

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022485Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 22-485 Supplement Number: _____ NDA Supplement Type (e.g. SE5): 505 b
2

Division Name: Division of Hematology Products PDUFA Goal Date: January 17, 2011 Stamp Date: 3/17/2010

Proprietary Name: Argatroban

Established/Generic Name: _____

Dosage Form: Injection

Applicant/Sponsor: Sandoz

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) _____
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Argatroban is indicated as an anticoagulant for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia and patients with or at risk for heparin-induced thrombocytopenia undergoing percutaneous coronary intervention (PCI)

Q1: Is this application in response to a PREA PMR? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.
 No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
 No. Please proceed to the next question.

Reference ID: 2877418

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

| |
|---|
| Section A: Fully Waived Studies (for all pediatric age groups) |
|---|

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

| | | Reason (see below for further detail): | | | | | |
|--------------------------|---------|--|---------------|---------------------------|---|------------------------------------|---------------------------------|
| | | minimum | maximum | Not feasible [#] | Not meaningful therapeutic benefit [*] | Ineffective or unsafe [†] | Formulation failed ^Δ |
| <input type="checkbox"/> | Neonate | __ wk. __ mo. | __ wk. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4)

additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

| Deferrals (for each or all age groups): | | | | Reason for Deferral | | | Applicant Certification † |
|--|---------------|---------------|--------------------------|------------------------------|---|---|---------------------------|
| | | | | Ready for Approval in Adults | Need Additional Adult Safety or Efficacy Data | Other Appropriate Reason (specify below)* | Received |
| Population | minimum | maximum | | | | | |
| <input type="checkbox"/> Neonate | __ wk. __ mo. | __ wk. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| <input type="checkbox"/> Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| <input type="checkbox"/> Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| <input type="checkbox"/> Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| <input type="checkbox"/> Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| <input type="checkbox"/> All Pediatric Populations | 0 yr. 0 mo. | 16 yr. 11 mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| Date studies are due (mm/dd/yy): _____ | | | | | | | |

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

| Pediatric subpopulation(s) in which studies have been completed (check below): | | | | | |
|--|------------------------------|---------------|---------------|---|-----------------------------|
| Population | | minimum | maximum | PeRC Pediatric Assessment form attached?. | |
| <input type="checkbox"/> | Neonate | __ wk. __ mo. | __ wk. __ mo. | Yes <input type="checkbox"/> | No <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | Yes <input type="checkbox"/> | No <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | Yes <input type="checkbox"/> | No <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | Yes <input type="checkbox"/> | No <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | Yes <input type="checkbox"/> | No <input type="checkbox"/> |
| <input type="checkbox"/> | All Pediatric Subpopulations | 0 yr. 0 mo. | 16 yr. 11 mo. | Yes <input type="checkbox"/> | No <input type="checkbox"/> |

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

| Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed: | | | | | |
|--|------------------------------|---------------|---------------|--|--|
| Population | | minimum | maximum | | |
| <input type="checkbox"/> | Neonate | __ wk. __ mo. | __ wk. __ mo. | | |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | | |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | | |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | | |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | | |
| <input type="checkbox"/> | All Pediatric Subpopulations | 0 yr. 0 mo. | 16 yr. 11 mo. | | |

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

| Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations: | | | | | |
|---|------------------------------|---------------|---------------|--------------------------|--------------------------|
| Population | | minimum | maximum | Extrapolated from: | |
| | | | | Adult Studies? | Other Pediatric Studies? |
| <input type="checkbox"/> | Neonate | __ wk. __ mo. | __ wk. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | All Pediatric Subpopulations | 0 yr. 0 mo. | 16 yr. 11 mo. | <input type="checkbox"/> | <input type="checkbox"/> |

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____**Q1:** Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

| | | | Reason (see below for further detail): | | | | |
|--------------------------|---------|---------------|--|---|------------------------------------|---------------------------------|--------------------------|
| | minimum | maximum | Not feasible [#] | Not meaningful therapeutic benefit [*] | Ineffective or unsafe [†] | Formulation failed ^Δ | |
| <input type="checkbox"/> | Neonate | __ wk. __ mo. | __ wk. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the

drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

| Deferrals (for each or all age groups): | | | | Reason for Deferral | | | Applicant Certification † |
|---|---------------------------|---------------|---------------|------------------------------|---|---|------------------------------|
| Population | | minimum | maximum | Ready for Approval in Adults | Need Additional Adult Safety or Efficacy Data | Other Appropriate Reason (specify below)* | Received |
| <input type="checkbox"/> | Neonate | __ wk. __ mo. | __ wk. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | All Pediatric Populations | 0 yr. 0 mo. | 16 yr. 11 mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Date studies are due (mm/dd/yy): _____ | | | | | | | |

