CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201743Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # **201-743**	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Argatroban Injection Established/Proper Name: **Argatroban Injection** Dosage Form: Injection Strengths: **1 mg/mL in 125 mL in Dextrose**		
Applicant: **Sandoz, Inc.**		
Date of Receipt: **April 14, 2010**		
PDUFA Goal Date: **February 14, 2011**	Action Goal Date (if different):	
Proposed Indication(s): **For the prophylaxis and/or treatment of thrombosis in patients with heparin-induced thrombocytopenia(HIT).**		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
NDA 20-883 Argatroban (reliance upon previous finding of safety and efficacy for listed drug)	**CMC data, results of bridging study, reference drug label**
	NDA 20-883 Argatroban (reliance upon previous finding of safety and efficacy for listed drug)

*each source of information should be listed on separate rows

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

No clinical or bioequivalence studies were conducted by the Applicant to bridge their product with the reference listed product. However, a waiver for the requirement to provide in vivo bioavailability/bioequivalence (BA/BE) data was granted for the proposed Argatroban Injection (in Dextrose) 1 mg/ml product.

To support the biowaiver request and according to 21 CFR 320.22 (d)(3), the applicant conducted an in vitro bridging study designed to evaluate the in vitro equivalence of the anticoagulant pharmacodynamic activity between the proposed (TEST) and the Reference Argatroban products. The pharmacodynamic effects were measured by determining the activated partial thromboplastin time (aPTT), the prothrombin time (PT), and the thrombin time (TT) in pooled donor human plasma spiked with clinically relevant concentrations of the proposed (TEST) and Reference Argatroban products. The results from the in vitro equivalence study supported the pharmacodynamic similarity of the proposed Argatroban Injection (TEST) product and the reference listed product.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES ☒ NO ☐

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☒ NO ☐

*If "**NO**", proceed to question #5.*
*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*
Argatroban, NDA 20-883

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☒ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Argatroban	**20-883**	**Y**

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*
*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a monograph?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES ☐ NO ☒

*If "**YES**", please list which drug(s) and answer question d) i. below.*

*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☒

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

Sandoz Canada has developed an argatroban formulation that differs from the current marketed product in that it does not contain any alcohol and does not require reconstitution.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

(***Pharmaceutical equivalents*** *are drug products in identical dosage forms that:* ***(1)*** *contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period;* ***(2)*** *do not necessarily contain the same inactive ingredients;* ***and*** ***(3)*** *meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

Note *that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

The listed product is presented as a concentrate that must be diluted prior to use. The 505(b)(2) product is a ready-to-use mixture that does not require dilution.

YES ☐ NO ☒

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES ☐ NO ☐

*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(***Pharmaceutical alternatives*** *are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

Note *that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☒ NO ☐

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☒ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES ☒ NO ☐

*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): **Argatroban/5,214,052**

No patents listed ☐ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☒ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☒ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s): **5,214,052**
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☒ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☒ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): **June 21, 2010**

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note *that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information* ***UNLESS*** *the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☒ Patent owner(s) consent(s) to an immediate effective date of approval ☐

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

/s/

EBLA ALI IBRAHIM
02/11/2011

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # **201-743** BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Established/Proper Name: **Argatroban** Dosage Form: **Injection** Strengths: **1 mg/mL**		
Applicant: Sandoz, Inc Agent for Applicant (if applicable):		
Date of Application: **April 13, 2010** Date of Receipt: **April 14, 2010** Date clock started after UN: **N/A**		
PDUFA Goal Date: **February 14, 2011**	Action Goal Date (if different):	
Filing Date: **June 13, 2010**	Date of Filing Meeting: **June 7, 2010**	
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): **Anticoagulant for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia. Anticoagulant in patients with or at risk for heparin-induced thrombocytopenia undergoing percutaneous coronary interventions (PCI).**		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html and refer to Appendix A for further information.***		☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***		☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐	
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Drug/Biologic ☐ Drug/Device ☐ Biologic/Device	
☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41)	

Other:	☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*): **N/A**	
List referenced IND Number(s): **PIND 101,957**	

Goal Dates/Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	✓			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	✓			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***	✓			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		✓		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	✓			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
Note: *505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).*	

505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		✓		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).		✓		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? ***Note:*** *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*		✓		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:	✓			

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration
NDA 20-883	**Argatroban**	**M-75**	**May 5, 2011**

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	YES	NO	NA	Comment
Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm***		✓		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)***				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*		✓		

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		✓		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***				

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance[1]? **If not,** explain (e.g., waiver granted).	✓			
Index: Does the submission contain an accurate comprehensive index?	✓			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	✓			
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? ***If yes,*** *date consult sent to the Controlled Substance Staff:*			✓	
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #			✓	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature? ***If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.***	✓			
Are all establishments and their registration numbers listed on the form/attached to the form?	✓			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a?	✓			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature? ***Forms must be signed by the APPLICANT, not an Agent.*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	✓			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature?	✓			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***(Certification is not required for supplements if submitted in the original application)*** ***If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification.*** ***Note:*** *Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	✓			

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			✓	

Pediatrics	YES	NO	NA	Comment
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)*** ***Note**: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*		✓		
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?			✓	
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***			✓	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) ***If no, request in 74-day letter***			✓	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***		✓		

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? ***If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.***			✓	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***	✓			
Is the PI submitted in PLR format?	✓			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	✓			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	✓			
REMS consulted to OSE/DRISK?			✓	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?	✓			
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***			✓	

Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***			✓	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***			✓	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?			✓	
Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***		✓		

Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s): N/A** ***If yes, distribute minutes before filing meeting***			✓	
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s): May 27, 2008** ***If yes, distribute minutes before filing meeting***	✓			
Any Special Protocol Assessments (SPAs)? **Date(s): N/A** ***If yes, distribute letter and/or relevant minutes before filing meeting***			✓	

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 3, 2010

BLA/NDA/Supp #: 201-743

PROPRIETARY NAME:

ESTABLISHED/PROPER NAME: Argatroban

DOSAGE FORM/STRENGTH: Injection

APPLICANT: Sandoz, Inc

PROPOSED INDICATION(S)/PROPOSED CHANGE(S):

Indicated as an anticoagulant for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT).

