel is the Reference Listed Drug (RLD), and there is one active generic application under ANDA # 083724, held by International Medication, that was approved on January 6, 1976.

The Applicant previously submitted this CMC supplement supporting reformulation of Isuprel. The reformulation includes the removal of Sodium Metabisulfite, Lactic Acid, and Sodium, and replacing them with Edetate Disodium, Sodium Citrate, and Citric Acid. Sodium Hydroxide has also been added as a pH adjuster. Only this product (the RLD) has undergone this reformulation using calcium chelators. Per discussion with the Medical Officer, this proposed reformulation was not submitted for safety reasons.

On February 3, 2012, the FDA issued a complete response due to CMC, facility inspection, label, and labeling deficiencies. The Division of Cardiovascular and Renal Products (DCRP) also requested for data supporting the safety of injecting the reformulated product, which contains two calcium chelators (EDTA and citrate), directly into the heart. (b) (4)

On January 17, 2013, DCRP held an internal meeting to discuss the clinical implications of injecting calcium chelators directly into the heart (b) (4)

(b) (4)

It was suggested that DCRP collaborate with ONDQA in creating a communication to the Applicant to discuss the safety issues with the reformulation.

Additionally, in order to help assess the impact of the [redacted] in the clinical setting, the Division of Epidemiology's Drug Utilization Team was consulted on January 17, 2013. However, DEPI-II indicated they were unable to capture data on the [redacted] with the databases available to the Agency. Therefore, they are unable to provide an estimate of drug usage for the [redacted] for this product.

On February 13, 2013, another internal meeting was held by DCRP to further discuss the course of action for this application. A decision was made by the review team that the Agency would conduct our own modeling to determine the clinical effects of the calcium chelators on the heart in order to inform our safety assessment of the new formulation. The results of the modeling demonstrated that there are insignificant amounts of calcium binding with the new formulation. Based on this finding, a decision was reached at a final team meeting held on March 8, 2013, to [redacted] in the labeling. Therefore, a request will be made to the Applicant to [redacted] the insert labeling.

1.2 PRODUCT INFORMATION

The following product information for Isuprel was found within the insert labeling submitted with the resubmission on November 21, 2012:

[redacted]

As noted in the insert labeling, there are no well-controlled studies in children to establish appropriate dosing; however, the American Heart Association recommends an initial infusion rate of 0.1 mcg/kg/min, with the usual range being 0.1 mcg/kg/min to 1 mcg/kg/min.

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA Adverse Event Reporting System (FAERS) database for Isuprel medication error reports. We also reviewed the Isuprel labels and package insert labeling submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FAERS database using the strategy listed in Table 1.

Table 1: FAERS Search Strategy	
Date	From November 15, 2011 to January 25, 2013 (from date of last AERS search conducted under review OSE RCM #2011-3824 to the present)
Drug Names	Isoproterenol (active ingredient) Isoproterenol Hydrochloride (active ingredient) Isuprel (product name)
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT

The FAERS database search did not identify any new cases.

2.2 LABELS AND LABELING

The Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Revised Ampul Labels (RL-3904) for the 1 mL presentation submitted November 21, 2012 (Appendix B)
- Revised Ampul Label for the 5 mL presentation submitted November 21, 2012 (Appendix C)
- Tray labeling (IM-2217) for the Uni-Amp™ ampuls (Appendix D)
- Revised "Shelf" Carton Labeling for 1 mL ampuls submitted November 21, 2012 (Appendix E)
- Revised Carton Labeling for 5 mL ampuls submitted November 21, 2012 (Appendix F)
- Revised Insert Labeling submitted November 21, 2012 (no image)

Note: In response to an Information Request for clarification regarding the ampul label and tray labeling submitted for the 1 mL presentation, the Applicant provided the following verification via emails on February 15, 2013 and March 12, 2013.

- Each individual 1 mL ampul is labeled with the "RL-3904" label which was previously reviewed by DMEPA.
- Twenty-five (25) of the labeled 1 mL ampuls are placed in a molded plastic tray which contains 25 single compartments for the individual ampuls. Between the individual compartments, there are perforations which allows for separation of the ampuls as necessary. The Tyvek lid for the molded plastic tray is imprinted with the information on label "IM-2217" and is aligned with the molded tray such that each individual compartment containing a 1 mL ampul would have the information contained on IM-2217 (see Appendix D). The 1 mL ampuls in individual compartments are called **UNI-AMP™** ampuls by the Applicant due to their unit dose packaging.
- The twenty-five (25) compartment tray above is then cut along some of the perforations resulting in five (5) packs containing 5 (five) self- contained compartments, each containing a 1 mL labeled ampul.
- The five (5) packs, each with 5 (five) self- contained compartments, are placed into a "shelf" carton for a total of twenty-five (25) ampuls per shelf carton (see Appendix E). This package configuration is referred to as a Uni-Amp unit dose pack by the Applicant.
- Forty (40) shelf cartons containing twenty-five (25) 1 mL ampuls are then placed into a case for shipping. The total number of ampuls in the shipping case would be 1000 (40 shelf cartons X 25- 1 mL ampuls in each shelf carton).

