

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

021883Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template for DALVANCE (dalbavancin)

NDA# 21883
Product Name: DALVANCE (dalbavancin) for injection, for intravenous use

PMR Description: **2145-1**: Conduct a single dose pharmacokinetic (PK) trial in children from 3 months to less than 12 years of age.

PMR Schedule Milestones: Final Protocol Submission: May 2013 (submitted)
Trial Completion: March 2015
Final Report Submission: September 2015

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Dalbavancin is ready for approval for the treatment of acute bacterial skin and skin structure infections in adults.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

There is a need to evaluate pharmacokinetic parameters and safety of dalbavancin in the pediatric population.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

Not Applicable

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An open-label, single-dose trial with dalbavancin administered intravenously in 36 patients aged from 3 months to less than 12 years of age who have bacterial infections and are receiving background antibacterial therapy.

Required

Pharmacokinetic studies or clinical trials

5. Is the PMR clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

NDA # 21883
Product Name: DALVANCE (dalbavancin) for injection, for intravenous use

PMR Description: **2145-2: Conduct a single dose PK trial in neonates/infants from 0 to less than 3 months of age.**

PMR Schedule Milestones: Final Protocol Submission: May 2015
Trial Completion: November 2016
Final Report Submission: May 2017

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Dalbavancin is ready for approval for the treatment of acute bacterial skin and skin structure infections in adults.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

There is a need to evaluate pharmacokinetic parameters and safety of dalbavancin in neonates/infants.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

Not Applicable

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An open-label, single-dose trial with dalbavancin administered intravenously in 10 patients aged from 0 to less than 3 months of age who have bacterial infections and are receiving background antibacterial therapy.

Required

Pharmacokinetic studies or clinical trials

5. Is the PMR clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

NDA # 21883
Product Name: DALVANCE (dalbavancin) for injection, for intravenous use

PMR Description: **2145-3:** Conduct a Phase 3, randomized, comparator-controlled trial of dalbavancin in children from 3 months to 17 years of age with acute bacterial skin and skin structure infections (ABSSSI).

PMR Schedule Milestones:	Final Protocol Submission:	<u>December 2014</u>
	Trial Completion:	<u>December 2016</u>
	Final Report Submission:	<u>June 2017</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Dalbavancin is ready for approval for the treatment of ABSSSI in adults.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

There is a need to evaluate safety and effectiveness of dalbavancin in children from 3 months to 17 years of age for the treatment of ABSSSI.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

Not Applicable

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A randomized comparative trial of dalbavancin in children from 3 months to 17 years with ABSSSI known or suspected to be caused by susceptible gram positive organisms hospitalization for intravenous antibiotics. Approximately 240 patients will be enrolled.

Required

X Pharmacokinetic studies or clinical trials

5. Is the PMR clear, feasible, and appropriate?

- X Does the study/clinical trial meet criteria for PMRs or PMCs?
- X Are the objectives clear from the description of the PMR/PMC?
- X Has the applicant adequately justified the choice of schedule milestone dates?
- X Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

Not Applicable

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A randomized comparative trial of dalbavancin in children from birth to less than 3 months of age with ABSSSI known or suspected to be caused by susceptible gram positive organisms hospitalization for intravenous antibiotics. Approximately 60 patients will be enrolled.

Required

X Pharmacokinetic studies or clinical trials

5. Is the PMR clear, feasible, and appropriate?

- X Does the study/clinical trial meet criteria for PMRs or PMCs?
- X Are the objectives clear from the description of the PMR/PMC?
- X Has the applicant adequately justified the choice of schedule milestone dates?
- X Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

NDA# 21883
Product Name: DALVANCE (dalbavancin) for injection, for intravenous use

PMR Description: **2145-5:** Conduct US surveillance studies for five years from the date of marketing DALVANCE to determine if resistance to dalbavancin has developed in those organisms specific to the indication in the label for ABSSSI.

PMR Schedule Milestones:	Final Protocol Submission:	<u>September 2014</u>
	Study Completion:	<u>September 2019</u>
	Final Report Submission:	<u>September 2020</u>
	Other: Interim Reports Submission	<u>March 2016 (1st)</u>
		<u>March 2017 (2nd)</u>
		<u>March 2018 (3rd)</u>
		<u>March 2019 (4th)</u>
		<u>March 2020 (5th)</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Long-term microbiologic surveillance data are needed to study development of bacterial resistance against dalbavancin.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Development of bacterial resistance with use of dalbavancin.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments.

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A prospective study over a five-year period on the susceptibility of target bacteria to dalbavancin.

Required

Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)

5. Is the PMR clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

NDA# 21883
Product Name: DALVANCE (dalbavancin) for injection, for intravenous use

PMR Description: **2145-6:** Conduct studies to define the mechanism(s) of resistance for isolates identified as being resistant to dalbavancin during the surveillance period (five years from the date of marketing).

PMR Schedule Milestones:	Final Protocol Submission:	<u>September 2014</u>
	Study Completion:	<u>September 2019</u>
	Final Report Submission:	<u>September 2020</u>
	Other: Interim Reports Submission	<u>March 2016 (1st)</u>
		<u>March 2017 (2nd)</u>
		<u>March 2018 (3rd)</u>
<u>March 2019 (4th)</u>		
	<u>March 2020 (5th)</u>	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The knowledge of the mechanisms of resistance to dalbavancin is needed to understand a potential of the resistance to spread and to impact the efficacy of dalbavancin and possibly of other antibacterial drugs.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Development and spread of bacterial resistance with use of dalbavancin.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments.

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A study of the mechanisms of resistance to dalbavancin on dalbavancin resistant isolates identified during the 5-year US surveillance study (PMR 2145-5).

Required

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)

5. Is the PMR clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

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/s/

SUSMITA SAMANTA
05/22/2014

DMITRI IARIKOV
05/22/2014

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # NDA 21883

Product Name:

PMC #1 Description: Replace (b) (4) used for preparing the Master Cell Bank with a (b) (4).

PMC Schedule Milestones:

Interim Report:	<u>06/30/2015</u>
Final Report Submission:	<u>06/30/2016</u>

PMC #2 Description:

PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>MM/DD/YYYY</u>
	Other: _____	<u>MM/DD/YYYY</u>

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDA AA OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The (b) (4) used in plating colonies for preparing the Master Cell Bank (MCB) contains (b) (4) as one of the ingredients. Because of the inherent risk associated in using (b) (4) components in media, the fermentation industry over the past several years has progressively substituted the media with (b) (4) components. Since (b) (4) is being used only for MCB preparation, the risk is significantly lower and therefore will not require a PMR. Furthermore, the company, in response to an IR has committed to replace the (b) (4).

2. Describe the particular review issue and the goal of the study.

The goal of the study is to replace (b) (4) component without impacting the viability of the cells or diminishing the dalbavancin producing capability of the MCB.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

Please see response to question 2.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs only)

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/s/

BALAJEE SHANMUGAM
05/20/2014

DOROTA M MATECKA
05/20/2014

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 21-883

Application Type: New NDA

Name of Drug/Dosage Form: Dalvance (dalbavancin hydrochloride) for injection

Applicant: Durata Therapeutics, BV

Receipt Date: September 26, 2013

Goal Date: May 26, 2014

1. Regulatory History and Applicant's Main Proposals

This application is in the 4th cycle of review, having originally been submitted on December 21, 2004. Review issues of note over the past 3 cycles have included various clinical and manufacturing issues. The Sponsor withdrew the application during the 3rd cycle review in September of 2008, indicating that they were preparing to conduct an additional Phase 3 clinical trial to generate additional clinical data to support a future filing.

The Sponsor submitted their 4th cycle marketing application on September 26, 2013, proposing the use of DALVANCE (dalbavancin hydrochloride) in a two dose regimen in the treatment of Acute Bacterial Skin and Skin Structure Infections (ABSSSI).

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

Selected Requirements of Prescribing Information

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment: None

- YES** 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period:**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of-Cycle Period:**

- Select “YES” in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment: None

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment: None

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment: None

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment: None

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format

Selected Requirements of Prescribing Information

is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment: None

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment: None

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment: None

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment: None

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment: None

Selected Requirements of Prescribing Information

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

N/A 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths in Highlights

N/A 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Selected Requirements of Prescribing Information

Comment:

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment: None

Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment: None

Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment: None

Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment: None

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.
Comment:
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- YES** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

Comment:

Selected Requirements of Prescribing Information

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

Comment:

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- N/A** 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment: *Corrected in Sponsor's May 1, 2014 version.*

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

- N/A** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- N/A** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for:

- [text]
- [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

- [text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

- 1.1 [text]
- 1.2 [text]

2 DOSAGE AND ADMINISTRATION

- 2.1 [text]
- 2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 [text]
- 5.2 [text]

6 ADVERSE REACTIONS

- 6.1 [text]
- 6.2 [text]

7 DRUG INTERACTIONS

- 7.1 [text]
- 7.2 [text]

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

- 9.1 Controlled Substance
- 9.2 Abuse
- 9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Microbiology
- 12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

- 14.1 [text]
- 14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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/s/

JOSEPH C DAVI
05/13/2014

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

CLINICAL INSPECTION SUMMARY ADDENDUM

DATE: May 5, 2014

TO: J. Christopher Davi, Senior Regulatory Health Project Manager
Dmitri Iarikov, M.D., Medical Officer
Division of Anti-Infective Products

FROM: Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Assessment Branch
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 21883

APPLICANT: Durata Therapeutics, Inc.