BACKGROUND:

Sandoz, Inc., Argatroban Injection drug product, 1 mg/mL (125mL) in Dextrose is a ready to use solution indicated as an anticoagulant for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT).

The Reference Listed Drug, ARGATROBAN Injection, was approved in June 30, 2008 under NDA 20-883 (Pfizer Pharmaceutical). Sandoz Argatroban has the same indication, route of administration, and dosing regimen (frequency and duration) but differs in the formulation composition.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	**Ebla Ali Ibrahim**	**Y**
	CPMS/TL:	**Janet Jamison**	**N**
Cross-Discipline Team Leader (CDTL)	**Janice Brown**		**Y**
Clinical	Reviewer:	**Firoozeh Alvandi**	**Y**
	TL:	**Kathy Robie Suh**	**Y**
Social Scientist Review (*for OTC products*)	Reviewer:		

	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	**Lillian Huan Zhang**	**Y**
	TL:	**Julie Bullock**	**Y**
Biostatistics	Reviewer:	**Kyung Y Lee**	**Y**
	TL:	**Mark Rothmann**	**Y**
Nonclinical (Pharmacology/Toxicology)	Reviewer:	**Shwu-Luan Lee**	**Y**
	TL:	**Haleh Saber**	**Y**
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	**Ravindra Kasliwal**	**Y**
	TL:	**Janice Brown**	**Y**
Quality Microbiology *(for sterile products)*	Reviewer:	**Stephen Langille**	**Y**
	TL:		
CMC Labeling Review *(for BLAs/BLA supplements)*	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		

OSE/DRISK (REMS)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		

Other reviewers		
Other attendees		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☐ Not Applicable ☐ YES ☒ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☐ NO
BIOSTATISTICS **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☐ Not Applicable ☒ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review (BLAs/BLA supplements only) **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Ebla Ali Ibrahim **21st Century Review Milestones (see attached)** (optional): **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review
ACTIONS ITEMS	
☒	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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/s/

EBLA ALI IBRAHIM
01/27/2011

Revised Deficiencies for NDA 22-485 and 201-743 Labeling

A. Container Label and Carton Labeling for Argatroban Injection 125 mg/125 mL in Sodium Chloride and Argatroban Injection 125 mg/125 mL in Dextrose

1. Place the name of diluents, Sodium Chloride or Dextrose, and their percent amounts on the principle display panel also immediately under the product's name to clearly differentiate the two Argatroban Products such as follows:

   Argatroban Injection
   in 0.9% Sodium Chloride
   125 mg/125 mL
   (1 mg/mL)
   Or
   Argatroban Injection
   in 5% Dextrose
   125 mg/125 mL
   (1 mg/mL)

   Additionally, to sufficiently distinguish between Argatroban in Sodium Chloride and Argatroban in Dextrose, print the name of the diluents and their percent amounts using contrasting colors and in the same font as the product's established name. As currently presented, the diluents blend with the other inactive ingredients on the side panel may be easily overlooked; thus, increasing the potential for selection error.

2. Place the statement "Do not dilute prior to administration" on the principle display panel to differentiate the dilution requirements from the reference listed drug, Argatroban Injection 250 mg/2.5 mL (100 mg/mL). The reference-listed drug (RLD), Argatroban Injection 250 mg/2.5 mL, is a concentrated solution that required dilution prior to administration. As a result, it is important to differentiate between the RLD and the new Argatroban Injection product, which does not require dilution prior to administration, to minimize medication errors associated with product's preparation for administration.

3. Add Bar Coding to the labeling per 21 CFR 201.25

4. Change the word "STERILE' to lower case to read "Sterile'

5. Decrease the prominence of the "Rx Only" statement by decreasing the type size and placing in less prominent location on the principle display panel. As currently presented, it is as prominent as concentration statement and other pertinent information.

6. Delete the statement "Do not Freeze" because this statement is unnecessary and occupies space.

B. Container Labels for Argatroban Injection 125 mg/125 mL in Sodium Chloride and Argatroban Injection 125 mg/125 mL in Dextrose

1. Allocate the space on the vial label (e.g., the bottom of the principle display panel or the side panel) to place the product's name, diluent, strength, and concentration in the inverted manner to increase the readability of the label when the product is hung upside down.

2. Replace the statement [redacted] (b) (4) with the statement "For Intravenous Infusion Only". Additionally, increase the prominence of the statement "For Intravenous Infusion Only" by relocating it from the side panel to the principle display panel under the product's concentration and increasing the font size.

3. Delete the phrase [redacted] (b) (4) located immediately next to the statement "Single Dose Vial" from the principle display panel because it is duplicative and clusters other important information.

4. Add the statement "Single Use Vial, Discard Unused Portion" to the principle display panel. We recommend this change because the vial is large and will contain 125 mL of the product. Thus, we are concerned about the secondary use of the vial.

5. Add 'Protect From Light" to the storage statement on the side panel.

6. Revise the statements on the side panel regarding the ingredients contained in each milliliter of Argatroban Injection to improve clarity. As the statements currently presented, it is unclear whether each mL contains the particular amount of active and inactive ingredients or entire vial; thus, creating confusion that may lead to errors.

    a. Argatroban Injection in Sodium Chloride should be revised to state, "Each milliliter contains: 1 mg argatroban, 9 mg sodium chloride, 3 mg sorbitol in water for injection, USP".

    b. Argatroban Injection in Dextrose should be revised to state, "Each mL contains 1 mg argatroban, 50 mg dextrose, 3 mg sorbitol in water for injection, USP".

C. Carton Labeling for Argatroban Injection 125 mg/125 mL in Sodium Chloride and Argatroban Injection 125 mg/125 mL in Dextrose

1. Delete the phrase [redacted] (b) (4) located under the statement [redacted] (b) (4) from the principle display panels, because it is duplicative and distracts from the concentration. Additionally, replace the statement [redacted] (b) (4) with the statement "For Intravenous Infusion Only".

2. Place the statement [redacted] (b) (4) on the bottom of the principle display panels as well as upper and lower panels.