We compared the revised Isuprel labels and labeling against our recommendations in OSE Review #2011-3824 dated December 30, 2011 to determine whether all our previous recommendations were implemented and whether the revised labels and labeling adequately address our concerns from a medication error perspective. We also considered if any issues or cases identified in the previous reviews could inform this current review.

3 MEDICATION ERROR RISK ASSESSMENT

The following section discusses our risk assessment of the reformulation of the product as well as the revised labels and labeling.

3.1 REFORMULATION OF ISUPREL

Isuprel (Isoproterenol HCl Injection, USP) is currently marketed in the United States and was approved on May 25, 1956. The Applicant is now proposing a reformulation that includes the removal of Sodium Metabisulfite, Lactic Acid, and Sodium, and replacing them with Edetate Disodium, Sodium Citrate, and Citric Acid. Sodium Hydroxide has also been added as a pH adjuster in addition to the calcium chelators. This new formulation will replace the current formulation that has been on the market the last five decades.

DCRP has determined that there are insignificant amounts of calcium binding based on modeling data. This determination will allow continued intracardiac administration of the reformulated Isuprel. Based on this information, DMEPA has determined that the reformulation will not impact the dosage and administration of this product, and providers can continue to use the reformulated Isuprel in the same manner as the currently marketed formulation. The Applicant will be informed by DCRP that the (b) (4)

Thus, DMEPA has no concerns regarding the reformulation itself.

We recognize that during the transition period, both the currently marketed formulation and the new formulation may be simultaneously on the market. To our knowledge, the reformulation does not impart a different pharmacokinetic or pharmacodynamic profile for the product. Therefore, it is expected that a patient receiving either formulation will achieve the same clinical outcome without increased risk for adverse events. However, since both formulations will have the same proprietary name, this may create some pharmacovigilance problems during the transition period. In particular, it may be difficult to determine whether adverse events and product complaints are attributable to the new or old formulation. Although modeling data indicates the reformulated product is safe for intracardiac administration, no human data was submitted by the Applicant. Therefore, we recommend the Applicant actively query reporters for lot information associated with complaints and adverse event reports. The active collection of lot information from reporters should help to minimize the pharmacovigilance challenges during the transition period. The Applicant should also ensure adequate availability of the new formulation prior to the discontinuation of the old formulation to prevent a disruption in product availability in the marketplace.

3.2 LABEL AND LABELING RISK ASSESSMENT

Our review of the revised labels and labeling show that the Applicant has implemented all of DMEPA's recommendations under OSE Review #2011-3824. However, DMEPA identified additional areas of deficiency including the following:

- Inadequate prominence of the routes of administration statement
- Overly prominent "protect from light" statement on ampul labels

- Overly prominent "sterile injection" statement on the carton labeling

The Applicant submitted tray labeling for the 1 mL Uni-Amp™ unit dose pak that DMEPA did not previously review. The additional tray labeling led to additional follow up with the Applicant to gain clarification regarding the proposed packaging configurations for this product (see IR response in Section 2.2 above). Upon reviewing the Applicant's IR response, we have additional recommendations for the carton labeling to improve clarity of the net quantity information, and our review of the tray labeling identified the following areas of vulnerability that will need to be addressed:

- Confusing net quantity statement
- Inadequate prominence of the routes of administration statement
- Location and prominence of information that can distract or decrease readability of more important information

(b) (4)

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA finds the reformulation of Isuprel acceptable from a medication error perspective; however, we have recommendations regarding the transition to the new formulation which we provide to DCRP in Section 4.1 below.

Review of the revised container labels and carton labeling show that the Applicant has implemented all of DMEPA's previous recommendations under OSE Review #2011-3824. However, DMEPA identified additional areas of deficiency that we provide recommendations for. Additionally, the Applicant submitted "tray" labeling that DMEPA did not previously review. Our review of the tray and carton labeling identified areas of vulnerability that can lead to medication error, and we provide recommendations for the Applicant in Section 4.2 below. We advise the recommendations are implemented prior to approval of the supplement.

If you have further questions or need clarifications, please contact Cherye Milburn, OSE Project Manager, at 301-796-2084.