DRUG: Dalbavancin (Dalvance™)

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority

INDICATION: For the treatment of acute bacterial skin and skin structure infections (abSSSI) caused by susceptible isolates of certain gram-positive microorganisms

CONSULTATION REQUEST DATE: November 1, 2013
INSPECTION SUMMARY GOAL DATE: March 28, 2014
DIVISION ACTION GOAL DATE: May 26, 2014
PDUFA DATE: May 26, 2014

ADDENDUM To CIS:

This is an addendum to the Clinical Inspection Summary for NDA 21883, dated April 10, 2014. The basis for this addendum is to provide the results of the complete review of the final Establishment Inspection Reports (EIR) for study Sites 118, 122 and 110, and to revise OSI's recommendation of the integrity of data generated by these sites in support of Study DUR001-301.

Background: The application is based, in part, on the results of two pivotal Phase 3 studies, DUR001-301, entitled, "A phase 3, randomized, double-blind, double-dummy study to compare the efficacy and safety of dalbavancin to a comparator regimen (vancomycin with possible switch to oral linezolid) for the treatment of acute bacterial skin and skin structure infections", and DUR001-302, entitled, "A phase 3, randomized, double-blind, double-dummy study to compare the efficacy and safety of dalbavancin to a comparator regimen (vancomycin with possible switch to oral linezolid) for the treatment of acute bacterial skin and skin structure infections". Six clinical sites were chosen for inspection: Site 118 (William Clark, M.D. (Deceased), Alan Nolasco, M.D. [Current]), Site 122 (Alan Nolasco, M.D.), Site 110 (Jennifer Johnson-Caldwell, M.D.), Site 121 (Robert Eyzaguirre, M.D.), Site 705 (Shaukat Shah, M.D.) and Site 607 (Vadym Shevchenko, M.D).

With respect to study Sites 118, 122 and 110, the sponsor closed these sites due to concerns related to Study DUR001-301 conduct by personnel at the sites. The nature of these concerns was not specified in the application. Based on the provided addresses; these sites used the same health care facilities and apparently were supported by the same Site Management Organization (SMO), (b) (4). Based upon the preliminary review of the EIRs and FDA Form 483s OSI recommended that the preliminary classification be upgraded to Official Action Indicated (OAI) for immediate enforcement review and follow up. In addition, OSI recommended that all data generated by these sites not be used in support of the respective indication. OSI indicated in the CIS dated April 10, 2014, that an addendum would be generated if conclusions change significantly upon final review of the EIRs.

Update: OSI held a Significant Action Meeting (SAM) on May 1, 2014, to review the final Establishment Inspection Reports' findings for Sites 118, 122 and 110 in detail and make a final consensus determination as to whether the data, all or in part, generated by these sites was reliable or not. The OSI consensus decision was made to downgrade the three site inspections to Voluntary Action Indicated (VAI), rather than OAI because there is evidence that the drug was prepared and administered to the patients. The unreliable drug transportation records should not have an impact on data integrity or human subject safety.

However, the site (Site 118) that Dr. Nolasco took over from Dr. Clark (deceased) was noted to have missing infusion records for 6/16 subjects (specifically 118-053, 118-068, 118-079, 118-108, 118-109 and 118-083) . Therefore, for these subjects, there were no drug administration

records. The review division may consider checking to see if these subjects completed the study and were considered in the analysis population. If they were, the review division may consider excluding these subjects from analysis, since there is no source documentation to confirm that the drug was administered. Alternatively, the review division might assess the treatment received for each impacted subject, and if treatment appears to be randomly distributed between the test article and active control, the missing infusion records are unlikely to make a difference in overall Study DUR001-301 interpretation.

The inspection findings conclude that the primary efficacy data were verifiable and there was no evidence of underreporting of SAEs. The remaining regulatory violations noted during the inspections of the three sites are considered unlikely to importantly impact data integrity.

Assessment of data integrity: Notwithstanding the six subjects referred to above, the data generated for Dr. Nolasco's site (118), for Dr. Nolasco's site (122) and Dr. Johnson-Caldwell's site (110), associated with Study DUR001-301 submitted to the Agency in support of NDA 21883, appear reliable based on available information.

The VAI classification will be finalized when a letter is issued to the inspected entity

{ See appended electronic signature page }

Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{ See appended electronic signature page }

Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
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CONCURRENCE:

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Kassa Ayalew, M.D., M.P.H.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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/s/

LAUREN C IACONO-CONNORS
05/05/2014

JANICE K POHLMAN
05/05/2014

KASSA AYALEW
05/06/2014

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: April 11, 2014

To: J. Christopher Davi, MS, Senior Regulatory Project Manager
Division of Anti-Infective Products

John Alexander, MD, Medical Team Leader/ CDTL
Division of Anti-Infective Products

From: Christine Corser, Pharm.D., Regulatory Review Officer
Office of Prescription Drug Promotion

Subject: NDA #021883
DALVANCE (dalbavancin) for injection, for intravenous infusion
only

As requested in your consult dated November 13, 2013, OPDP has reviewed the draft labeling for DALVANCE (dalbavancin) for injection, for intravenous infusion only.

The Office of Prescription Drug Promotion (OPDP) has reviewed the proposed PI. Our comments are based on the substantially complete version of the labeling titled, "DalvanceFDAProposedCLEAN27Mar14.doc" which was sent via email from DAIP on March 28, 2014.

OPDP's comments are provided in the attached, clean version of the labeling.

If you have any questions about our comments, please contact Christine Corser at 6-2653 or at Christine.Corser@fda.hhs.gov.

Thank you for the opportunity to provide comments on this PI.

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

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/s/

CHRISTINE G CORSER
04/11/2014

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: April 10, 2014

TO: J. Christopher Davi, Senior Regulatory Health Project Manager
Dmitri Iarikov, M.D., Medical Officer
Division of Anti-Infective Products

FROM: Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 21883

APPLICANT: Durata Therapeutics, Inc.

DRUG: Dalbavancin (Dalvance™)

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority

INDICATION(S): For the treatment of acute bacterial skin and skin structure infections (abSSSI) caused by susceptible isolates of certain gram-positive microorganisms

CONSULTATION REQUEST DATE: November 1, 2013
INSPECTION SUMMARY GOAL DATE: March 28, 2014
DIVISION ACTION GOAL DATE: May 26, 2014
PDUFA DATE: May 26, 2014

I. BACKGROUND:

Durata Therapeutics, Inc., seeks approval to market dalbavancin for injection for the treatment of acute bacterial skin and skin structure infections (abSSSI) caused by susceptible isolates of the following gram-positive microorganisms:

- *Staphylococcus aureus* (including methicillin-resistant [MRSA] isolates)
- *Streptococcus pyogenes*
- *Streptococcus agalactiae*
- *Streptococcus anginosus* group (including *S. anginosus*, *S. intermedius*, *S. constellatus*)

Dalbavancin is a second generation semi-synthetic lipoglycopeptide antibiotic structurally related to teicoplanin. Its mechanism of action involves the interruption of cell wall synthesis by binding to the terminal D-alanyl-D-alanine of the stem peptide in nascent cell wall peptidoglycan, thereby preventing cross-linking (transpeptidation and transglycosylation) of disaccharide subunits. This disruption of the cell wall results in bacterial cell death. During in vitro studies, dalbavancin was active against gram-positive bacteria. Its potent in vitro activity has been substantiated in various animal models of infection and it possesses a pharmacokinetic (PK) profile with a prolonged half-life, which allows once-weekly intravenous (IV) dosing.

The application is based, in part, on the results of two pivotal Phase 3 studies, DUR001-301, entitled, "A phase 3, randomized, double-blind, double-dummy study to compare the efficacy and safety of dalbavancin to a comparator regimen (vancomycin with possible switch to oral linezolid) for the treatment of acute bacterial skin and skin structure infections", and DUR001-302, entitled, "A phase 3, randomized, double-blind, double-dummy study to compare the efficacy and safety of dalbavancin to a comparator regimen (vancomycin with possible switch to oral linezolid) for the treatment of acute bacterial skin and skin structure infections". Study DUR001-301 planned for enrollment of 556 patients, 278 patients in each treatment group. In total, 573 patients were randomly assigned and included in the intent-to-treat (ITT) population. This was a multisite study: patients from 54 sites in 7 countries were enrolled, including 27 sites in the US. Study DUR001-302 planned for enrollment of 556 patients. In total, 739 patients were randomly assigned and included in the intent-to-treat (ITT) population. This was a multisite study: patients from 86 sites in 14 countries were enrolled. These studies were conducted under IND 60613.

Six clinical sites were chosen for inspection: Site 118 (William Clark, M.D. (Deceased), Alan Nolasco, M.D. [Current]), Site 122 (Alan Nolasco, M.D.), Site 110 (Jennifer Johnson-Caldwell, M.D.), Site 121 (Robert Eyzaguirre, M.D.), Site 705 (Shaukat Shah, M.D.) and Site

607 (Vadym Shevchenko, M.D). With respect to study Sites 118, 122 and 110, the sponsor closed these sites due to concerns related to study conduct by personnel at the site. The nature of these concerns was not specified. Based on the provided addresses; these sites used the same health care facilities and apparently were supported by the same Site Management Organization (SMO), (b)(4). Of note, the sponsor reported that for Site 122, the site records indicated that they enrolled 6 subjects, but the study dataset includes only 1 subject for this site. Also, the sponsor reported that for Site 110, the records indicated that only 1 subject was enrolled, but the dataset includes 6 subjects for this site.