3. Revise the statement and change its prominence to read “Protect from light and store in original carton” in increasing the font size.

4. Add the statement "“(See USP Controlled Room Temperature)” to the existing storage statement “Store at 20° – 25°C (68° – 77°F)”.

5. See comments in Sections B.4 and B.6, which also apply to this Section.

D. Provide amended drug product specifications that address the following:

- Change impurity [redacted] (b) (4)
- Report all impurities above 0.1%. Amend the specification to reflect this.
- It does not appear your method can sufficiently resolve impurities [redacted] (b) (4)

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/s/

EBLA ALI IBRAHIM
12/21/2010

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	December 13, 2010
Application Type/Number:	NDA 201743 NDA 022485
To:	Ann Farrell, MD, Director
Through:	Zachary Oleszczuk, Pharm.D., Team Leader Carol Holquist, R.Ph., Director Division of Medication Error Prevention and Analysis
From:	Yelena Maslov, Pharm.D., Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name(s):	Argatroban Injection (1 mg/ml) in Sodium Chloride 125 mg/125 mL Argatroban Injection (1mg/mL) in Dextrose 125 mg/125 mL
Applicant/sponsor:	Sandoz
OSE RCM #:	2010-1010; 2010-1341

CONTENTS

EXECUTIVE SUMMARY

This review summarizes the Division of Medication Error Prevention and Analysis (DMEPA) evaluation of the labels and labeling of Sandoz's Argatroban Injection 125 mg/125 mL in Sodium Chloride (NDA 022485) and Argatroban Injection 125 mg/125 mL in Dextrose (NDA 201743). The difference between the two products, Sodium Chloride or Dextrose as diluent, is not clearly differentiated on the labels and labeling, which may lead to selection errors.

We noted areas where the presentation of information can be improved to provide clarity to the labels and labeling and minimize the risk of the potential for medication errors. We have provided our recommendations for both Argatroban Injections regarding package insert labeling in Section 4.1 and we have provided our recommendations regarding container labels and carton labeling in Section 4.2.

1 BACKGROUND

1.1 INTRODUCTION

This review responds to requests from the Division of Hematology Products dated May 11, 2010 and June 9, 2010, for DMEPA's evaluation of the container labels, carton, and package insert labeling for Sandoz's Argatroban Injections 125 mg/125 mL (1 mg/mL). The request dated May 11, 2010 pertains to Argatroban Injection 125 mg/125 mL in Sodium Chloride. The request dated June 9, 2010 pertains to the Argatroban Injection 125 mg/125 mL in Dextrose. There is no proposed proprietary name for either product at this time.

1.2 REGULATORY HISTORY

Argatroban Injection 125 mg/125 mL (1 mg/mL) in Sodium Chloride is the subject of a 505 (b)(2) application submitted on March 17, 2010 that references Argatroban Injection 250 mg/2.5 mL (100 mg/mL) sponsored by Pfizer. Argatroban Injection 250 mg/2.5 mL, a concentrated solution for injection, was approved on June 30, 2000 under NDA 020883.

Additionally, Argatroban Injection 125 mg/125 mL (1 mg/mL) in Dextrose is the subject of a 505 (b)(2) application submitted on April 13, 2010 that also references Argatroban Injection 250 mg/2.5 mL (100 mg/mL) sponsored by Pfizer.

2 METHODS AND MATERIALS

Since the referenced listed product, Argatroban Injection 250 mg/2.5 mL (100 mg/mL), has been marketed since 2000, DMEPA conducted a search for medication errors involving Argatroban using FDA Adverse Event Reporting System (AERS) database. Identification of these errors may be indicative of potential issues with the proposed 505 (b)(2) Argatroban Injections 125 mg/125 mL (1 mg/mL). We eliminated reports not pertaining to medication errors (e.g. medication errors due to another drug product or adverse events related to the use of the drug) and grouped duplicate reports into cases. The cases were further grouped by the type of error and evaluated for the root cause.

Additionally, DMEPA evaluated the proposed labels and labeling for Argatroban using Failure Mode and Effects Analysis[1] (FMEA), principles of human factors, and lessons learned from the post marketing experience to identify areas that can contribute to medication errors.

2.1 ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE SEARCH CRITERIA

The AERS search conducted on July 2, 2010, used the following MedDRA High Level Group Terms (HLGT) "Medication Errors" and "Product Quality Issues" along with active ingredient names of "Argatroban," the trade name "Argatroban," and the verbatim name (b) (4) without dates limitations.

2.2 LABELS AND LABELING RISK ASSESSMENT

For Argatroban Injection in Sodium Chloride, the Applicant submitted the following container label and carton labeling as well as package insert labeling on March 17, 2010 (See Appendix A for container label and carton labeling images):

- Container Label and Carton Labeling: 125 mg/125 mL (1 mg/mL)

[1] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

For Argatroban Injection in Dextrose, the Applicant submitted the following container label and carton labeling as well as package insert labeling on April 13, 2010 (See Appendix B for container label and carton labeling images):

- Container Label and Carton Labeling: 125 mg/125 mL (1 mg/mL)

- **RESULTS AND DISCUSSION**

The following sections describe the results of the DMEPA's medication error searches and label and labeling evaluation.

3.1 ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE CASES

In total DMEPA evaluated twenty five (n=25) cases of medication errors involving Argatroban, twenty cases (n=20) from the United States and five (n=5) foreign. The errors included overdose (n=16), wrong dose (n=4), wrong dilution technique (n=3), and the drug name confusion (n=2). Table 1 describes the breakdown of these cases by type and cause.

Table 1: Total Number of Errors (n=25) By Type and Cause

Type of Error	Subtype of Error or Cause	Untied States (N=20)	Foreign (N=5)
Overdose (N=16)			
	Monitoring Error	None	N=2
	Infusion Pump	N=5	None
	Wrong Rate of Administration	N=2	None
	No contributing Factors	N=4	N=2
	Wrong Drug	None	N=1
Wrong Dose (N=4)	*Lack of Total Drug Content on the container label*	N=4	None
Wrong Dilution (N=3)		N=3	None
Drug Confusion (N=2)		N=2	None

The following sections discuss these errors in detail.