4.1 COMMENTS TO THE DIVISION

1. We recognize that during the transition period, both the currently marketed formulation and the new reformulation may be simultaneously available on the market. To our knowledge, the reformulation does not impart a different pharmacokinetic or pharmacodynamic profile for the product. Therefore, it is expected that a patient receiving either formulation will achieve the same clinical outcome without increased risk for adverse events. However, since both formulations will have the same proprietary name, this may create some pharmacovigilance problems during the transition period. In particular, it may be difficult to determine whether adverse events and product complaints are attributable to the new or old formulation. Therefore, we recommend the

Division request the Applicant actively query reporters for lot information associated with complaints and adverse event reports. The active collection of lot information from reporters should help to minimize the pharmacovigilance challenges during the transition period. The Applicant should also ensure adequate availability of the new formulation prior to the discontinuation of the old formulation to prevent a disruption in product availability in the marketplace.

4.2 COMMENTS TO THE APPLICANT

A. General Comments

(b) (4)

B. Ampul Label (1 mL)

1. Relocate the route of administration statement to directly beneath the statement of strength.
2. Decrease the prominence of the "Protect from light" statement by unbolding to avoid competing with other important information.
3. (b) (4)

C. Ampul Label (5 mL)

1. See comments B.1 and B.2 above.
2. (b) (4)
3. Remove the statement "See package insert" to minimize crowding on the principal display panel.

D. Tray Labeling (1 mL)

1. See comments B.1 and B.2 above.
2. (b) (4)

E. "Shelf" Carton Labeling (1 mL ampuls)

1. See comments B.1 above.
2. The statement "Sterile Injection" is overly prominent and detracts from other important information on the principal display panel. Minimize and debold this statement and move it to the side panel.

F. Carton Labeling (5 mL ampuls)

1. See comments B.1 and E.2 above.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

3 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

KIMBERLY A DE FRONZO
03/14/2013

IRENE Z CHAN
03/15/2013

SCOTT M DALLAS
03/15/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

10-515/S031

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

From:	Defronzo, Kimberly
To:	Nguyen, Quynh M
Cc:	Vyas, Kavita; Chidambaram, Nallaperumal; Milburn, Cherye; Chan, Irene Z.
Subject:	RE: Successfully Processed eCTD: nda010515 in DARRTS
Date:	Monday, April 15, 2013 4:46:17 PM

Hi Quynh,

We have reviewed the final label/labeling and they appear fine from DMEPA's perspective. Please let me know if you need anything else. Thanks.

Kim DeFronzo
DMEPA

-----Original Message-----
From: Nguyen, Quynh M
Sent: Friday, April 12, 2013 2:48 PM
To: Defronzo, Kimberly
Cc: Vyas, Kavita; Chidambaram, Nallaperumal; Milburn, Cherye; Chan, Irene Z.
Subject: FW: Successfully Processed eCTD: nda010515 in DARRTS

Kim,

For Isuprel (NDA 10-515/S-031), Hospira has submitted the final carton and container labeling for your review. The EDR link is below.

Thanks,
Quynh

-----Original Message-----
From: asr-dontreply@fda.hhs.gov [mailto:asr-dontreply@fda.hhs.gov]
Sent: Friday, April 12, 2013 1:48 PM
To: Nguyen, Quynh M; CDER-OND-DCRP-EDRNOTIFY; CDER-EDR_ASR_Document_Coordinators; CDER-EDRSTAFF; CDER-EDRADMIN; CDER ESUB; CDER-EDROIM; Khalsa, Gurminders J; Thompson, Douglas L. *; CDER-EDRSTAFF
Subject: Successfully Processed eCTD: nda010515 in DARRTS

Successfully Processed eCTD: nda010515 in DARRTS. Details below:

EDR Location: \\CDSESUB1\EVSPROD\NDA010515\010515.enx

For Document Room Staff Use:
Application Type/Number: nda010515
Incoming Document Category/Sub Category: Electronic_Gateway
Supporting Document Number: 125
eCTD Sequence Number: 0007
Letter Date: 04/12/2013
Stamp Date: 4/12/2013

Receipt Date/Time from Notification: 04-12-2013, 12:35:05
Origination Date/Time from Notification: 04-12-2013, 12:34:39
DOCUMENT ID: 5271555

356H/2252 Form: \\CDSESUB1\EVSPROD\NDA010515\0007\m1\us\356h-2013-04-12.pdf

Cover Letter: \\CDSESUB1\EVSPROD\NDA010515\0007\m1\us\cover-2013-04-12.pdf

3397 Form: NOT FOUND

3674 Form: NOT FOUND

For EDR Staff Use:
The submission has already been processed. The following information is provided if verification is required. No additional action is required on your part

EDR Location: \\CDSESUB1\EVSPROD\NDA010515\0007
Submission Size: 2308625
Gateway Location: \\chdc9681\cderesub\inbound\ectd\ci1365784475498.324843@llnap32_te

Copy to EDR Status: Good-1. Files were copied successfully

For CDER Project Manager Use:
The following submission received through the Electronic Submission Gateway has been processed using the following information. This information will be updated once Document Room personnel have been able to verify the content of the submission.