Site 121 was the largest US site for Study DUR001-301, and Site 705 was the largest US site for Study DUR001-302. Site 607 was the largest site for enrollment in study DUR001-301 with a very high clinical response rate of approximately 99%. The applicant, Durata, was inspected to assess overall performance of these pivotal studies.

II. RESULTS (by Site):

Name of CI or Sponsor/CRO, Location	Protocol #, Site #, and # of Subjects	Inspection Date	Final Classification
CI#1: William Clark, M.D. (Deceased (b)(6)) Nolasco Alan, M.D. (Current since 2/12) Little York Medical Center 2708 Little York Rd Houston, TX 77093 Houston Foot and Ankle Care 7777 SW Freeway, Ste 506 Houston, TX 77074	Protocol: DUR001-301 Site Number: 118 Subjects: 16	February 12-24, 2014	Pending Interim classification: OAI
CI#2: Nolasco, Alan E, M.D. Westbury Medical Clinic 3400 Bissonnet St, 165 Houston, TX 77005 Houston Foot and Ankle Care 7737 Southwest Freeway Ste 790 Houston, TX 77023	Protocol: DUR001-301 Site Number: 122 Subjects: 1	February 10-12, 2014	Pending Interim classification: OAI

Name of CI or Sponsor/CRO, Location	Protocol #, Site #, and # of Subjects	Inspection Date	Final Classification
CI#3: Jennifer Johnson-Caldwell, M.D. 1315 St Joseph Pkwy, Ste 140 Houston, TX 77002 Houston Foot and Ankle Care 7777 SW Freeway, Ste 506 Houston, TX 77074	Protocol: DUR001-301 Site Number: 110 Subjects: 6	January 22, 2014 to February 6, 2014	Pending Interim classification: OAI
CI#4: Eyzaguirre, Robert D, M.D. Alliance Research 1932 E Anaheim St, Suite A Long Beach, CA 90813	Protocol: DUR001-301 Site Number: 121 Subjects: 38	December 13-26, 2013	Pending Interim classification: VAI
CI#5: Shah, Shaikat, M.D. St Joseph's Medical Associates 1805 N California St, Ste 201 Stockton, CA 95204	Protocol: DUR001-302 Site Number: 705 Subjects: 33	January 21-31, 2014	Pending Interim classification: VAI
CI#6: Vadym Shevchenko, M.D. Municipal Institution "Regional Hospital-Centre of Emergency and Disaster Medicine" of Cherkasy Regional Council, The Department of Orthopaedics and Traumatology, Vulytsya Mendelejeva, 3 Cherkasy, 18009 Ukraine	Protocol: DUR001-301 Site Number: 607 Subjects: 84	CANCELLED by FDA due to developing unrest in the region.	N/A

Name of CI or Sponsor/CRO, Location	Protocol #, Site #, and # of Subjects	Inspection Date	Final Classification
Sponsor: Durata Therapeutics, Inc. 322 East Main Street Branford, CT 06405	Protocol: DUR001-301 DUR001-302 Sites Reviewed: 607 110 118 122	February 11, 2014 To March 6, 2014	Pending Interim classification: VAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. CI#1: William Clark, M.D. (Original/Now Deceased) Nolasco Alan, M.D. (Current) (Site 118)

- a. What was inspected:** The site screened 90 subjects, 16 subjects were enrolled, and 11 completed the study. All available study records for the site subjects were audited. The site had no records for 74 prescreen failures. The record audit was conducted in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included informed consent review, entry criteria compliance, and comparison of source documentation to CRFs and data listings submitted to NDA 21883. Particular attention was paid to overall protocol compliance, adverse events, treatment regimens, and reporting of AEs in accordance with the protocol. The FDA field investigator also assessed patient histories/medical records, laboratory results, drug accountability, concomitant medication, monitoring activity and sponsor correspondence.
- b. General observations/commentary:** Dr. Nolasco assumed responsibility for this site, and signed a Form FDA 1572 in April 2012, after the previous Principal Investigator, Dr. William D. Clark, passed away (b) (6). Dr. Nolasco also assumed follow-up for all study subjects enrolled in the trial after November 2011, as well as all other Principal Investigator duties.

Overall the investigator's oversight of study conduct and execution of the protocol was not adequate. The inspection revealed potentially major GCP compliance violations. Briefly, study documentation/source records were

incomplete. For example, there were no study documents maintained/available for 74 study prescreen failures, and there were no signed informed consent documents for those 74 prescreen failures. Therefore, it appears that 74 of 75 subjects were not properly consented and the validity for the screen failures designation could not be verified.

Review of the drug accountability records included assessment of records for study drug preparation by the unblinded study-site pharmacist, transport of the study drug material from the pharmacy to the study site, and infusion records for each subject. Each of these events had a date and time attribution. Upon detailed review by the FDA field investigator, it was found that these records were not credible. There was conflict between the IV dosing time, test article transport time from unblinded study-site pharmacist to the principal investigator and the IV drug preparation time.

The site pharmacist and the site lead research coordinator, who were delegated the responsibility for maintaining CRFs and source data, along with investigational drug accountability, apparently were not documenting information contemporaneously according to the FDA field investigator. During the inspection the site staff admitted to creating source documentation related to the drug accountability records. The principal investigator, Dr. Nolasco, informed that he was not aware that test article accountability records were being created after the Monitor's review. He delegated the obligation of Test Article Accountability to the CRO's (b) (4).

He also stated that (b) (4) was delegated to CRF & document review and assured him that all documentation was compliant.

In addition, the site had numerous protocol violations, and had generally poor oversight of study conduct by the Principle Investigator.

REFUSALS: The site's Lead Research Coordinator would not make available the queries from the Monitor (CRO: (b) (4)) Site Visits used to assess protocol compliance.

A Form FDA 483 was issued, citing 3 inspectional observations.

Observation 1: Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation.

Specifically, source data, to include medical histories, photos and Informed Consent were missing or inaccurate.

Potential study subjects for the clinical trial, DUR001-301, were listed on the “Pre-Screening Log”. This form notates in a column entitled “Reason patient does not qualify”, specific reasons why the potential study subject does not qualify for this study, i.e., meet inclusion/exclusion criteria, required for randomization. This is a Screening Log that lists all Screen Failures.

Below is a list of approximately 74 potential study subjects who were “Screened” but not randomized into the clinical study.

#	Subject Initials	Screening Date	#	Subject Initials	Screening Date	#	Subject Initials	Screening Date
01	(b) (6)	04JUN2011	26	(b) (6)	06AUG2011	51	(b) (6)	06SEP2011
02		07JUN2011	27		09AUG2011	52		06SEP2011
03		10JUN2011	28		10AUG2011	53		07SEP2011
04		16JUN2011	29		12AUG2011	54		09SEP2011
05		20JUN2011	30		12AUG2011	55		09SEP2011
06		22JUN2011	31		15AUG2011	56		12SEP2011
07		24JUN2011	32		17AUG2011	57		12SEP2011
08		27JUN2011	33		17AUG2011	58		12SEP2011
09		01JUL2011	34		17AUG2011	59		13SEP2011
10		02JUL2011	35		18AUG2011	6		13SEP2011
11		05JUL2011	36		18AUG2011	61		14SEP2011
12		07JUL2011	37		20AUG2011	62		14SEP2011
13		07JUL2011	38		23AUG2011	63		14SEP2011
14		11JUL2011	39		23AUG2011	64		16SEP2011
15		13JUL2011	40		23AUG2011	65		16SEP2011
16		15JUL2011	41		24AUG2011	66		17SEP2011
17		15JUL2011	42		24AUG2011	67		19SEP2011
18		18JUL2011	43		26AUG2011	68		20SEP2011
19		21JUL2011	44		27AUG2011	69		21SEP2011
20		22JUL2011	45		29AUG2011	70		21SEP2011
21		23JUL2011	46		31AUG2011	71		26SEP2011
22		25JUL2011	47		31AUG2011	72		28SEP2011
23		26JUL2011	48		01SEP2011	73		28SEP2011
24		30JUL2011	49		01SEP2011	74		03OCT2011
25		01AUG2011	50		02SEP2011			

Observation 2: An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.

- a) Failed to notify the IRB of SAEs and study subject status. For example, several study subjects were hospitalized after receiving study drug but this was not reported to the IRB. In addition, study Subject #s 118-108 and 118-109 did not meet the minimum treatment period of 10-14 days treatment per the DUR001-301 protocol (Section 3.4-Duration of Treatment), based upon their randomization into this clinical trial.

However, the Principal Investigator considered both study subjects a “Clinical Success” at the End-Of-Trial (EOT).

b) Failed to supervise all participants in the clinical trial.

For example, the IV infusion documentation was the responsibility of the un-blinded Pharmacist and the other clinical staff. It included maintaining evidence of proper IV drug preparation, IV Infusion and IV drug transportation from the Pharmacist to the Principal Investigator.

However, for an extended period of time many of the documents needed to show protocol compliance of the study drug had not been documented. The IV Infusion logs for 06/16 (38%) randomized study subjects were not documented.