3.1.1 Overdoses (n=16)

Foreign Cases (n=5)

Five of sixteen cases that resulted in Argatroban overdose, were foreign cases from Japan (n=3), Germany (n=1), and Austria (n=1). Two cases (ISR #5960863-5 and ISR #6779016-6) reported overdoses due to failure to monitor coagulation parameters; and thus, the dose was not reduced after anticoagulation occurred. One case (ISR #4943357-5) reported the overdose of Argatroban occurred as a result of confusion with Vancomycin. The case did not report any additional details regarding these medication errors. Since no further details were provided, we could not determine the root cause of these errors. The remaining two cases (n=2, ISR #4730332-9 and ISR #6158031-X) did not provide any contributing factors to the overdose; thus, we are unable to determine why this error occurred.

United States Cases (n=11)

Eleven of the 16 overdose cases were reported in the United States. These cases involved infusion pumps errors and wrong rate of administration errors.

Infusion Pump Cases (n=5)

Five of the US overdose cases were practice related and not caused by the labels and labeling. These cases include infusion pump failure (n=2) and incorrect infusion pump programming (n=3). One of the cases (ISR #5146803-X) that reported incorrect infusion pump programming reported that that the error resulted from misinterpretation of a total dose of Argatroban. Although the physician ordered the medication correctly as 5 mcg/min, the dose was misinterpreted at some point in the medication process as 5 mcg/kg/min. No additional details regarding contributing factors were

provided. This type of medication error does not seem to be related to the Argatroban labeling since the medication was ordered correctly.

Wrong Rate of Administration Cases (n=2)

Two medication error cases of overdose resulted from infusion of Argatroban at a rate that was too fast. These cases did not specifically state that an infusion pump was involved. Only one case (ISR #5066934-2,) provided the actual rate of infusion and reported that the patient was administered Argatroban at the rate of 250 mL/2 hours, although the medication was prescribed correctly as 1.2 mL/hour (2.4 mL/2 hours). No additional details regarding contributing factors were provided. This type of medication error does not seem to be related to the Argatroban labeling since the medication was ordered correctly. The case reported patient outcome of no harm.

The remaining case (ISR #5168208-8) reported that patient was administered Argatroban at the correct rate of 2 mcg/kg/minute. However, at some point the administration process patient was inadvertently administered 50 mg bolus over 30 minutes. No additional details regarding the case were provided. The patient experienced an increase in activated partial thromboplastin time (aPTT) and INR levels. However, we note that the package insert labeling for Argatroban Injection 250 mg/2.5 mL presents complete information regarding the correct administration and monitoring of patients receiving the product.

Unspecified Overdose (n=4)

The remaining four medication error cases resulting in overdose did not report the reason for the overdose. Three (n=3) of the four cases reported a patient outcome as a temporary increase in activated partial thromboplastin time (aPTT), which normalized. The remaining case (n=1) did not report patient outcome. Since there are no details regarding the errors, we are unable to evaluate these four cases further.

3.1.2 Wrong Dose (n=4)

Four cases (n=4) reported an unspecified incorrect dose of Argatroban. These errors are due to the lack of expressing how much drug per total volume is contained in each vial (i.e., total drug content) on the labeling. All four cases reported the excessive dose withdrawal. One of the four cases (ISR #4157136-2) stated that the error reached the patient and required monitoring to preclude patient harm. Another case (ISR #4035778-2) described patient outcome of no harm because the error was quickly discovered after the product was dispensed. In the remaining two cases (ISR #3783566-4 and ISR #4363879-7), the error occurred, but did not reach the patient.

3.1.3 Wrong Dilution (n=3)

Three cases were categorized as wrong dilution technique.

Two cases (ISR #3853326-3, ISR # 5367276-8) were associated with previously marketed labels that included the inaccurate term “Reconstitution” on Argatroban’s container label and carton labeling. Argatroban does not require reconstitution; however the word “Reconstitution” appeared on older labels. In both cases, technicians attempted to reconstitute Argatroban after reading this term, and the product precipitated. Additionally, in both cases, this type of error was intercepted by the pharmacists and did not reach patients.

The Sponsor (Pfizer) of Argatroban reported in these cases that they revised the label and labeling to include the total drug content and replaced the term “reconstitution” with the term “dilution” on container label and carton labeling in January of 2003. Since these revisions, no additional medication error cases involving wrong dilution technique pertaining to the lack of total drug content or incorrect infusion preparation terms have been reported. Although a lack of reported errors can not guarantee that errors are not occurring, it does provide some reassurance that the revisions may have minimized the errors.

The remaining medication error case (n=1) occurred because the physician diluted Argatroban Injection 250 mg/2.5 mL incorrectly. The patient outcome was reported as fluid overload. Although the case did not report the contributing factors for incorrect product dilution, we note that the package insert labeling for Argatroban Injection 250 mg/2.5 mL presents complete information regarding the correct product preparation for administration.

In comparison to the reference listed drug product, Argatroban Injection 250 mg/2.5 mL, the proposed product contains the total drug content as well as the statement “Dilute prior to Use” on the container label and carton labeling. Thus, DMEPA believes that incorrect dilution errors will be minimized with the proposed product.

3.1.4 Drug Name Confusion (n=2)

Two cases of drug name confusion were reported in the US. One case (ISR #3855407-8) occurred in 2002, and involves confusion between Argatroban Injection and Orgaran Injection due to phonetic similarities. Although the wrong product (Orgaran) was prepared and delivered to patient's room, the error did not reach the patient. Subsequently, Orgaran Injection was discontinued and there are no available generics currently on the market. As a result, no additional errors pertaining to mix-up between Argatroban and Orgaran were identified.