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

| Pediatric subpopulation(s) in which studies have been completed (check below): | | | | | |
|--|------------------------------|---------------|---------------|--|-----------------------------|
| Population | | minimum | maximum | PeRC Pediatric Assessment form attached? | |
| <input type="checkbox"/> | Neonate | __ wk. __ mo. | __ wk. __ mo. | Yes <input type="checkbox"/> | No <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | Yes <input type="checkbox"/> | No <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | Yes <input type="checkbox"/> | No <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | Yes <input type="checkbox"/> | No <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | Yes <input type="checkbox"/> | No <input type="checkbox"/> |
| <input type="checkbox"/> | All Pediatric Subpopulations | 0 yr. 0 mo. | 16 yr. 11 mo. | Yes <input type="checkbox"/> | No <input type="checkbox"/> |

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

| Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed: | | | |
|--|------------------------------|---------------|---------------|
| Population | | minimum | maximum |
| <input type="checkbox"/> | Neonate | __ wk. __ mo. | __ wk. __ mo. |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. |
| <input type="checkbox"/> | All Pediatric Subpopulations | 0 yr. 0 mo. | 16 yr. 11 mo. |

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

| Population | minimum | maximum | Extrapolated from: | |
|---|---------------|---------------|--------------------------|--------------------------|
| | | | Adult Studies? | Other Pediatric Studies? |
| <input type="checkbox"/> Neonate | __ wk. __ mo. | __ wk. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> All Pediatric Subpopulations | 0 yr. 0 mo. | 16 yr. 11 mo. | <input type="checkbox"/> | <input type="checkbox"/> |

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

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
12/14/2010

REQUEST FOR CONSULTATION

TO (Office/Division): **Pediatric and Maternal Health Staff**

FROM (Name, Office/Division, and Phone Number of Requestor): **Ebla Ali Ibrahim, RPM, Division of Hematology Products**

DATE
May 11, 2010

IND NO.

NDA NO.
22-485

TYPE OF DOCUMENT
NDA - 505(b)(2)

DATE OF DOCUMENT
March 16, 2010

NAME OF DRUG
Argatroban

PRIORITY CONSIDERATION
Standard

CLASSIFICATION OF DRUG
Antithrombin

DESIRED COMPLETION DATE
August 11, 2010

NAME OF FIRM: **Sandoz, Inc**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Sandoz, Inc submitted a 505(b)(2) NDA for Argatroban used as an anticoagulant for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia. Please find attached the packet insert (PI). Please review.
This consult is for both Peds and MHT.

SIGNATURE OF REQUESTOR
Ebla Ali Ibrahim

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|-------------------------|------------------------|----------------|------------------------------|
| NDA-22485 | ORIG-1 | SANDOZ INC | ARGATROBAN INJECTION 1 MG/ML |

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

05/12/2010

This consult is for both Peds and MHT.

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO:

CDER-DDMAC-RPM

FROM: (Name/Title, Office/Division/Phone number of requestor)

Ebla Ali Ibrahim, RPM, Division of Hematology Products

REQUEST DATE
May 11, 2010

IND NO.

NDA/BLA NO.
22-485

TYPE OF DOCUMENTS
NDA

NAME OF DRUG
Argatroban

PRIORITY CONSIDERATION
Standard

CLASSIFICATION OF DRUG
Antithrombin

DESIRED COMPLETION DATE
August 11, 2010

NAME OF FIRM:
Sandoz, Inc

PDUFA Date:
January 17, 2011

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:

(Check all that apply)

- PACKAGE INSERT (PI)
- PATIENT PACKAGE INSERT (PPI)
- CARTON/CONTAINER LABELING
- MEDICATION GUIDE
- INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION

- ORIGINAL NDA/BLA
- IND
- EFFICACY SUPPLEMENT
- SAFETY SUPPLEMENT
- LABELING SUPPLEMENT
- PLR CONVERSION

REASON FOR LABELING CONSULT

- INITIAL PROPOSED LABELING
- LABELING REVISION

EDR link to submission:

NDA# N22485

Incoming Document Type: N

Incoming Document Type Sequence Number: 1

Supplement Modification Type:

Letter Date: 16-MAR-2010

It has sections 1, 2, 3, 4, 5, 20

The network location is : \\FDSWA150\NONECTD\N22485\N_000\2010-03-16

Supplement Modification Type: LP

Letter Date: 01-APR-2010

It has section 1, 2

The network location is : \\FDSWA150\NONECTD\N22485\N_000\2010-04-01

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.