In addition, the site deviated from the Sponsor prescribed dosing formulation in calculating Creatine Clearance. This calculation is used to determine the randomization scheme (Study drug or placebo) of all patients in the clinical study.

c) Failed to follow the protocol. For example,

- i. Laboratory testing was not conducted in a timely manner. ASO/anti-DNAse titers are measured at BASELINE and at Short-Term Follow-Up (SFU), approximately four weeks into treatment. The DNAse titers 16 study subjects were not submitted to the laboratory for analysis in a timely manner.
- ii. Investigational drug was not dispensed per protocol. According to the protocol (Section 5.3.4 - Compliance), Intravenous treatment will be administered under the supervision of investigative site personnel and documented in the CRF. During the inpatient treatment phase, oral dosing date(s) and time(s) will be recorded in the CRF. However, study Subject #118-109 was infused on Day 08 at the Pharmacy instead of the location of the Principal Investigator. The Principal Investigator did not supervise this infusion and the CRF was not available to document this study drug infusion, contemporaneously.
- iii. Clinician (PI) progress notes were missing. The Principal Investigator for the DUR001-301 Clinical trial at Site #118 used electronic notes to document all office/outpatient visits and progress notes. They were added to the CRF in both electronically signed and unsigned forms. However, there were no physician’s notes documented or retained for study subject(s) #118-005, 118-017 and 118-068, to document as source data that a medical history and examination was conducted by the PI.

- iv. Infusion Logs were missing. The IV INFUSION WORKSHEET(s), used to document the date, start/stop times and the identification of the staff member who infused study drug, were not completed or retained for study subject(s) #118-053, 118-068, 118-079, 118-083, 118-108 and 118-109.

Observation 3: Investigational drug disposition records are not adequate with respect to dates and use by subjects.

Specifically, there appeared to be conflicts between the Interactive Randomization System (IVRS): a telephone system used to obtain the study treatment assignment and dispense blinded therapy and associate that patient with the next available treatment in the appropriate stratum on the randomization schedule, Investigational drug preparation logs (CRF), Investigation Drug - Transportation Logs from the Pharmacist location to the Principal Investigator's office and the Dosing times (per IV Infusion Logs).

For example,

- i. Infusion #01 - Subject #118002, dated 19APR2011, shows the IV Preparation time was equal to IVRS randomization call time.
- ii. Infusion #08 - Subject #118003, dated 29APR2011, shows the IV drug was transported to the PI before it was prepared.
- iii. Infusion #09 - Subject #118003, dated 29APR2011, shows the IV drug was transported to the PI before it was prepared.
- iv. Infusion #15 - Subject #118004, dated 02MAY2011, shows the IV drug was infused before it was prepared.
- v. Infusion #01 - Subject #118017, dated 31MAY2011, shows the IV drug was infused before it was prepared.
- vi. Infusion #06 - Subject #118020, dated 03JUN2011, shows the IV Preparation time & IV Dose time were 33.5 hours apart
- vii. Infusion #08 - Subject #118020, dated 08JUN2011, shows the IV drug Transport time (PI) was equal to IV drug infusion time.

The data for Investigational Drug Accountability were inaccurate and not written contemporaneously.

OSI Reviewer Comments: According to [REDACTED] (b) (4) - Lead Research Coordinator), Dr. [REDACTED] (b) (4) - Pharmacist) had not been maintaining the Investigational Drug Transportation Logs, therefore, when the Monitor persisted in her request to see them, [they] made them up. Since the dates and times were made up, they did not correlate to the actual drug preparation or IV infusion dates and times.

OSI reviewer Dr. Lauren Iacono-Connors discussed these inspectional observations with the FDA field investigator to gain insight into the preliminary inspection observations. Serious violations include alleged falsification of drug accountability and

use records prepared and/or maintained by this site. These actions appear to be deliberate in order to achieve site GCP compliance. In addition, the site did not retain attributable medical records, study records or obtained informed consent from prescreen failures assessed at this site for study entry criteria. Finally, it appears that study-site staff refused to provide certain study documents related to Monitoring activities to the FDA field investigator upon their request during the inspection.

This site is responsible for 90 screened subjects of whom 74 were prescreened and 16 of whom were enrolled and treated on study. Based upon a preliminary review of the EIR and FDA Form 483 OSI recommends that the preliminary classification be upgraded to OAI for immediate enforcement review and follow up. In addition, OSI recommends that all data generated by this site not be used in support of the respective indication. It is unclear at this time the extent to which source documentation is affected by these site practices.

- c. Assessment of data integrity:** The data for Dr. Nolasco's site (118), associated with Study DUR001-301 submitted to the Agency in support of NDA 21883, appear unreliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator and preliminary review of the EIR. An inspection summary addendum will be generated if conclusions change upon final review of the EIR.

CI#2: Nolasco Alan E, M.D. (Site 122)

- a. What was inspected:** The site screened 21 subjects, and 1 subject was enrolled. All available study records for the site subjects were audited. The site had no records for 17 prescreen failures. The record audit was conducted in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included informed consent review, entry criteria compliance, and comparison of source documentation to CRFs and data listings submitted to NDA 21883. Particular attention was paid to overall protocol compliance, adverse events, treatment regimens, and reporting of AEs in accordance with the protocol. The FDA field investigator also assessed patient histories/medical records, laboratory results, drug accountability, concomitant medication, monitoring activity and sponsor correspondence.
- b. General observations/commentary:** Overall the investigator's oversight of study conduct and execution of the protocol was not adequate. The inspection revealed potentially major GCP compliance violations. Briefly, study documentation/source records were incomplete. For example, there were no study documents maintained/available for all 17 study prescreen failures, and there were no signed informed consent documents for those 17 prescreen failures. However, the remaining 3 screen failures did have medical history and signed informed consent documents as well as records of laboratory testing.

Therefore, it appears that 17 of 20 subjects were not properly consented and the validity for the screen failures designation could not be verified.

Review of the drug accountability records included assessment of records for study drug preparation by the unblinded study-site pharmacist, transport of the study drug material from the pharmacy to the study site, and infusion records for each subject. Each of these events had a date and time attribution. Upon detailed review by the FDA field investigator, it was found that these records were not credible. There was conflicting information between the IV dosing time, test article transport time from unblinded study-site pharmacist to the principal investigator and the IV drug preparation time. There were inconsistencies among the times recorded for the investigational drug preparation and administration. For example, based upon site records, for infusion number 15 for Subject #122-213, the administration time was 0600 to 0630 on February 7, 2012. However, the drug preparation log completed by the study site pharmacist shows no study drug was prepared on February 7, 2012.

The site pharmacist and the site lead research coordinator, who were delegated the responsibility for maintaining CRFs and source data, along with investigational drug accountability, apparently were not documenting information contemporaneously according to the FDA field investigator. During the inspection the site staff admitted to creating source documentation related to the drug accountability records. The principle investigator, Dr. Nolasco, informed that he was not aware that test article accountability records were being created after the Monitor's review. He delegated the obligation of Test Article Accountability to the CRO's (b)(4) Pharmacist, Dr. (b)(4).

He also stated that (b)(4) was delegated to CRF & document review and assured him that all documentation was compliant.

REFUSALS: The Site's Lead Research Coordinator would not make available the queries from the Monitor (CRO: (b)(4)) Site Visits used to assess protocol compliance.

A Form FDA 483 was issued, citing 2 inspectional observations.

Observation 1: Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation.

Specifically, source data, to include case histories, Informed Consent and Physician's notes were missing or inaccurate.

- a) Potential study subjects for the clinical trial, DUR001-301 (Site 122), were listed on the "Pre-Screening Log". The form notates in the column

entitled “Reason patient does not qualify”, specific reasons why the potential study subject does not qualify for this study, i.e., does not meet inclusion/exclusion criteria, required for randomization. This is a Screening Log that lists all Screen Failures.

There were approximately 17 potential study subject initials documented.

Subject Initials	Screening Date	Subject Initials	Screening Date
(b) (6)	04JUL/2011	(b) (6)	22/AUG/2011
	08/JUL/2011		24AUG/2011
	12/JUL/2011		13/SEP/2011
	14/JUL/2011		15/SEP/2011
	18/JUL/2011		19/SEP/2011
	20/JUL/2011		20/SEP/2011
	20/JUL/2011		03/OCT/2011
	03/AUG/2011		
	11/AUG/2011		
	18/AUG/2011		

- b) There were no photo(s) maintained for the 09/17 (53%) study subject(s) that were prescreen failures due to the size or severity of their abSSSI as determined by the study subject during the consultation process (Screening) as documented on the “Pre-Screening Log”.
- c) There were no medical histories maintained for the 06/17 (35%) study subject(s) that were prescreen failures due to health questions asked during the consultation process (Screening) as documented on the “Pre-Screening Log”.
- d) 02/17 (12%) prescreened study subject(s) were minors diagnosed as having “cellulitis” although the age requirements for this clinical trial were 18 - 85 years of age.

Although an assessment of Inclusion/Exclusion criteria and an examination of the wound type(s) were conducted, there were no Informed Consent forms signed to identify these study subjects:

Patients having an abSSSI (suspected or confirmed to be caused by Gram-positive bacteria) defined for purposes of this study as an infection either involving deeper soft tissue or requiring significant surgical intervention due to. . .

- (01) Major cutaneous abscess,
- (02) Surgical site infection or Traumatic wound or
- (03) Cellulitis

Observation 2: Investigational drug disposition records are not adequate with respect to dates and quantity.

Specifically, drug accountability records are not accurate.

The study site had only one study subject complete the clinical trial: DUR001-301 (Site #122).

Study subject #122-213 had an IV Infusion Worksheet which documented that an infusion occurred on 07 FEB 2012 from 0600 to 0630 hours.