The second medication error case (ISR #3971285-0) involved a complaint regarding the look-alike and sound-alike names between Argatroban and Aggrastat. A student asked a pharmacist whether Argatroban and Aggrastat were different names for the same product due to their phonetic and orthographic similarity. The case of confusion between two products was reported in 2002 and does not appear to be an ongoing problem. Although these two names do have some orthographic similarity (both start with the letter 'A' and contain 3 upstrokes and 1 down stroke in the approximately same position), the name Argatroban is longer than Aggrastat and does not contain a wide down stroke (two lower case letters 'gg' together). Additionally, the two medications have different product characteristics such as strength and concentration (Aggrastat 12.5 mg/250 mL (50 mcg/mL) vs. Argatroban Injection 250 mg/2.5 mL or Argatroban Injection 125 mg/125 mL as well as dose (Aggrastat 0.4 mcg/kg for 30 minutes followed up 0.1 mcg/kg/min vs. Argatroban 25 mcg/kg/min bolus, if needed; followed by infusion of 2 mcg/kg/min-30 mcg/kg/min depending on indication). Thus, we believe that drug confusion between Argatroban and Aggrastat will be minimized by the orthographic and phonetic differences in addition to the different product characteristics. Additionally, this error is not related to the information provided on the labels and labeling.

3.1 LABELS AND LABELING RISK ASSESSMENT

Our evaluation of the proposed container labels as well as carton and package insert labeling noted areas of needed improvement in order to minimize the potential for medication errors. Specifically, neither of the proposed products require dilution, unlike the reference product, Argatroban Injection 250 mg/2.5 mL. Thus, it is important to highlight that information on the labeling to avoid medication errors associated with preparation of the product for administration. Additionally, the proposed Argatroban products will contain different diluents. Thus, this difference needs to be clearly labeled to avoid selection errors as well.

4 RECOMMENDATIONS

Since the only difference between the proposed Argatroban Injections 125 mg/125 mL is the presence of Sodium Chloride and Dextrose as a diluent for argatroban, our recommendations regarding labels and labeling pertain to both products.

Our evaluation of the medication errors as well as proposed container labels, carton and package insert labeling noted areas of needed improvement in order to minimize the potential for medication errors. Section 4.1 *Comments to the Division* contains our recommendations regarding package insert labeling. Section 4.2 *Comments to the Applicant* contains our recommendations for the container labels and the carton labeling. We request the recommendations in Section 4.2 be communicated to the Applicant prior to approval.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager Sue Kang at 301-796-4216.

4.1 COMMENTS TO THE DIVISION FOR ARGATROBAN INJECTION IN SODIUM CHLORIDE AND ARGATROBAN INJECTION IN DEXTROSE

1. Highlights of Prescribing Information, Section 2 Dosage and Administration Section

   We note the use dangerous abbreviation 'IV' in your insert labeling. The abbreviation 'IV' is on the dangerous abbreviations, List of Error-Prone Abbreviations, Symbols, and Dose Designations[2] because the abbreviation has been confused with the abbreviations 'IM' (intramuscular), 'IU' (international units), and 'IN'(intranasal). Thus, we request you replace all instances of the abbreviation 'IV' with the word "intravenously."

   Please make these revisions in accordance with the agreement FDA made as part of a national campaign to reduce medication errors related to error prone medical abbreviations and dose designations. As part of that campaign the FDA agreed not to approve labels and labeling that included the use of error prone abbreviations.

2. Full Prescribing Information, Section 2.2 Dosing in Patients Undergoing Percutaneous Coronary Intervention

We note the use of dangerous abbreviations and symbols in your insert labeling. The first dangerous abbreviation is "IV". The abbreviation 'IV' is on the dangerous abbreviations, List of Error-Prone Abbreviations, Symbols, and Dose Designations[2] because the abbreviation has been confused with the abbreviations 'IM' (intramuscular), 'IU' (international units), and 'IN'(intranasal). Thus, we request you replace all instances of the abbreviation 'IV' with the word "intravenously."

The second dangerous abbreviation or symbol is the "<" and ">". The symbols '<' and '>' are dangerous symbols that appear on the List of Error-Prone Abbreviations, Symbols, and Dose Designations[1]. These symbols are often mistaken and used as opposite of intended. Replace all instances of the symbol '<' with phrase "less than" and symbol '>' with phrase "greater than."

Please make these revisions in accordance with the agreement FDA made as part of a national campaign to reduce medication errors related to error prone medical abbreviations and dose designations. As part of that campaign the FDA agreed not to approve labels and labeling that included the use of error prone abbreviations.

3. Full Prescribing Information, Section 3 Dosage Forms and Strength

The sentence "Vial: 125 mg in 125 mL vial" does not include the product's concentration. Revise this sentence to include the concentration. The revised statement should read, "Argatroban Injection is a clear and colorless solution available in sterile single-use vials containing 125 mg/125 mL (1 mg/mL)."

4.2 COMMENTS TO THE APPLICANT FOR ARGATROBAN INJECTION IN SODIUM CHLORIDE AND ARGATROBAN INJECTION IN DEXTROSE

A. Container Label and Carton Labeling for Argatroban Injection 125 mg/125 mL in Sodium Chloride and Argatroban Injection 125 mg/125 mL in Dextrose

1. Place the name of diluents, Sodium Chloride or Dextrose, and their percent amounts on the principle display panel also immediately under the product's name to clearly differentiate the two Argatroban Products such as follows:

Agratroban Injection
in 0.9% Sodium Chloride
125 mg/125 mL
(1 mg/mL)

Or

Agratroban Injection
in 5% Dextrose
125 mg/125 mL
(1 mg/mL)

Additionally, to sufficiently distinguish between Argatroban in Sodium Chloride and Argatroban in Dextrose, print the name of the diluents and their percent amounts using contrasting colors and in the same font as the product's established name. As currently presented, the diluents blend with the other inactive ingredients on the side panel may be easily overlooked; thus, increasing the potential for selection error.

2. Place the statement "Do not dilute prior to administration" on the principle display panel to differentiate the dilution requirements from the reference listed drug, Argatroban Injection 250 mg/2.5 mL (100 mg/mL). The reference-listed drug (RLD), Argatroban Injection 250 mg/2.5 mL, is a concentrated solution that required dilution prior to administration. As a result, it is important to differentiate between the RLD and the new Argatroban Injection product, which does not require dilution prior to administration, to minimize medication errors associated with product's preparation for administration.