COMMENTS/SPECIAL INSTRUCTIONS:

Mid-Cycle Meeting: **around August 11, 2010**

Labeling Meetings: **In November**

Wrap-Up Meeting: **December 13, 2010**

SIGNATURE OF REQUESTER

Ebla Ali Ibrahim

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)

eMAIL

HAND

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|-------------------------|------------------------|----------------|------------------------------|
| NDA-22485 | ORIG-1 | SANDOZ INC | ARGATROBAN INJECTION 1 MG/ML |

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
05/11/2010

ACTION PACKAGE CHECKLIST

| APPLICATION INFORMATION ¹ | | |
|---|---------------------------------------|--|
| NDA # 22485 BLA # N/A | NDA Supplement # N/A BLA STN # N/A | If NDA, Efficacy Supplement Type: N/A |
| Proprietary Name: Established/Proper Name: Argatroban Injection Dosage Form: Injection | | Applicant: Sandoz, Inc Agent for Applicant (if applicable): |
| RPM: Ebla Ali ibrahim | | Division: Division of Hematology Products |
| <p><u>NDA's:</u> NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A 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). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p> | | <p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u> Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)): NDA 20883</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>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.</p> <p>If no listed drug, explain.</p> <p><input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> Other (explain)</p> <p><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p> |
| ❖ Actions | | |
| <ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>June 21, 2011</u> | | <input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR |
| <ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) | | <input type="checkbox"/> None TA, January 13, 2011 |

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

| | |
|--|---|
| <p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p> | <input type="checkbox"/> Received |
| <p>❖ Application Characteristics²</p> | |
| <p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <input type="checkbox"/> Restricted distribution (21 CFR 601.42)</p> <p>Subpart I Subpart H <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Communication Plan <input type="checkbox"/> Submitted in response to a Pediatric Written Request <input type="checkbox"/> ETASU <input type="checkbox"/> REMS not required</p> <p>Comments:</p> | |
| <p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p> | <input type="checkbox"/> Yes, dates N/A |
| <p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p> | <input type="checkbox"/> Yes <input type="checkbox"/> No |
| <p>❖ Public communications (<i>approvals only</i>)</p> | |
| <ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |
| <ul style="list-style-type: none"> Press Office notified of action (by OEP) | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |
| <ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated | <input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other |

² Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

| | |
|--|--|
| ❖ Exclusivity | |
| <ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes |
| <ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires: |
| <ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires: |
| <ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires: |
| <ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires: |
| <ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires: |
| ❖ Patent Information (NDAs only) | |
| <ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. | <input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic. |
| <ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. | 21 CFR 314.50(i)(1)(i)(A) <input checked="" type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii) |
| <ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). | <input checked="" type="checkbox"/> No paragraph III certification Date patent will expire |
| <ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> | <input type="checkbox"/> N/A (no paragraph IV certification) <input checked="" type="checkbox"/> Verified |

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

| | |
|---|---|
| <p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p> | <p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> |
|---|---|

CONTENTS OF ACTION PACKAGE

| | |
|---|---|
| ❖ Copy of this Action Package Checklist ³ | May 9, 2011 |
| Officer/Employee List | |
| ❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>) | <input checked="" type="checkbox"/> Included |
| Documentation of consent/non-consent by officers/employees | <input checked="" type="checkbox"/> Included |
| Action Letters | |
| ❖ Copies of all action letters (<i>including approval letter with final labeling</i>) | Action(s) and date(s) TA, January 13, 2011, AP, May 9, 2011 |
| Labeling | |
| ❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>) | |
| <ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. | AP Label May 9, 2011 |
| <ul style="list-style-type: none"> • Original applicant-proposed labeling | March 17, 2010 |
| <ul style="list-style-type: none"> • Example of class labeling, if applicable | N/A |

³ Fill in blanks with dates of reviews, letters, etc.

| | |
|---|--|
| ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) | <input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None |
| <ul style="list-style-type: none"> Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. | N/A |
| <ul style="list-style-type: none"> Original applicant-proposed labeling | N/A |
| <ul style="list-style-type: none"> Example of class labeling, if applicable | N/A |
| ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) | |
| <ul style="list-style-type: none"> Most-recent draft labeling | |
| ❖ Proprietary Name <ul style="list-style-type: none"> Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) Review(s) (<i>indicate date(s)</i>) | |
| ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) | <input type="checkbox"/> RPM <input type="checkbox"/> DMEPA <input type="checkbox"/> DRISK <input type="checkbox"/> DDMAC <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews |
| Administrative / Regulatory Documents | |
| ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) | |
| ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte | <input type="checkbox"/> Not a (b)(2) May 9, 2011 |
| ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) | <input type="checkbox"/> Not a (b)(2) May 9, 2011 |
| ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) | <input type="checkbox"/> Included |
| ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm | |
| <ul style="list-style-type: none"> Applicant is on the AIP | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |
| <ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> If yes, Center Director's Exception for Review memo (<i>indicate date</i>) If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input checked="" type="checkbox"/> Not an AP action |
| ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> Date reviewed by PeRC <u>N/A</u> If PeRC review not necessary, explain: <u>505(b)(2)</u> Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) | <input checked="" type="checkbox"/> Included |
| ❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>) | <input checked="" type="checkbox"/> Verified, statement is acceptable |
| ❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>) | |