However, the Study Drug Preparation Log shows that study drug had not yet been prepared on 07 FEB 2012. The timeline for this activity is evidence that the data for Investigational Drug Accountability was not written contemporaneously.

***OSI Reviewer Comments:** OSI reviewer Dr. Lauren Iacono-Connors discussed these inspectional observations with the FDA field investigator to gain insight into the preliminary inspection observations. Serious violations include alleged falsification of drug accountability and use records prepared and/or maintained by this site. These actions appear to be deliberate in order to achieve site GCP compliance. In addition, the site did not retain attributable medical records, study records or obtained informed consent from prescreen failures assessed at this site for study entry criteria. Finally, it appears that study-site staff refused to provide certain study documents related to Monitoring activities to the FDA field investigator upon their request during the inspection.*

This site is responsible for 21 screened subjects, 17 of whom were prescreened and one of whom was enrolled and treated on study. Based upon a preliminary review of the EIR and FDA Form 483 OSI recommends that the preliminary classification be upgraded to OAI for immediate enforcement review and follow up. In addition, OSI recommends that all data generated by this site not be used in support of the respective indication. It is unclear at this time the extent to which source documentation is affected by these site practices.

- c. Assessment of data integrity:** The data for Dr. Nolasco's site (122), associated with Study DUR001-301 submitted to the Agency in support of NDA 21883, appear unreliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator and preliminary review of the EIR. An inspection summary addendum will be generated if conclusions change upon final review of the EIR.

2. CI#3: Jennifer Johnson-Caldwell, M.D. (Site 110)

- a. What was inspected:** The site screened 45 subjects (including 39 prescreened subjects), and 6 subjects were enrolled. Of the 6 enrolled subjects, 5 completed the study. All available study records for the 6 enrolled subjects were audited. The site had no records for the prescreen failures. The record audit was conducted in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included informed consent review, entry criteria compliance, and comparison of source documentation to CRFs and data listings submitted to NDA 21883. Particular attention was paid to overall protocol compliance, adverse events, treatment regimens, and reporting of AEs in accordance with the protocol. The FDA field investigator also assessed patient histories/medical records, laboratory results, drug accountability, concomitant medication, monitoring activity and sponsor correspondence.
- b. General observations/commentary:** Overall the investigator's oversight of study conduct and execution of the protocol was not adequate. The inspection revealed potentially major GCP compliance violations, and numerous inspection observations. Briefly, study documentation/source records were incomplete. For example, there were no study documents maintained/available for all 39 study prescreen failures, and there were no signed informed consent documents for the 39 prescreen failures. Therefore, it was not possible to verify that these subjects were properly consented prior to study-specified procedures. In addition, it was not possible to verify that the basis for the prescreen failures was valid.

Review of the drug accountability records included assessment of records for study drug preparation by the unblinded study-site pharmacist, transport of the study drug material from the pharmacy to the study site, and infusion records for each subject. Each of these events had a date and time attribution. Upon detailed review by the FDA field investigator, it was found that these records were not credible. There were numerous inconsistencies among the times recorded for the investigational drug preparation, transportation and administration. For example, based upon site records, for infusion number 14 for Subject #110-019, the administration time was initiated at the same time the study drug was in transit to the site. The site pharmacist and the site lead research coordinator, who were delegated the responsibility for maintaining CRFs and source data, along with investigational drug accountability, apparently were not documenting information contemporaneously according the FDA field investigator. During the inspection the site staff admitted to creating source documentation related to the drug accountability records. The principle investigator, Dr. Johnson-Caldwell informed that she was not aware that test article accountability records were being fabricated by her study staff.

REFUSALS: The Site’s Lead Research Coordinator would not make available the queries from the Monitor (CRO: (b)(4)) Site Visits used to assess protocol compliance.

A Form FDA 483 was issued, citing 4 inspectional observations. Below reflects the findings reported on an Amended Form FDA 483, dated March 13, 2014.

Observation 1: Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation.

Specifically, source data, to include case histories, Informed Consent and Physician's notes were missing or inaccurate.

- a) Potential study subjects for the clinical trial, DUR001-301 (Site 110), were listed on the “Pre-Screening Log”. The form notates in the column entitled “Reason patient does not qualify”, specific reasons why the potential study subject does not qualify for this study, i.e., does not meet inclusion/exclusion criteria, required for randomization. This is a Screening Log that lists all Screen Failures.

There were 39 initials documented.

Subject Initials	Screening Date						
(b)(6)	23/SEP/2011	(b)(6)	15/SEP/2011	(b)(6)	29/SEP/2011	(b)(6)	13/JUL/2011
	27/SEP/2011		04/AUG/2011		02/SEP/2011		13/JUL/2011
	29/SEP/2011		08/AUG/2011		03/SEP/2011		18/JUL/2011
	05/OCT/2011		11/AUG/2011		08/SEP/2011		21/JUL/2011
	16/SEP/2011		14/AUG/2011		09/SEP/2011		22/JUL/2011
	19/SEP/2011		18/AUG/2011		27/JUN/2011		22/JUL/2011
	21/SEP/2011		18/AUG/2011		27/JUN/2011		27/JUL/2011
	22/SEP/2011		20/AUG/2011		05/JUL/2011		29/JUL/2011
	12/SEP/2011		23/AUG/2011		08/JUL/2011		01/AUG/2011
	13/SEP/2011		24/AUG/2011		12/JUL/2011		

In addition, the log also documents that the study subjects do not have a fever, which is a study-related test, but there were no Informed Consent forms maintained or relevant medical histories.

There was no source data maintained to verify and corroborate why these study subjects were excluded.

- b) Protocol DUR001-301 (Site #110) incurred approximately 12 site visits. In 10 of 12 visits, there were monitoring errors attributed to failure to meet ALCOA standards – Attributable (who did what, when and why), Legible, Contemporaneous, Original (maintain original records of observations, it must match duplicates) and be Accurate (honesty).

An overall lack of progress notes and source discrepancies revealed source documentation which is not contemporaneous and, less often, inaccurate.

For example,

i. Monitoring Visit report dated 09APR12 found the following:

The Temperature Log eCRF page for Subject #110019 listed 1-2 temperatures obtained by site staff on 05, 06, 07, 09, 10, 11, 12 and 13 June 2011, however none of these temperatures were located in the subject's source record. For this reason, they were deleted from the eCRF during the visit.

ii. Monitoring Visit report dated 30AUG12 found the following:

The transport times from the time of drug prep to the time of delivery do not always appear to be realistic, for example delivery from pharmacy to infusion center in 10-15 minutes at 4 or 5 pm in Houston traffic. Conflicts in IVRS, drug prep, transportation and dosing times were due to the fact that the site personnel did not record times when the procedures were completed but recorded them later from memory which resulted in incorrect times.

iii. All CRF(s) showed the following on Baseline, Day 1, 2, 3, 8 and SFU:

I observed a pattern of not documenting the times in which temperatures were taken because these times could be used to cross-reference all test article accountability and IV study drug dosing.

iv. No source data (Physician's notes) in the file:

Study Subject #110-006

Study Subject #110-008

Observation 2: An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.

An observation concerning "a failure to report Adverse Events/Serious Adverse Events to the Sponsor and a failure to report Protocol Deviations to the IRB" was removed [from the original Form FDA 483] based upon a discussion with management.

Observation 3: Investigational drug disposition records are not adequate with respect to dates, quantity, and use by subjects.

Specifically, drug accountability records are not accurate.

For example, according to the drug accountability logs,

Study Subject #110-006:

- The study drug dose was prepared prior to receipt of lab report for creatinine. This level is required to determine the dosing for the IV study drug.

Study Subject #110-019:

- Infusion bags 14 & 15: administration time is prior to delivery time according to transport log
- Infusion bag 18: administration time is prior to prep time. In addition, the Transport Log shows delivery to infusion site occurred the day prior to prep.
- Infusion bag 20: Administration time is prior to prep time
- Infusion bag 22: Administration time is prior to prep time
- Infusion bag 24: Administration time is prior to prep time
- Infusion bag 25: Administration time is prior to delivery time per Transport Log
- Infusion bag 26: Administration time is prior to prep time
- Infusion bag 28: Administration time is prior to prep time

Study Subject #110-133

- Infusion bags 1, 2, & 3: prep time is prior to time of randomization call.
- Infusion bag 16: Administration time is prior to delivery time according to the transport log

Study Subject #110-154

- Infusion bag 1: drug was administered prior to delivery according to transport log, and at exact time physician's orders were signed; prep occurred two hours prior to receipt of lab report for creatinine. This level is required to determine the dosing for the IV study drug.
- Infusion bag 4: drug administration time is prior to delivery time per transport log.

The timeline for these activities is evidence that the data for Investigational Drug Accountability was not written contemporaneously.

Observation 4: Your computerized records do not provide that appropriate controls are implemented to ensure the integrity of the electronic data and signatures.

Specifically, the Principal Investigator stated during this inspection that she has been utilizing electronic records for submission of study-related physician's notes in the clinical trial: DUR001-301 (Site 110).

However, the clinic notes reviewed did not have an electronic signature.

For example, clinic notes for study Subject #110-019 on Visit Date 02/03/2011, show a printout of electronic transcription notes that do not document when the notes were written and can also be changed after input without changing the date.

There was no system validation conducted to show that the electronic notes are unalterable after signature, thus establishing a clear audit trail.

Observation 5: Failure to obtain informed consent in accordance with 21 CFR Part 50 from each human subject prior to conducting study-related tests.