[2] Institute for Safe Medication Practices, "List of Error-Prone Abbreviations, Symbols, and Dose Designations. www.ismp.org.

3. Add Bar Coding to the labeling per 21 CFR 201.25
4. Remove of the word (b) (4) from the principle display panel. This word is not important and clusters and labels and labeling.
5. Decrease the prominence of the "Rx Only" statement. As currently presented, it is as prominent as concentration statement and other pertinent information. Additionally, relocate the "Rx Only" statement to a less prominent location on the principle display panel such as upper right corner.
6. Delete the statement "Do not Freeze" because this statement is unnecessary and occupies space.

B. Container Labels for Argatroban Injection 125 mg/125 mL in Sodium Chloride and Argatroban Injection 125 mg/125 mL in Dextrose

1. Allocate the space on the vial label (e.g., the bottom of the principle display panel or the side panel) to place the product's name, diluent, strength, and concentration in the inverted manner to increase the readability of the label when the product is hung upside down.
2. Increase the prominence of the statement "For Intravenous Use" by relocating it from the side panel to the principle display panel under the product's concentration and increasing the font size.
3. Delete the phrase (b) (4) located immediately next to the statement "Single Use Vial" from the principle display panel because it is duplicative and clusters other important information.
4. Add the statement "Single Use Vial, Discard Unused Portion" to the principle display panel.
5. Revise the statements on the side panel regarding the ingredients contained in each milliliter of Argatroban Injection to improve clarity. As the statements currently presented, it is unclear whether each mL contains the particular amount of active and inactive ingredients or entire vial; thus, creating confusion that may lead to errors.
    a. Argatroban Injection in Sodium Chloride should be revised to state, "Each mL contains 1 mg argatroban, 9 mg sodium chloride, and 3 mg D-sorbitol".
    b. Argatroban Injection in Dextrose should be revised to state, "Each mL contains 1 mg argatroban, 50 mg dextrose, and 3 mg D-sorbitol".

C. Carton Labeling for Argatroban Injection 125 mg/125 mL in Sodium Chloride and Argatroban Injection 125 mg/125 mL in Dextrose

1. Delete the phrase (b) (4) located under the statement "For Intravenous Use" from the principle display panels, because it is duplicative and distracts from the concentration.
2. Place the statement "Each Carton Contains 2 Single Use Vials" on the bottom of the principle display panels as well as upper and lower panels.
3. Increase the prominence of the statement "Protect from light and store in carton" in increasing the font size.
4. See comments in Sections B.4, which also apply to this Section.

<u>Appendix A</u>: Argatroban Injection 125 mg/125 mL (1 mg/mL) in Sodium Chloride Container Label and Carton Labeling (NDA 022485)

Container Label

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/s/

YELENA L MASLOV
12/13/2010

ZACHARY A OLESZCZUK
12/13/2010

CAROL A HOLQUIST
12/13/2010

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
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Maternal Health Team Label Review

Date: July 12, 2010 **Date Consulted:** June 9, 2010

From: Tammie Howard, RN, MSN
Regulatory Reviewer, Maternal Health Team
Pediatric and Maternal Health Staff

Through: Karen Feibus, MD
Team Leader, Maternal Health Team
Pediatric and Maternal Health Staff

Lisa Mathis, MD
Associate Director, Office of New Drugs
Pediatric and Maternal Health Staff

To: The Division of Hematology Products (DHP)

Drug: Argatroban Injection, NDA 201-743

Subject: Labeling Review

Materials Reviewed: Pregnancy and Nursing Mothers subsections of Argatroban labeling

Consult Question: Please review the Pregnancy and Nursing Mothers subsections of Argatroban labeling.

BACKGROUND

On April 13, 2010, Sandoz Incorporated submitted a 505 (b)(2) new drug application (NDA 201-743) to the Division of Hematology Products (DHP) (formerly the Division of Medical Imaging and Hematology Products) for Argatroban Injection 1mg/ml (125 mL) in a dextrose/sorbitol solution. The sponsor's proposed indication for Argatroban is prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT) and anticoagulation in patients with or at risk for HIT undergoing percutaneous coronary intervention (PCI).

On June 9, 2010, DHP consulted the Maternal Health Team (MHT) to review the pregnancy and nursing mothers section of the Argatroban labeling. This review provides the MHT recommendations regarding the sponsor's proposed Pregnancy and Nursing Mother's subsections of Argatroban labeling.

SUBMITTED MATERIAL

Sponsor's Proposed Pregnancy and Nursing Mothers Labeling

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

(b) (4)

Pregnancy Category B

(b) (4) performed in rats with intravenous doses up to 27 mg/kg/day (0.3 times the recommended maximum human dose based on body surface area) and rabbits at intravenous doses up to 10.8 mg/kg/day (0.2 times the recommended maximum human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus (b) (4) Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers

(b) (4) Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from argatroban, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

DISCUSSION AND CONCLUSIONS

In response to the division's consult, the MHT reviewed the Argatroban labeling. The Maternal Health Team (MHT) has been working to develop a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of labeling. This approach complies with current regulations but incorporates "the spirit" of the Proposed Pregnancy and

Lactation Labeling Rule (published on May 29, 2008). The MHT reviewer ensures that the appropriate regulatory language is present and that available information is organized and presented in a clear and useful manner for healthcare practitioners. Animal data in the pregnancy subsection is presented in an organized, logical format that makes it as clinically relevant as possible for prescribers. This includes expressing animal data in terms of species exposed, timing and route of drug administration, dose expressed in terms of human exposure or dose equivalents (with the basis for calculation), and outcomes for dams and offspring. For nursing mothers, when animal data are available, only the presence or absence of drug in milk is considered relevant and presented in the label, not the amount.

The first paragraph of the pregnancy subsection is a summary paragraph that includes the required regulatory language for the designated pregnancy category and statements that briefly describe the outcomes from available human and animal studies. Subsequent paragraphs describe the available data in greater detail.

Multiple argatroban applications are under review, and the MHT is working with the review division to ensure consistency as appropriate based on the data reviewed and relied upon for labeling.