Application Type/Number: nda010515
Incoming Document Category/Sub Category: Electronic_Gateway
Supporting Document Number: 125
eCTD Sequence Number: 0007
Letter Date: 04/12/2013

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/s/

KIMBERLY A DE FRONZO
04/16/2013

IRENE Z CHAN
04/16/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Mail: OSE

FROM: Quynh Nguyen, Project Manager
OND/Division of Cardiovascular and Renal Products (DCRP)
Ph: (301) 796-0510

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
1-17-13		10-515/S-031	CMC sNDA resubmission	11-20-13

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Isuprel (isoproterenol HCl) Injection	High		2-17-13

NAME OF FIRM: Hospira

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- XX DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Hospira has resubmitted this CMC supplement in response to the 2-3-12 Complete Response Letter. In their response to Question #8, the sponsor proposes [redacted] (b) (4) from the labeling. Please provide drug use data on how often the [redacted] (b) (4) is being administered so that DCRP can be informed of the impact of this change.

The resubmission is in the EDR at: \\CDSESUB1\EVSPROD\NDA010515\010515.enx

PDUFA Goal Date: March 21, 2013

SIGNATURE OF REQUESTER Quynh Nguyen, RPM	METHOD OF DELIVERY (Check one) XX MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

QUYNH M NGUYEN
01/17/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 010515/S-031

COMPLETE RESPONSE – CMC

Hospira, Inc.
Attention: Ms. Karen R. Tubergen
275 North Field Drive
Dept. 0389, Bldg. H2-2
Lake Forest, IL 60045

Dear Ms. Tubergen:

We acknowledge receipt on November 21, 2012 of your November 20, 2012 resubmission to your supplemental new drug application for Isuprel (Isoproterenol HCl) Injection, 0.2 mg/mL.

This amendment constitutes a complete response to our February 3, 2012 action letter. The user fee goal date is March 21, 2013.

If you have any questions, please contact:

Quynh Nguyen, Pharm.D., RAC
Regulatory Health Project Manager
(301) 796-0510

Sincerely,

{See appended electronic signature page}

Edward Fromm, R.Ph., RAC
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

EDWARD J FROMM
01/04/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

CMC MICRO & STERILITY ASSURANCE REVIEW REQUEST

TO *(Division/Office)*: **New Drug Microbiology Staff**

E-mail to: **CDER OPS IO MICRO**

Paper mail to: **WO Bldg 51, Room 4193**

FROM: Denyse D Baker

PROJECT MANAGER *(if other than sender):Teshara Bouie*

REQUEST DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
December 14, 2012		10515 S031	sNDA Resubmission	

NAMES OF DRUG	PRIORITY CONSIDERATION	PDUFA DATE	DESIRED COMPLETION DATE
Isuprel (Isoproterenol HCl) Injection	Standard	March 21, 2013	March 1, 2013

NAME OF APPLICANT OR SPONSOR: Hospira, Inc.

GENERAL PROVISIONS IN APPLICATION

- ☐ 30-DAY SAFETY REVIEW NEEDED
- ☐ NDA FILING REVIEW NEEDED BY: _____
- ☐ BUNDLED
- X DOCUMENT IN EDR
- ☐ CBE-0 SUPPLEMENT
- ☐ CBE-30 SUPPLEMENT
- ☐ CHANGE IN DOSAGE, STRENGTH / POTENCY

COMMENTS / SPECIAL INSTRUCTIONS:

No deficiencies in the previous submission. However, page 6 of the resubmission cover letter mentions an error in the validation of sterility methods in 3.2.P.5.3.4

SIGNATURE OF REQUESTER

REVIEW REQUEST DELIVERED BY (Check one):

X DARRTS ☐ EDR ☐ E-MAIL ☐ MAIL ☐ HAND

DOCUMENTS FOR REVIEW DELIVERED BY (Check one):

X EDR ☐ E-MAIL ☐ MAIL ☐ HAND

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/s/

DENYSE D BAKER
12/14/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Director, OSE, Division of Medical Errors and Prevention, HFD-420

FROM: Denyse Baker for Teshara G. Bouie, ONDQA, Division of New Drug Quality Assessment I, 301-796-1649

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT nSNDA	DATE OF DOCUMENT
12/14/2012		10515/S031	Response to CR	11/21/2012

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Isuprel (Isoproterenol HCl) Injection	Standard		

NAME OF FIRM: Hospira, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- X RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- X LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:
PDUFA Date: March 21, 2013
Dextrose Injection, USP needed for dilution of Isuprel administered as a bolus intravenous injection in the dosage tables

NAME AND PHONE NUMBER OF REQUESTER	METHOD OF DELIVERY (Check one)
Teshara G. Bouie, 301-796-1649	X DARRTS ONLY ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

/s/

DENYSE D BAKER
12/14/2012