Specifically, Study Subject #110-019 had blood tests (CLINICAL HAEMATOLOGY and CLINICAL CHEMISTRY) conducted on May 31, 2011 but their Informed Consent Form (ICF) was not signed until June 01, 2011.

There was no copy of the Informed Consent Form dated May 31, 2011, in the CRF as reported by a Research Coordinator, nor at the time of this inspection.

***OSI Reviewer Comments:** OSI reviewer Dr. Lauren Iacono-Connors discussed these inspectional observations with the FDA field investigator to gain insights into the preliminary inspection observations. Serious violations include alleged falsification of drug accountability and use records prepared and/or maintained by this site. These actions appear to be deliberate in order to achieve site GCP compliance. In addition, the site did not retain attributable medical records, study records or obtained informed consent from prescreen failures assessed at this site for study entry criteria. Finally, it appears that study-site staff refused to provide certain study documents related to Monitoring activities to the FDA field investigator upon their request during the inspection.*

This site is responsible for 45 screened subjects, 39 of whom were prescreened and 6 of whom were enrolled and treated on study. Based upon a preliminary review of the EIR and FDA Form 483 OSI recommends that the preliminary classification be upgraded to OAI for immediate enforcement review and follow up. In addition, OSI recommends that all data generated by this site not be used in support of the respective indication. It is unclear at this time the extent to which source documentation is affected by these site practices.

- c. Assessment of data integrity:** The data for Dr. Johnson-Caldwell's site (110), associated with Study DUR001-301 submitted to the Agency in support of NDA 21883, appear unreliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator and preliminary review of the EIR. An inspection summary addendum will be generated if conclusions change upon final review of the EIR.

3. CI#4: Robert D. Eyzaguirre, M.D. (Site 121)

- a. What was inspected:** The site screened 48 subjects, and 38 subjects were enrolled. Of the 38 enrolled subjects, 29 completed the study. The study records of 20 enrolled subjects were audited. The record audit was conducted in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to eCRFs and data listings submitted to NDA 21883, and focused on inclusion/exclusion criteria, adverse events, treatment regimens, reporting of AEs in accordance with the protocol, informed consent documents, patient histories, laboratory results, drug accountability, sponsor correspondence, and progress notes.
- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. The inspection revealed no significant deficiencies. Records and procedures were clear, and generally well organized. With one minor exception, there was no evidence of underreporting of adverse events. The primary efficacy endpoint data were verified. Procedures were observed to be performed by the appropriate personnel delegated with the task. Dr. Eyzaguirre appeared to maintain adequate oversight of the study. The study staff was relatively new to clinical trials and some mistakes were attributed to the lack of experience. For example, the site relied on the source documents from the sponsor to dictate all the procedures needed at each visit. The first 3 subjects did not have their Day 2 and Day 3 assessments done twice because the source documents provided only listed the assessments once. This was corrected with subsequent subjects once the site was notified. A Form FDA 483 was issued, citing one inspectional observation.

Observation 1: An investigation was not conducted in accordance with the investigational plan.

- a) The infection types for nine subjects were incorrectly categorized at the Baseline visit as "Abscess" when the correct categorization was "Cellulitis". The infection type was used as a stratification factor in the randomization of the study subjects.

- b) Safety assessments of study subjects did not take place as specified in the Protocol. For example,
 - i. Subject #121037 was missing EOT for serum clinical chemistry. The subject had blood drawn for EOT visit as required, however, the laboratory report stated “Wrong Sample Matrix Received” and did not provide any analytical results. The site did not follow up.
 - ii. Subject #121089 was missing EOT for hematology. The subject had blood drawn for EOT visit as required, however, the laboratory report stated “Insufficient Sample” and did not provide any analytical results. The site did not follow up.
 - iii. Subject #121032 did not have a pregnancy test performed at the Short-Term Follow-up visit (day 28). The subject had a urine pregnancy test at baseline.
 - iv. Subject #121093 did not have a pregnancy test performed at the Short-Term Follow-up visit (day 28). The subject had a urine pregnancy test at baseline.
- c) Nine subjects did not have temperatures taken during their Day 8 visit per protocol. Temperatures were to be taken at every visit to indicate any signs of systemic inflammation.
- d) Two subjects were switched from the twice daily IC study drug to oral therapy prior to meeting the criteria of at least six doses of vancomycin or vancomycin placebo per protocol.

OSI Reviewer Comments: With respect to item 1.a., the observation and OSI concern for possible incorrect categorization of these subjects for randomization purposes was discussed with the Review Division Medical Officer, Dr. Dmitri Iarikov on March 27, 2014. Dr. Iarikov explained that subjects may have presented with an infection type at baseline that included features of both abscess and cellulitis as evidenced by photographs of some skin lesions submitted in the application. The remaining inspectional observations summarized above were isolated or did not have an impact on efficacy and safety assessments.

- c. **Assessment of data integrity:** The data for Dr. Eyzaguirre’s site, associated with Study DUR001-301 submitted to the Agency in support of NDA 21883, appear reliable based on available information.

Note: Observations noted for this site are based on preliminary communications with the FDA investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the Establishment Inspection Report (EIR).

4. CI#5: Shaukat Shah, M.D. (Site 705)

- a. **What was inspected:** The site screened 39 subjects, and 33 subjects were enrolled. Of the 33 enrolled subjects 31 completed the study. The study

records of 20 enrolled subjects were audited. The record audit was conducted in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to eCRFs and data listings submitted to NDA 21883, and focused on inclusion/exclusion criteria, laboratory values, adverse events, treatment regimens, reporting of AEs in accordance with the protocol, informed consent documents, site monitoring, drug accountability, sponsor correspondence, and progress notes.

- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. The inspection revealed no significant deficiencies. Records and procedures were clear, and generally well organized. There was no evidence of underreporting of adverse events. The primary efficacy endpoint data were verified. Dr. Shah appeared to maintain adequate oversight of the study. There were some protocol deviations observed, as well as incidences of failure to maintain adequate and accurate records. Monitoring was performed at frequent intervals and appeared adequate. A Form FDA 483 was issued, citing two inspectional observations.

Observation 1: An investigation was not conducted in accordance with the investigational plan.

- a) Not all subjects were infused with study drug(s) within 24 hours of their preparation. Specifically, Subjects 705013-Infusion #4, 705017-infusion #7, and 705025-infusion #11 were infused with study drug that was beyond the 24 hour "Use By" limit by 12 minutes, 15 minutes and 90 minutes, respectively. The protocol specifies that reconstituted study drug material must be further diluted and administered within 24 hours.
- b) The site did not adequately ensure that study drug material was stored at temperatures with continuous monitoring, as specified by the protocol. The site stored study drug material in refrigerated storage that was not monitored for continuous temperature. On multiple occasions, the single once-daily ambient temperature in the storage container was recorded at 34°F, 2 degrees outside of the protocol-specified temperature range of 36- 46°F (2-8°C).

OSI Reviewer Comment: OSI Team Leader Jan Pohlman queried Dr. Mark Seggel, CMC reviewer, as well as Dr. Steven Donald, Microbiology Reviewer, to gain insight as to whether these two observations may have impacted safety or efficacy of dalbavancin. Dr. Seggel responded that based on the CMC available information, the storage conditions noted above should not impact on safety or efficacy of the drug. Reconstituted dalbavancin is stable for up to 48 hours and although the storage temperature was slightly lower than the reference range, the product was not frozen. Dr. Donald responded similarly. Specifically he informed that reconstituted vials may be stored either refrigerated at 2-8 °C (36-46 °F), or at controlled room temperature 20-25 °C (68-77 °F), but not frozen. Once diluted

into an IV bag or bottle as described, Dalbavancin may be stored either refrigerated at 2-8 °C (36-46 °F) or at a controlled room temperature of 20-25 °C (68-77 °F). The total time from reconstitution to dilution to administration should not exceed 48 hours. In addition, growth promotion studies using the reconstituted and diluted drug product over a 96 hour period indicated no detrimental effects over this time period in terms of growth of potential microbial contaminants. Therefore, the inspectional observations noted above should not impact the safety or efficacy of investigational product.

Observation 2: Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation.

- a) The site's record keeping practice was inconsistent, often having corrections without attribution and dating or reason for the change. White-out was used in pharmacy records. The site did maintain notes to file but inconsistently.

OSI Reviewer Comments: With respect to item 2.a., the FDA field investigator reported that the document control issues did not appear to be deliberate and no significant information changes were observed. Overall, records were maintained in reasonable order.

- c. **Assessment of data integrity:** The data for Dr. Shah's site, associated with Study DUR001-302 submitted to the Agency in support of NDA 21883, appear reliable based on available information.

Note: Observations noted for this site are based on preliminary communications with the FDA investigator. An inspection summary addendum will be generated if conclusions change upon review of the Establishment Inspection Report (EIR).

5. Sponsor: – Durata Therapeutics, Inc.

322 East Main Street, 3rd Floor
Branford, CT 06405

- a. **What was inspected:** The sponsor was inspected in accordance with the Sponsor/Monitor/CRO data validation compliance program, CP 7348.810. The inspection focused on adherence to protocol, and review of the firm's SOPs, monitoring reports and actions related to monitoring deficiencies.