RECOMMENDATIONS

1. The MHT recommends the following revisions to the language for the Highlights, Pregnancy, and Nursing Mothers sections of Argatroban labeling. Appendix A of this review provides a track changes version of the labeling that highlights all changes made.

   Highlights

   ----------USE IN SPECIFIC POPULATIONS ----------
   - Nursing Mothers: Discontinue nursing or drug, taking into account the importance of the drug to the mother. (8.3).

   8 USE IN SPECIFIC POPULATIONS

   8.1 Pregnancy

   Pregnancy Category B.
   There are no adequate and well-controlled studies of argatroban use in pregnant women. Developmental studies performed in rats with argatroban at intravenous doses up to 27 mg/kg/day (0.3 times the maximum recommended human dose, based on body surface area) and in rabbits at intravenous doses up to 10.8 mg/kg/day (0.2 times the maximum recommended human dose, based on body surface area) have revealed no evidence of impaired fertility or harm to the fetus. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers

It is not known whether argatroban is excreted in human milk. Argatroban is detected in rat milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from argatroban, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Reviewer Comments

Please note that a statement regarding Nursing Mothers was added to Highlights under the USE IN SPECIFIC POPULATIONS section. The header (b) (4) *under section 8.1 Pregnancy was deleted. The above recommended language should be considered for all Argatroban products that rely on the same non-clinical developmental studies.*

Appendix A-
Track Changes Version of Labeling

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/s/

TAMMIE B BRENT HOWARD
07/27/2010

Karen B FEIBUS
07/27/2010
I agree with the labeling recommendations contained in this review. I am also signing for CAPT Lisa Mathis, MD.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Pediatric and Maternal Health Staff – Pediatric Memorandum

Date: June 15, 2010

From: Jeanine Best, MSN, RN, PNP, Senior Clinical Analyst
Pediatric and Maternal Health Staff

Through: Hari Cheryl Sachs, MD, Team Leader – Pediatric Team
Pediatric and Maternal Health Staff

Lisa Mathis, M.D., OND Associate Director,
Pediatric and Maternal Health Staff

To: Division of Hematology Products (DHP)

Drug: Argatroban Injection, NDAs 22-359, 22-485, and 201-743

Subject: 505(b)(2) Applications and Pediatric Exclusivity

Materials Reviewed:

- Current approved Argatroban labeling – pediatric labeling changes approved for Argatroban Injection – S-014 (May 5, 2008)
- Patent and Exclusivity data for NDA 20-883
- PeRC Meeting Minutes, January 30, 2008
- Medical Officer Review of the Pediatric Exclusivity Studies, NDA 20-883/S-014, February 15, 2008
- Medical Team Leader Review of the Pediatric Labeling Supplement Resubmission, February 22, 2008
- Clinical Pharmacology Review Summary of the pharmacokinetics study in pediatric patients NDA 20-883/S-014, February 13, 2008
- DMIHP Division Director Pediatric Review Memo, May 2, 2008
- PMHS Office of Generics Pediatric Carve-out Review, September 9, 2009

Consult Question: Please review and update pediatric use information in labeling for these 505(b)(2) applications.

BACKGROUND

The Division of Hematology Products (DHP) consulted the Pediatric and Maternal Health Staff (PMHS) - Pediatric Team to review pediatric use information in labeling for three 505(b)(2) applications submitted for Argatroban Injection (NDAs 22-359, 22-485, and 201-743). The referenced product is Pfizer's Argatroban Injection, NDA 20-883. None of the 505(b)(2) applicants submitted labeling that contains the complete pediatric use information which appears throughout Pfizer's Argatroban Injection labeling. One 505(b)(2) applicant included no pediatric use information (22-359), and instead, directed clinicians to use other Argatroban products with pediatric data in labeling.

Argatroban is a synthetic thrombin inhibitor derived from L-arginine that reversibly binds to the thrombin active site. Argatroban Injection was initially approved on June 30, 2000, as an anticoagulant for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia. An additional indication was approved on April 3, 2002, for use as an anticoagulant in patients with or at risk for heparin-induced thrombocytopenia undergoing percutaneous coronary intervention (PCI).

Pediatric studies were required for Argatroban under the Pediatric Research Equity Act (PREA), as well as a postmarketing commitment for pediatric pharmacokinetic and safety studies to allow for appropriate dosing and safety. In addition, Encysive Pharmaceuticals, Inc. (now Pfizer, Inc.) submitted a Proposed Pediatric Study Request (PPSR) on April 26, 2002, and in response, FDA issued a Pediatric Written Request (PWR) on April 2, 2003, (amended on February 13, 2004 and April 7, 2005) requesting information from studies in pediatric patients birth to < 16 years of age for the prophylaxis and/or treatment of thrombosis in patients who: 1) have a diagnosis of heparin-induced thrombocytopenia and thrombosis syndrome (HIT/HITTS), or 2) require anticoagulation and have documented histories of positive HIT antibody test in the absence of thrombocytopenia or heparin challenge (patients with latent disease), or 3) require alternative anticoagulation (i.e., not heparin) due to an underlying condition, including patients with anti-thrombin 3 deficiency or hypercoagulable states. The PWR requested safety, clinical outcomes data, and pharmacokinetic/pharmacodynamic parameters on a minimum of 24 patients.

Although these studies were considered sufficient to fulfill the PREA pediatric study requirement, Pediatric Exclusivity was not granted because the terms of the PWR were not adequately met (inadequate enrollment). However, three years of Waxman-Hatch (WH) Exclusivity was granted to Encysive Pharmaceuticals, Inc. (now Pfizer) for revisions to labeling based on data submitted in response to the Pediatric Written Request. The WH Exclusivity expires May 5, 2011.