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

| | |
|---|---|
| ❖ Internal memoranda, telecons, etc. | |
| ❖ Minutes of Meetings | |
| • Regulatory Briefing (<i>indicate date of mtg</i>) | <input type="checkbox"/> No mtg |
| • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) | <input type="checkbox"/> N/A or no mtg |
| • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) | <input type="checkbox"/> No mtg |
| • EOP2 meeting (<i>indicate date of mtg</i>) | <input type="checkbox"/> No mtg |
| • Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) | |
| ❖ Advisory Committee Meeting(s) | <input type="checkbox"/> No AC meeting |
| • Date(s) of Meeting(s) | |
| • 48-hour alert or minutes, if available (<i>do not include transcript</i>) | |
| Decisional and Summary Memos | |
| ❖ Office Director Decisional Memo (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |
| Division Director Summary Review (<i>indicate date for each review</i>) | <input type="checkbox"/> None May 9, 2011 |
| Cross-Discipline Team Leader Review (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |
| PMR/PMC Development Templates (<i>indicate total number</i>) | <input checked="" type="checkbox"/> None |
| Clinical Information⁵ | |
| ❖ Clinical Reviews | |
| • Clinical Team Leader Review(s) (<i>indicate date for each review</i>) | |
| • Clinical review(s) (<i>indicate date for each review</i>) | |
| • Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) | <input type="checkbox"/> None |
| ❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>) | |
| ❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) | <input type="checkbox"/> None |
| ❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>) | <input type="checkbox"/> Not applicable |
| ❖ Risk Management <ul style="list-style-type: none"> • REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) • REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) • Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) | <input type="checkbox"/> None |
| ❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>) | <input type="checkbox"/> None requested |

⁵ Filing reviews should be filed with the discipline reviews.

| | |
|---|---|
| Clinical Microbiology <input type="checkbox"/> None | |
| ❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>) | <input type="checkbox"/> None |
| Clinical Microbiology Review(s) (<i>indicate date for each review</i>) | <input type="checkbox"/> None |
| Biostatistics <input type="checkbox"/> None | |
| ❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>) | <input type="checkbox"/> None |
| Statistical Team Leader Review(s) (<i>indicate date for each review</i>) | <input type="checkbox"/> None |
| Statistical Review(s) (<i>indicate date for each review</i>) | <input type="checkbox"/> None |
| Clinical Pharmacology <input type="checkbox"/> None | |
| ❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>) | <input type="checkbox"/> None |
| Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>) | <input type="checkbox"/> None |
| Clinical Pharmacology review(s) (<i>indicate date for each review</i>) | <input type="checkbox"/> None |
| ❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>) | <input type="checkbox"/> None |
| Nonclinical <input type="checkbox"/> None | |
| ❖ Pharmacology/Toxicology Discipline Reviews | |
| • ADP/T Review(s) (<i>indicate date for each review</i>) | <input type="checkbox"/> None |
| • Supervisory Review(s) (<i>indicate date for each review</i>) | <input type="checkbox"/> None |
| • Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>) | <input type="checkbox"/> None |
| ❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>) | <input type="checkbox"/> None |
| ❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>) | <input type="checkbox"/> No carc |
| ❖ ECAC/CAC report/memo of meeting | <input type="checkbox"/> None Included in P/T review, page |
| ❖ DSI Nonclinical Inspection Review Summary (<i>include copies of DSI letters</i>) | <input type="checkbox"/> None requested |
| Product Quality <input type="checkbox"/> None | |
| ❖ Product Quality Discipline Reviews | |
| • ONDQA/OBP Division Director Review(s) (<i>indicate date for each review</i>) | <input type="checkbox"/> None |
| • Branch Chief/Team Leader Review(s) (<i>indicate date for each review</i>) | <input type="checkbox"/> None |
| • Product quality review(s) including ONDQA biopharmaceutics reviews (<i>indicate date for each review</i>) | <input type="checkbox"/> None |
| ❖ Microbiology Reviews | <input type="checkbox"/> Not needed |
| <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (<i>indicate date of each review</i>) | |
| <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) (<i>indicate date of each review</i>) | |
| ❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (<i>indicate date of each review</i>) | <input type="checkbox"/> None |

| | |
|---|--|
| ❖ Environmental Assessment (check one) (original and supplemental applications) | |
| <input type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>) | |
| <input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>) | |
| <input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>) | |
| ❖ Facilities Review/Inspection | |
| <input type="checkbox"/> NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁶</i>) | Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable |
| <input type="checkbox"/> BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>) (<i>original and supplemental BLAs</i>) | Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation |
| ❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>) | <input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review) |

⁶ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental 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) **Or** 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.
- (3) **Or** 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) **And** 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.
- (3) **And** 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) **Or** 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.
- (3) **Or** 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 ODE's ADRA.

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
05/10/2011

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Monday, March 28, 2011 12:15 PM
To: 'lara.hansen@sandoz.com'
Cc: Akinsanya, Lara
Subject: Information Request: NDA 22-485 - Argatroban Injection (in Sodium Chloride)/ Sandoz

Dear Lara Hansen,

My name is Lara Akinsanya; I am the new Regulatory Project Manager assigned to NDA 22-485. The reviewers from the Division of Medication Error Prevention and Analysis are reviewing the Argatroban labels and labeling and have requested to see a sample of the bottle.

Please respond to this request by submitting a sample of the NDA 22-485 - Argatroban Injection (in Sodium Chloride) bottle officially to the NDA for review.