The firm's files were reviewed to verify that there was documentation to show that the firm met the general responsibilities of a sponsor. The sponsor contracted with CROs for project management, clinical supply management, clinical monitoring, medical monitoring, data management and biostatistical analyses. Documentation was reviewed during this inspection for selected sites/personnel for the following: 1) organization and personnel including review of written agreements with CROs, 2) registration of studies on

clinicaltrials.gov, 3) selection and monitoring of clinical investigators including agreements, non-compliance, and training (including protocol specific and GCP training), 4) selection of monitors, monitoring procedures, plans and reports for the selected clinical sites, 5) Quality Assurance (QA) including the audit plan and QA audits, 6) safety and adverse event reporting, 7) data collection and handling including Standard Operating Procedures (SOPs), 8) record retention, 9) financial disclosure, 10) electronic records including transmission of data and system security, and 11) test article integrity and accountability.

- b. General observations/commentary:** Records and procedures were clear, and generally well organized. Comparison of primary efficacy endpoint data reported on the case report forms for Site #607 (Shevchenko, Ukraine) to the data listings provided with the assignment noted no discrepancies. There was no evidence of under-reporting of AEs/SAEs.

Monitoring files were reviewed extensively for the sites identified in the assignment and selected records from four other sites identified during the inspection. GCP deficiencies were noted at three sites (Sites 110, 118 and 122). Briefly, creatinine clearance was not calculated as required to properly determine dosing; study monitors failed to identify inconsistencies among the times recorded for the investigational drug preparation, transportation and administration of study drug at two sites, monitoring visit reports were not completed in accordance with the Clinical Monitoring Plan (specifically when clinical investigator non-compliance was identified), and there was a ten month interval between the site initiation visit and enrollment of a subject at one site.

The sponsor/monitor/CRO took appropriate steps to bring noncompliant sites into compliance. When the three sites could not be brought into compliance the sponsor took appropriate actions and closed these sites, then reported the site closures to the FDA in a timely fashion. Sites 110, 118 and 122 were closed during the study and FDA was notified. With the exceptions of Sites 110, 118 and 122, site monitoring appeared adequate for the overall study.

A one item Form FDA 483 was issued.

Observation 1: Failure to ensure proper monitoring of the study and ensure the study is conducted in accordance with the protocol and/or investigational plan.

- a) Investigational drug was prepared at and transported from an off-site Pharmacy for Site 110 (Johnson-Caldwell) and Site 118 (Clark/Nolasco). Study monitors failed to identify inconsistencies among the times recorded for the investigational drug preparation, transportation and administration. For example:

Subject #	Date	Infusion #	Preparation Time	Transport Time	Infusion Time
110019	06/07/11	14	16:30	18:35-18:55	18:30-20:30
110019	06/09/11	18	10:15	15:10-15:30*	06:00-08:00
110019	06/10/11	20	14:25	14:30-14:46	06:00-08:00
110019	06/11/11	22	09:15	09:30-09:52	06:30-08:30
110019	06/12/11	24	17:30	17:45-18:01	06:00-08:00
110019	06/12/11	25	17:30	17:45-18:01	18:00-20:00
110019	06/13/11	26	09:00	09:15-09:33	06:30-08:30
110019	06/14/11	28	09:00	09:10-09:38	06:30-08:30
110133	11/08/11	16	07:00	07:10-07:59	07:30-08:00
110154	11/19/11	1	10:40	10:50-11:08	10:45-11:15
110154	11/20/11	4	10:40	10:55-11:16	10:45-12:45
118003	04/29/11	8	08:45	06:00-06:22	18:05-18:40 NI**
118003	04/29/11	9	08:45	06:00-06:22	18:45-20:48 NI**
118004	05/02/11	15	07:30***	07:35-07:58	07:00-09:00
118017	05/31/11	1	17:00	17:05-17:30	16:30-17:00

* Delivery date is 06/08/11

**No inconsistency noted

***Date is recorded as 05/01/2011 yet date appears to be actually 05/02/2011 in that it follows a 05/01/2011 preparation time of 14:00 for Infusion #14 on the Study Drug Preparation Record.

- b) The Pharmacy Manual for Protocol DUR001-301 states that the initial dosing regimen of both dalbavancin and vancomycin should be chosen based on an assessment of renal clearance or creatinine clearance as calculated by the Cockcroft-Gault equation, based on serum creatinine concentrations obtained at Baseline, and using ideal body weight instead of actual weight. The creatinine clearance was not calculated as required for all subjects treated with study drug at Clinical Sites #110 (Caldwell-Johnson), #118 (Clark/Nolasco), and #122 (Nolasco). Study monitors did not identify this protocol deviation until several months after all 23 of the subjects from these three sites completed the study. In addition, this protocol deviation was not reported for Site #118 (Clark/Nolasco) in the Clinical Study Report Listing 16.8.1.1 entitled "Listing of Important Protocol Deviations".
- c) According to the Clinical Monitoring Plan, the Monitor has five working days from the last day of the monitoring visit to write the monitoring visit report and the Reviewer has five working days for review and resolution of corrections by the Monitor. The report must be finalized and sent to the Sponsor within 15 working days after the monitoring

visit. Monitoring Visit Reports were not always completed in accordance with the Clinical Monitoring Plan. For example:

Site #	Monitoring Visit Date	Date Signed by Monitor	Date Signed by Reviewer	Number of Working Days after Monitoring Visit
110	01/11-12/12	03/04/12	03/06/12	36
110	03/12-22/12	04/17/12	04/17/12	18
118	1/19/12	02/29/12	02/29/12	28
122	02/14/12	04/13/12	04/13/12	42
122	05/02-03/12	05/31/12	05/31/12	19

- d) Clinical Site #122 (Nolasco) had a site initiation visit on 03/28/11. The first subject was screened on 01/30/12. Although 10 months had passed since the initial study protocol training, the site received no additional training prior to screening the first subject. The first monitoring visit was performed on 02/14/12 and the monitor answered "no" to the question "were all study-related duties appropriately conducted by qualified, authorized & trained individuals only?" and commented that the clinical investigator would be informed that "it is recommended that he ensure that his study coordinators are provided with adequate education on microbiology procedures."

- c. **Assessment of data integrity:** The data generated at this site, as it pertains to Studies DUR001-301 and DUR001-302 were audited in accordance with the sponsor-monitor oriented BIMO compliance program, CP 7348.810. The findings are that the data from this sponsor, with the exception of Sites #110, 118 and 122 [Study DUR001-301], submitted to the Agency in support of NDA 21883, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Based on the review of preliminary inspectional findings for clinical investigators Robert Eyzaguirre, M.D. (Site 121) and Shaukat Shah, M.D. (Site 705), and the Sponsor, Durata Therapeutics, Inc., the overall data for studies DUR001-301 and DUR001-302, submitted to the Agency in support of NDA 21883, appear reliable based on available information, with the exception of data generated by Sites 110, 118 and 122 (Study DUR001-301).

Based on the review of preliminary inspectional findings for clinical investigators William Clark, M.D. (Deceased), Alan Nolasco, M.D. [Current] (Site 118), Alan Nolasco, M.D. (Site 122) and Jennifer Johnson-Caldwell, M.D. (Site 110), the data generated by these sites appear unreliable based on available information and, as such, it is recommended that it not be used in support of the respective indication.

The preliminary classification for clinical investigators Dr. Robert Eyzaguirre, Dr. Shaukat Shah and for the sponsor, Durata Therapeutics, Inc., is Voluntary Action Indicated (VAI). The record audit of subject records at these clinical sites (121 and 705) included comparison of source documentation to CRFs and data listings submitted to NDA 21833, and focused on inclusion/exclusion criteria, laboratory values, adverse events, treatment regimens, reporting of AEs in accordance with the protocol, informed consent documents, site monitoring, drug accountability, sponsor correspondence, and progress notes.

With respect to Site #121 (Dr. Robert Eyzaguirre) the inspection revealed no significant deficiencies. Records and procedures were clear, and generally well organized. With one minor exception, there was no evidence of underreporting of adverse events. The primary efficacy endpoint data were verified. Procedures were observed to be performed by the appropriate personnel delegated with the task. Dr. Eyzaguirre appeared to maintain adequate oversight of the study. The inspectional observations should not importantly impact study DUR001-301 safety and efficacy assessments.

With respect to Site #705 (Dr. Shaukat Shah) the inspection revealed no significant deficiencies. Records and procedures were clear, and generally well organized. There was no evidence of underreporting of adverse events. The primary efficacy endpoint data were verified. Dr. Shah appeared to maintain adequate oversight of the study. There were some protocol deviations observed, as well as incidences of failure to maintain adequate and accurate records. Monitoring was performed at frequent intervals and appeared adequate. The inspectional observations should not importantly impact study DUR001-302 safety and efficacy assessments.

With respect to the sponsor's conduct of Studies DUR001-301 and DUR001-302, the inspection assessed of primary efficacy endpoint data reported on the case report forms for Site #607 (Shevchenko, Ukraine) to the data listings provided with the assignment noted no discrepancies. There was no evidence of under-reporting of AEs/SAEs. Monitoring files were reviewed extensively for the sites identified in the assignment and selected records from four other sites identified during the inspection. GCP deficiencies were noted at three sites (Sites #110, 118 and 122). Briefly, creatinine clearance was not calculated as required to properly determine dosing; study monitors failed to identify inconsistencies among the times recorded for the investigational drug preparation, transportation and administration of study drug at two sites, monitoring visit reports were not completed in accordance with the Clinical Monitoring Plan (specifically when clinical investigator non-compliance was identified), and there was a ten month interval between the site initiation visit and enrollment of a subject at one site. The sponsor/monitor/CRO took appropriate steps to bring noncompliant sites into compliance. When three sites could not be brought into compliance the sponsor took

appropriate actions and closed these sites, then reported the site closures to the FDA in a timely fashion. Sites #110, 118 and 122 were closed during the study and FDA was notified. With the exceptions of Sites #110, 118 and 122, site monitoring appeared adequate for the overall study.