A pediatric indication was not approved for Argatroban Injection because the limited data submitted did not support safe and effective use in pediatric patients. Much internal discussion occurred around the placement of the pediatric study information in labeling because the product is used in critically ill pediatric patients and the differences in pediatric and adult pharmacokinetic parameters are clinically significant. Argatroban has lower clearance in pediatric patients compared to healthy adult patients, and also lower clearance in pediatric patients with increased bilirubin levels; thus, recommended starting doses based on PK are lower than those customarily used in adult practice. Since efficacy

was not established in pediatric patients, the Pediatric Review Committee (PeRC) recommended that all information from this pediatric study be placed only in the Pediatric Use subsection of labeling. Due to the difference and variability in drug clearance in children and pediatric dosing safety concerns, the Division of Medical Imaging and Hematology Products (DMIHP) decided to place the pediatric PK/PD information in the CLINICAL PHARMACOLOGY/Special Populations section of Argatroban labeling, rather than in the Pediatric Use subsection (cross-referencing used), and included a statement in the DOSAGE AND ADMINISTRATION/ Dosing in Special Populations section directing the physician to the PRECAUTIONS/Pediatric Use subsection section for information on pediatric dosing. The following sections of Argatroban labeling were revised on May 5, 2008, to include the clinical data from the study conducted in pediatric patients with Heparin-Induced Thrombocytopenia (HIT) or Heparin-Induced Thrombocytopenia with Thrombosis (HITTS):

- CLINICAL PHARMACOLOGY/ SPECIAL POPULATIONS/Age: Pediatric
- PRECAUTIONS /Pediatric Use
- DOSAGE AND ADMINISTRTION/Dosing in Special Populations/Pediatric HIT/HITTS Patients

Reviewer Comments:

1. *All of the pediatric use information added to Pfizer's Argatroban Injection labeling on May 5, 2008, is "protected" information.*

2. *The innovator Argatroban labeling is in the old labeling format and the 505(b)(2) Argatroban labeling is in the Physicians Labeling Rule (PLR) format. The Pediatric Use subsection is located in USE IN SPECIAL POPULATIONS section of labeling (a new section) in the PLR format.*

Best Pharmaceuticals for Children Act of 2007

The Best Pharmaceuticals for Children Act (BPCA) (section 505A of the Food, Drug and Cosmetic Act) addresses the approval of drugs under 505(j) when pediatric information protected by exclusivity [either six-month pediatric exclusivity (BPCA) or three-year new clinical studies exclusivity (Waxman-Hatch)] has been added to the labeling.

505A(l)(2) states:
PEDIATRIC INFORMATION IS ADDED TO LABELING.—''(1) GENERAL RULE.—A drug for which an application has been submitted or approved under section 505(j) shall not be considered ineligible for approval under that section or misbranded under section 502 on the basis that the labeling of the drug omits a pediatric indication or any other aspect of labeling pertaining to pediatric use when the omitted indication or other aspect is protected by patent or by exclusivity under clause (iii) or (iv) of section 505(j)(5)(F).
''(2) LABELING.— Notwithstanding clauses (iii) and (iv) of section 505(j)(5)(F), the Secretary may require that the labeling of a drug approved under section 505(j) that omits a pediatric indication or other aspect of labeling as described in paragraph (1) include —
''(A) a statement that, because of marketing exclusivity for a manufacturer — ''(i) the drug is not labeled for pediatric use; or ''(ii) in the case of a drug for which there is an additional

pediatric use not referred to in paragraph (1), the drug is not labeled for the pediatric use under paragraph (1); and ‘‘(B) a statement of any appropriate pediatric contraindications, warnings, or precautions that the Secretary considers necessary.”

In addition, FDA added a provision on pediatric risk information in § 201.56(d)(5) of the January 24, 2006, Final Rule: Requirements on Content and Format of Labeling for Human Prescription Drugs and Biological Products to avoid any possible confusion as to what information the agency may require in generic labeling that otherwise omits a pediatric indication or other aspect of labeling pertaining to pediatric use protected by patent or exclusivity.

§ 201.56(d)(5) states:
“Any risk information that is required under § 201.57(c)(9)(iv) is considered appropriate pediatric contraindications, warnings, or precautions within the meaning of 505A(1)(2) of the Federal Food Drug and Cosmetic Act (the act) (21 U.S.C. 355A(1)(2)), whether such information appears in the Contraindications, Warnings and Precautions, or Use in Specific Populations section of labeling.”
In summary, 1) when new pediatric information in labeling is protected by patent or exclusivity [either six-month pediatric exclusivity (BPCA) or three-year new clinical studies exclusivity (Waxman-Hatch)] and “carved out,” a disclaimer is necessary; and, 2) important pediatric safety information, particularly if related to Contraindications, Warnings and Precautions, or Use in Specific Populations (Pediatric Use) may be retained.

RECOMMENDATIONS
PMHS-Pediatric Team has the following recommendations for Argatroban Injection 505(b)(2) labeling:

1. Retain all protected pediatric use information (added to Pfizer’s Argatroban Injection labeling on May 5, 2008) for safe use reasons in all 505(b)(2) Argatroban Injection labeling. Clinicians using Argatroban in critically ill pediatric patients must be informed of the available pediatric use information and related safety concerns, including dosing recommendations due to differences and variability in pediatric PK parameters and the risk of overdosing. Protected pediatric use information appears in the following sections of Pfizer’s Argatroban Injection labeling:

    - CLINICAL PHARMACOLOGY/ SPECIAL POPULATIONS/Age: Pediatric
    - PRECAUTIONS /Pediatric Use

- DOSAGE AND ADMINISTRTION/Dosing in Special Populations/Pediatric HIT/HITTS Patients

2. Request all 505(b)(2) Argatroban Injection applicants to submit revised labeling that incorporates all of the pediatric use information that appears in Pfizer's Argatroban Injection labeling. The pediatric information which appears in PRECAUTIONS/Pediatric Use in Pfizer's Argatroban Injection labeling (old labeling format) should be placed in USE IN SPECIAL POPULATIONS/Pediatric Use in any 505(b)(2) Argatroban Injection labeling submitted in the PLR format.

3. 

4. DHP can ensure that all 505(b)(2) Argatroban Injection labeling, when resubmitted, contain the identical pediatric use information throughout labeling, which appears in Pfizer's Argatroban Injection labeling.

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/s/

JEANINE A BEST
06/15/2010

HARI C SACHS
06/15/2010
I agree with the recommendations contained in this consult