Thank You
Lara

Lara Akinsanya, M.S.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

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

/s/

LARA M AKINSANYA
03/28/2011

ACTION PACKAGE CHECKLIST

| APPLICATION INFORMATION ¹ | | |
|---|---------------------------------------|---|
| NDA # 22-485 BLA # N/A | NDA Supplement # N/A BLA STN # N/A | If NDA, Efficacy Supplement Type: N/A |
| Proprietary Name: Established/Proper Name: Argatroban Injection Dosage Form: Injection | | Applicant: Sandoz Inc. Agent for Applicant (if applicable): |
| RPM: Ebla Ali Ibrahim | | Division: Division of Hematology Products |
| <p>NDA: NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A 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). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p> | | <p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)): NDA 20-883 (Argatroban)</p> <p>Provide a brief explanation of how this product is different from the listed drug. 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. If no listed drug, explain.</p> <p><input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> Other (explain)</p> <p><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p> |
| ❖ Actions | | |
| <ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>January 17, 2011</u> | | <input type="checkbox"/> AP <input checked="" type="checkbox"/> TA <input type="checkbox"/> CR |
| <ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) | | <input checked="" type="checkbox"/> None |

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

| | |
|--|---|
| <p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p> | <input type="checkbox"/> Received |
| <p>❖ Application Characteristics²</p> | |
| <p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <input type="checkbox"/> Restricted distribution (21 CFR 601.42)</p> <p>Subpart I Subpart H <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Communication Plan <input type="checkbox"/> Submitted in response to a Pediatric Written Request <input type="checkbox"/> ETASU <input type="checkbox"/> REMS not required</p> <p>Comments:</p> | |
| <p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p> | <input type="checkbox"/> Yes, dates N/A |
| <p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p> | <input type="checkbox"/> Yes <input type="checkbox"/> No |
| <p>❖ Public communications (<i>approvals only</i>)</p> | |
| <ul style="list-style-type: none"> • Office of Executive Programs (OEP) liaison has been notified of action | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |
| <ul style="list-style-type: none"> • Press Office notified of action (by OEP) | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |
| <ul style="list-style-type: none"> • Indicate what types (if any) of information dissemination are anticipated | <input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other |

² Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

| | |
|--|--|
| ❖ Exclusivity | |
| <ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? | <input type="checkbox"/> No <input checked="" type="checkbox"/> Yes |
| <ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires: |
| <ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires: |
| <ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> | <input type="checkbox"/> No <input checked="" type="checkbox"/> Yes If yes, NDA # 20-883 and date exclusivity expires: May 5, 2011 |
| <ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires: |
| <ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires: |
| ❖ Patent Information (NDAs only) | |
| <ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. | <input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic. |
| <ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. | 21 CFR 314.50(i)(1)(i)(A) <input checked="" type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii) |
| <ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). | <input checked="" type="checkbox"/> No paragraph III certification Date patent will expire |
| <ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> | <input type="checkbox"/> N/A (no paragraph IV certification) <input checked="" type="checkbox"/> Verified |

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

| | |
|---|---|
| <p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p> | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |
|---|---|

CONTENTS OF ACTION PACKAGE

| | |
|---|--|
| ❖ Copy of this Action Package Checklist ³ | January 17, 2011 |
| Officer/Employee List | |
| ❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>) | <input checked="" type="checkbox"/> Included |
| Documentation of consent/non-consent by officers/employees | <input checked="" type="checkbox"/> Included |
| Action Letters | |
| ❖ Copies of all action letters (<i>including approval letter with final labeling</i>) | Action(s) and date(s) TA, January 13, 2011 |
| Labeling | |
| ❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>) | |
| <ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. | TA Label January 13, 2011 |
| <ul style="list-style-type: none"> • Original applicant-proposed labeling | March 17, 2010 |
| <ul style="list-style-type: none"> • Example of class labeling, if applicable | N/A |

³ Fill in blanks with dates of reviews, letters, etc.
Version: 8/25/10

| | |
|---|---|
| <ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) | <input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None |
| <ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. | N/A |
| <ul style="list-style-type: none"> • Original applicant-proposed labeling | N/A |
| <ul style="list-style-type: none"> • Example of class labeling, if applicable | N/A |
| <ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) | |
| <ul style="list-style-type: none"> • Most-recent draft labeling | |
| <ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) | N/A N/A |
| <ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) | <input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA December 13, 2010 <input type="checkbox"/> DRISK <input type="checkbox"/> DDMAC <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews MH - July 12, 2010; Peds - June 15, 2010 |
| Administrative / Regulatory Documents | |
| <ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) | December 13, 2010 <input type="checkbox"/> Not a (b)(2) December 21, 2010 <input type="checkbox"/> Not a (b)(2) January 12, 2011 |
| <ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) | <input type="checkbox"/> Included |
| <ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm | |
| <ul style="list-style-type: none"> • Applicant is on the AIP | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |
| <ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action |
| <ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>N/A</u> If PeRC review not necessary, explain: <u>505(b)(2)</u> • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) | <input checked="" type="checkbox"/> Included |
| <ul style="list-style-type: none"> ❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>) | <input checked="" type="checkbox"/> Verified, statement is acceptable |