The preliminary classification for clinical investigators William Clark, M.D. (Deceased), Alan Nolasco, M.D. [Current] (Site 118), Alan Nolasco, M.D. (Site 122) and Jennifer Johnson-Caldwell, M.D. (Site 110) is Official Action Indicated (OAI). The data generated by these sites, as it pertains to Study DUR001-301, appear unreliable based on available information and, as such, it is recommended that it not be used in support of the respective indication.

Briefly, these three Sites were all supported by the same Site Management Organization (SMO), (b) (4). Inspection of the three sites revealed similar significant compliance violations related to records management and drug accountability. It is these observations that call into question the ability to verify the integrity of protocol practices at the sites, as well as source data. Serious violations include alleged falsification of drug accountability and use records prepared and/or maintained by these sites. These actions appear to be deliberate in order to achieve site GCP compliance. In addition, these sites did not retain attributable medical records, study records or obtained informed consent from prescreen failures assessed for study entry criteria. Finally, it appears that study-site staff refused to provide certain study documents related to Monitoring activities to the FDA field investigator upon their request during the inspection.

Note: The observations noted above are based on the preliminary communications provided by the FDA field investigators and preliminary review of available EIRs. An inspection summary addendum will be generated if conclusions change significantly upon receipt and/or final review of the EIRs.

{ See appended electronic signature page }

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04/11/2014

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: February 28, 2014
Requesting Office or Division: Division of Anti-Infective Products (DAIP)
Application Type and Number: NDA 021883
Product Name and Strength: Dalvance (Dalbavancin) for Injection, 500 mg per vial
Product Type: Single Ingredient Product
Rx or OTC: Rx
Applicant/Sponsor Name: Durata Therapeutics
Submission Date: September 25, 2013
OSE RCM #: 2013-2605
DMEPA Primary Reviewer: Aleksander Winiarski, PharmD
DMEPA Acting Team Leader: Julie Neshiewat, PharmD, BCPS

1 REASON FOR REVIEW

Durata Therapeutics submitted labels and labeling for Dalvance (Dalbavancin) for Injection, 500 mg per vial, under NDA 021883. Dalvance is a new molecular entity.

The Division of Anti-Infective Products (DAIP) requested that we review the submitted Dalvance label and labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	N/A
Previous DMEPA Reviews	N/A
Human Factors Study	N/A
ISMP Newsletters	N/A
Other	N/A
Proposed Labels and Labeling	B

N/A = Not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The submitted insert labeling contains symbols which are listed on Institute for Safe Medication Practices' (ISMP) list of error-prone abbreviations¹ throughout the dosage and administration sections and require replacement with the corresponding words. Additionally, some important use and administration information may require further revisions to clearly communicate important information. We provide recommendations in section 4.1 below.

¹ Available at: www.ismp.org/tools/errorproneabbreviations.pdf. Accessed January 30, 2014.

The submitted Dalvance carton labeling and container label contain several unclear and/or non-customary statements in non-customary locations, which require revision to effectively communicate important prescribing and use information and to help minimize medication errors. Also, the Applicant did not indicate where the lot and expiration dates will be presented, which are regulatory requirements on container labels and carton labeling. Additional changes to improve readability may also be appropriate. We provide recommendations in section 4.2 below.

4 CONCLUSION & RECOMMENDATIONS

The submitted label and labeling for Dalvance 500 mg per vial may be improved to communicate important prescribing and use information and to improve readability.

4.1 RECOMMENDATIONS FOR THE DIVISION

DMEPA provides the following comments for the Division's consideration.

A. Full Prescribing Information (FPI) and Highlights of Prescribing Information (HPI) section 2 Dosage and Administration

1. The sections contain the symbol and abbreviation '<' and 'IV' which are listed on Institute for Safe Medication Practices' (ISMP) list of error-prone abbreviations². Replace '<' with the word "less than" and 'IV' with the word "intravenous" to help prevent misinterpretation. Additionally, replace the hyphen symbol '-' between numbers with the word "to" for clarity.

B. Full Prescribing Information (FPI) section 2.3 Preparation and Administration

1. A number corresponding to a measurement should always contain the corresponding units. Therefore, include the units mg/mL after the number 1 to read "...concentration of 1 mg/mL to 5 mg/mL."
2. To help ensure correct use of the product and reduce clutter and redundant statements (dilution and reconstitution subsections), in the second paragraph, delete the negative statement "(b) (4)" and "Saline-based infusion solutions may cause precipitation and should not be used".

Additionally, revise the statement "(b) (4)"
"DALVANCE (dalbavancin) for injection must be reconstituted with Sterile Water for

² Available at: www.ismp.org/tools/errorproneabbreviations.pdf. Accessed January 30, 2014.

Injection, USP, and subsequently diluted **only** with 5% Dextrose Injection, USP, to a final concentration of 1 mg/mL to 5 mg/mL.”

3. To help ensure correct use of the product, revise the order of the negative statement [REDACTED] ^{(b) (4)} to appear after the affirmative/informational statement, to read: “The compatibility of reconstituted DALVANCE with intravenous medications, additives, or substances other than 5% Dextrose Injection, USP has not been established”. “Do Not Co-Infuse Dalvance with other medications or electrolytes”.

C. Full Prescribing Information (FPI) and Highlights of Prescribing Information (HPI) section 3 Dosage Forms and Strengths

1. We recommend revising “single-use” to “single-dose.”

4.2 RECOMMENDATIONS FOR THE APPLICANT

DMEPA recommends the following revisions prior to the approval of the NDA:

A. Vial Labels

1. Revise the presentation of the strength statement to “500 mg per vial”, which is the customary format for injectable products that require reconstitution. Additionally, revise the order of important prescribing information on the Principal Display Panel (PDP) to the customary format, to appear as:

Dalvance

(dalbavancin) for injection

500 mg per vial

2. Revise the statement “[REDACTED]” ^{(b) (4)} to the following customary statement “Sterile Single Dose Vial” and relocate it from above the proprietary name to under the “For Intravenous Infusion Only” statement.
3. Revise the statement “[REDACTED]” ^{(b) (4)} to the following customary statement “Discard Unused Portion” and relocate it from the side panel to under the “Sterile Single Dose Vial” statement, as per A2 above.
4. The Durata logo and manufactured for information is redundant on the PDP and creates clutter. To improve the prominence of important prescribing information and to accommodate appropriate space for the revisions above, significantly reduce

the size of the logo (by a least half or more) or consider removing the logo. Additionally, reduce the size of the “manufactured for” information and relocate it to the side panel.

5. Please indicate where the required lot number and expiration date will appear on the label as per 21 CFR 201.100(b) and 21 CFR 201.17.
6. The location of the “Rx only” statement appears in close proximity to the proprietary name and may be distracting, reduce the size of the statement and relocate it away from other important prescribing information, such as to the upper left corner.
7. To help ensure correct use of the product and reduce clutter and redundant statements, delete the negative statement “(b) (4).” In addition, revise the following statement from all capitals “FOR INFUSION, DILUTE THE RECONSTITUTED SOLUTION WITH 5% DEXTROSE INJECTION, USP, to a ...” to bolded title case and to appear as “**For Infusion, dilute the reconstituted solution only with 5% dextrose injection, USP, to a ...**”
8. To reduce clutter on the side panel, revise the following statement “(b) (4)
(b) (4)
(b) (4)” to read: “Dosage and Administration: See full prescribing information”.
9. A number associated with measurement should always contain the corresponding units. Therefore, include the units mg/mL after the number 1 to read “...concentration of 1 mg/mL to 5 mg/mL.

B. Carton Labeling

1. See A1 through A9 above.
2. Revise the net quantity statement from “one” (which was part of the statement (b) (4)) to either “1 vial” or “one vial”, and relocate it away from important prescribing information, such as to the bottom right or left corner of the panel.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Dalvance from the submitted insert labeling on January 9, 2014.

Table 2. Relevant Product Information for Dalvance	
Active Ingredient	Dalbavancin
Indication	Treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible strains of the following Gram-positive microorganisms: <i>Staphylococcus aureus</i> (including methicillin-susceptible and methicillin-resistant strains) <i>Streptococcus pyogenes</i> <i>Streptococcus agalactiae</i> <i>Streptococcus anginosus</i> group (including <i>S. anginosus</i> , <i>S. intermedius</i> , <i>S. constellatus</i>)
Route of Administration	Intravenous infusion
Dosage Form	Powder for injection
Strength	500 mg per vial
Dose and Frequency	Adults: 1 g on day 1 then 500 mg on day 8 Dose adjustments for renal function include a reduction to 750 mg on Day 1 and 375 mg on Day 8
How Supplied	Individually packaged vials
Storage	Prior to reconstitution, store at room temperature After reconstitution and/or dilution store at room temperature or under refrigerated conditions for up to 48 hours
Container Closure	Glass vial

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,³ along with postmarket medication error data, we reviewed the following Dalvance labels and labeling submitted by Durata Therapeutics on January 9, 2014.

B.2 Label and Labeling Images



(b) (4)

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

³ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI: 2004.

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/s/

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