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.
Version: 8/25/10

| | |
|---|---|
| ❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>) | December 21, 10, 2010, May 11, 2010, March 23, 2010 |
| ❖ Internal memoranda, telecons, etc. | |
| ❖ Minutes of Meetings | |
| • Regulatory Briefing (<i>indicate date of mtg</i>) | <input checked="" type="checkbox"/> No mtg |
| • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) | <input checked="" type="checkbox"/> N/A or no mtg |
| • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) | <input type="checkbox"/> No mtg 05/28/2008 |
| • EOP2 meeting (<i>indicate date of mtg</i>) | <input checked="" type="checkbox"/> No mtg |
| • Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) | |
| ❖ Advisory Committee Meeting(s) | <input checked="" type="checkbox"/> No AC meeting |
| • Date(s) of Meeting(s) | |
| • 48-hour alert or minutes, if available (<i>do not include transcript</i>) | |
| Decisional and Summary Memos | |
| ❖ Office Director Decisional Memo (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |
| Division Director Summary Review (<i>indicate date for each review</i>) | <input type="checkbox"/> None January 13, 2011 |
| Cross-Discipline Team Leader Review (<i>indicate date for each review</i>) | <input type="checkbox"/> None December 27, 2010 |
| PMR/PMC Development Templates (<i>indicate total number</i>) | <input checked="" type="checkbox"/> None |
| Clinical Information⁵ | |
| ❖ Clinical Reviews | |
| • Clinical Team Leader Review(s) (<i>indicate date for each review</i>) | December 14, 2010 |
| • Clinical review(s) (<i>indicate date for each review</i>) | December 14, 2010 |
| • Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |
| ❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input checked="" type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>) | Not Applicable - 505(b)(2) |
| ❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) | <input checked="" type="checkbox"/> None |
| ❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>) | <input checked="" type="checkbox"/> Not applicable |
| ❖ Risk Management | |
| • REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) | |
| • REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) | |
| • Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) | <input checked="" type="checkbox"/> None |
| ❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>) | <input checked="" type="checkbox"/> None requested |

⁵ Filing reviews should be filed with the discipline reviews.
Version: 8/25/10

| | |
|---|--|
| Clinical Microbiology <input checked="" type="checkbox"/> None | |
| ❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |
| Clinical Microbiology Review(s) (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |
| Biostatistics <input checked="" type="checkbox"/> None | |
| ❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |
| Statistical Team Leader Review(s) (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |
| Statistical Review(s) (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |
| Clinical Pharmacology <input type="checkbox"/> None | |
| ❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |
| Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>) | <input type="checkbox"/> None December 17, 2010 |
| Clinical Pharmacology review(s) (<i>indicate date for each review</i>) | <input type="checkbox"/> None December 14, 2010 |
| ❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>) | <input checked="" type="checkbox"/> None |
| Nonclinical <input type="checkbox"/> None | |
| ❖ Pharmacology/Toxicology Discipline Reviews | |
| • ADP/T Review(s) (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |
| • Supervisory Review(s) (<i>indicate date for each review</i>) | <input type="checkbox"/> None December 20, 2010 |
| • Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>) | <input type="checkbox"/> None December 20, 2010 |
| ❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |
| ❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> No carc |
| ❖ ECAC/CAC report/memo of meeting | <input checked="" type="checkbox"/> None Included in P/T review, page |
| ❖ DSI Nonclinical Inspection Review Summary (<i>include copies of DSI letters</i>) | <input checked="" type="checkbox"/> None requested |
| Product Quality <input type="checkbox"/> None | |
| ❖ Product Quality Discipline Reviews | |
| • ONDQA/OBP Division Director Review(s) (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |
| • Branch Chief/Team Leader Review(s) (<i>indicate date for each review</i>) | <input type="checkbox"/> None December 21, 2010 |
| • Product quality review(s) including ONDQA biopharmaceutics reviews (<i>indicate date for each review</i>) | <input type="checkbox"/> None December 21, 2010 |
| ❖ Microbiology Reviews | <input type="checkbox"/> Not needed December 21, 2010 |
| <input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (<i>indicate date of each review</i>) | |
| <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) (<i>indicate date of each review</i>) | |
| ❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (<i>indicate date of each review</i>) | <input checked="" type="checkbox"/> None |

| | |
|--|---|
| ❖ Environmental Assessment (check one) (original and supplemental applications) | |
| <input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>) | December 21, 2010 |
| <input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>) | |
| <input checked="" type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>) | December 21, 2010 |
| ❖ Facilities Review/Inspection | |
| <input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁶</i>) | Date completed: September 9, 2010 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable |
| <input type="checkbox"/> BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>) (<i>original and supplemental BLAs</i>) | Date completed: N/A <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation |
| ❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>) | <input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review) |

⁶ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental 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) **Or** 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.
- (3) **Or** 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) **And** 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.
- (3) **And** 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) **Or** 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.
- (3) **Or** 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 ODE's ADRA.

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/s/

EBLA ALI IBRAHIM
02/14/2011



NDA 22-485

FILING COMMUNICATION

Sandoz Inc.
Attention: Alison Sherwood
Manager, Regulatory Affairs
2555 W. Midway Blvd.
P.O. Box 446
Broomfield, CO 80038-0446

Dear Ms. Sherwood:

Please refer to your new drug application (NDA) dated March 16, 2010, received March 17, 2010, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Argatroban Injection (in Sodium Chloride).

We also refer to your submission dated April 1, 2010.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Standard**. Therefore, the user fee goal date is January 17, 2011.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by December 17, 2010.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Ebla Ali Ibrahim, Regulatory Project Manager, at (301) 796-3691.

Sincerely,

{See appended electronic signature page}

Janet Jamison, R.N., C.C.R.P
Acting Chief Project Management Staff
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|----------------------------|---------------------------|---------------------|--|
| ----- NDA-22485 | ----- ORIG-1 | ----- SANDOZ INC | ----- ARGATROBAN INJECTION 1 MG/ML |

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/s/

JANET K JAMISON
05/11/2010



NDA 22-485

NDA ACKNOWLEDGMENT

Sandoz Inc.
Attention: Alison Sherwood
Manager, Regulatory Affairs
2555 W. Midway Blvd.
P.O. Box 446
Broomfield, CO 80038-0446

Dear Ms. Sherwood:

We have received your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Argatroban Injection

Date of Application: March 16, 2010

Date of Receipt: March 17, 2010

Our Reference Number: NDA 22-485

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 16, 2010 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>

If you have any questions, call me at (301) 796-3691.

Sincerely,

{See appended electronic signature page}

Ebla Ali Ibrahim, M.S.
Regulatory Health Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|-------------------------|------------------------|-------------------|------------------------------|
| NDA-22485 | ORIG-1 | SANDOZ CANADA INC | ARGATROBAN INJECTION 1 MG/ML |

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/s/

EBLA ALI IBRAHIM
03/23/2010



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

P-IND 101,957

Sandoz Inc.
Attention: Beth Brannan
Director, Regulatory Affairs
2555 W. Midway Blvd.
Broomfield, CO 80038-0446

Dear Ms. Brannan:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Argatroban Injection.

We also refer to the telecon between representatives of your firm and the FDA on May 27, 2008. The purpose of the meeting was to discuss the content requirements for a drug application for Argatroban Injection.

A copy of the official minutes of the telecom is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1424.

Sincerely,

{See appended electronic signature page}

Diane Leaman
Acting Safety Project Manager
Division of Medical Imaging and Hematology
Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF TELECONFERENCE MINUTES

MEETING DATE: May 27, 2008
TIME: 12:30 PM to 2:00 PM
LOCATION: White Oak Campus Building 22, Room 1415
APPLICATION: IND 101,957
DRUG NAME: Argatroban, injection
TYPE OF MEETING: Type B (Pre-NDA)

MEETING CHAIR: Dr. Kathy Robie-Suh

MEETING RECORDER: Mrs. Diane Leaman

FDA ATTENDEES:

Division of Medical Imaging and Hematology Products (DMIHP)

Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader, Hematology
Min Lu, M.D., Medical Officer
Minh Ha Tran, D.O., Medical Officer
Diane Leaman, Acting, Safety Project Manager

Office of Pharmaceutical Science, Office of New Drug Quality Assurance, Division of
Pre-Marketing Assessment and Manufacturing Science, Branch V

Ravi Harapanhalli, Ph.D., Branch Chief
Dr. Eldon Leutzinger, Ph.D., Pre-Marketing Assessment Leader

Office of Clinical Pharmacology (OCP)

Young-Moon Choi, Ph.D., Clinical Pharmacology Team Leader

Office of Regulatory Policy/Division of Regulatory PI

Nancy Boocker, Supervisory Regulatory Counsel

Office of Pharmaceutical Science/Office of Generic Drugs

Tom Hinchliffe, Regulatory Manager, Team 10

Office of Pharmaceutical Science/Office of Generic Drugs/Division of Chemistry II

Naiqi Ya, Team Leader, Team 10
David Skanchy, Reviewer, Team 10

EXTERNAL CONSTITUENT ATTENDEES:

Sandoz, Inc. (USA)

Ms. Beth Brannan, Director Regulatory Affairs
Ms. Alison Sherwood, Senior Regulatory Affairs Associate

Sandoz Canada, Inc. (Boucherville, QC)

Ms. Suzanne Levesque, Head, Development Center
Ms. Maria Garofalo, Manager, Development Regulatory Center
Mr. Bocar Guisse, Regulatory Affairs Associate
Ms. Marie-Elaine Pepin, Project Manager
Mr. Daniel Abran, Manager, Pharmaceutical & Analytical Development
Ms. Anne-Marie Pépin, Manager, Clinical Research
Mr. Eric Vincent, Pharmaceutical Development Specialist

BACKGROUND:

On March 7, 2008, Sandoz, Inc. (Sandoz) requested a Pre-NDA meeting for argatroban injection to discuss the content requirements for this drug application. The sponsor plans to submit a 505 (b) (2) application. On April 24, 2008, Sandoz submitted the background package for this meeting. On May 27, 2008, Diane Leaman, SRPM sent Ms. Alison Sherwood, Senior Regulatory Affairs Associate, a copy of the draft FDA responses to Sandoz's meeting questions.

DISCUSSION ITEMS:

The following are the FDA responses to the questions in the April 24, 2008, background package from Sandoz. The format provides the firm's questions in *italics* followed by DMIHP's responses in **bolded** lettering. Discussion at the meeting is displayed in unbolded, un-italicized letters below subheads entitled "Discussion."

1. *Does the Agency concur with Sandoz Canada Inc 505(b)(2) filing strategy for the proposed new product? Sandoz Canada Inc, intends to file a 505(b)(2) application and support clinical safety and efficacy of the proposed Sandoz Argatroban Injection based on the following evidence:*
 - *Reference to previous findings of Safety and Efficacy Encysive's Argatroban Injection for use as an anti-coagulant in heparin-induced thrombocytopenia*
 - *Published scientific literature*

FDA Response:

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 C.F.R. 314.54, and the October 1999 Draft Guidance for Industry Applications Covered

by Section 505(b)(2)” available at <http://www.fda.gov/cder/guidance/guidance.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the agency's interpretation of this statutory provision. See Dockets 2001P-0323, 2002P-0447, and 2003P-0408.

If you intend to submit a 505(b)(2) application that relies for approval on FDA’s finding of safety and/or effectiveness for a listed drug, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug. In this case, you should establish a “bridge” between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is appropriate. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.

Discussion

It is your responsibility to make the case that reliance upon the available information supporting safety and efficacy of argatroban is scientifically appropriate for your application. Demonstration of biologic effects of your drug product may be helpful in supporting your application. You may propose to demonstrate pharmacodynamic activity in people. Pharmaceutical equivalence is a bridge. Please also refer to our comment in question 4.

2. *Can an AP rating be granted to Sandoz’ product?*

FDA Response:

No. Your proposed product would not be able to be AP rated to the Encysive Argatroban NDA due to it being a different potency, i.e., 1mg/ml (Sandoz product) vs 100mg/mL (Encysive product). The two are not pharmaceutical equivalents.

3. *Can both formulations be submitted under one NDA application?*

FDA Response:

No. The two formulations differ in regard to the sodium chloride and the dextrose components. Both sodium chloride and dextrose are considered as active ingredients and also constitute different formulations when in combination with other active ingredients. Therefore, your two proposed formulations must be submitted under separate NDA applications.

4. *Are comparative physico-chemical tests and the proposed anticoagulant in vitro test adequate to demonstrate equivalence between the Sandoz Canada product and the RLD and to request an in vivo bioequivalence waiver?*

Your approach to *in vitro* equivalence testing is inadequate as it relies only on anticoagulation activity testing from the USP Heparin Sodium monograph. We

recommend aPTT, PT, ACT and TT tests on pooled human plasma as a bridge to demonstrate sufficient similarity to the listed drug (21 CFR 320.22(d)(3)). You should also separately determine the effects of the other excipients in both products on coagulation parameters to ensure that none of the *in vitro* effects are caused by a change in excipients. We recommend a clinical pharmacodynamic (PD) study to support the *in vitro* study, depending on the findings of the CMC review and the *in vitro* data.

Provide comparative impurity profiles for your product and the listed drug. If any of the impurities in the drug product exceed the qualification thresholds based on ICH Q3BR2, then they need to be qualified.

Discussion

A one-time demonstration of product similarity, using all standard coagulation tests would be adequate. Appropriate placebos with saline and dextrose should be used in such studies and the listed drug should also be used as a comparator. Based on the adequacy of the results, a need for further PD study may be assessed.

5. *Can six months stability data be submitted at the time of filing?*

FDA Response:

This is acceptable provided you submit timely stability updates by the mid-cycle time-point. We expect to see at least 12 months of long-term stability data, 6 months of accelerated stability data or 12 months of intermediate stability data. The stability studies should include both upright and inverted configurations.

Discussion:

Because the formulation does not contain a solubilizer, it may be prone to crystallization on stability. The sponsor should provide a developmental report and risk assessment on the potential for crystallization of the drug from the formulation.

DECISIONS (AGREEMENTS) REACHED:

Sandoz said that they understood the FDA clarifications.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

None

ACTION ITEMS:

Meeting minutes will be sent to sponsor within 30 days.

ATTACHMENTS/HANDOUTS:

None.

Linked Applications

Sponsor Name

Drug Name

IND 101957

SANDOZ INC

ARGATROBAN

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/s/

DIANE V LEAMAN

05/28/2008