

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125422Orig1s000**

**OTHER REVIEW(S)**



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/s/  
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WILLIAM M BOYD  
10/17/2012

WILEY A CHAMBERS  
10/17/2012

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

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NDA/BLA # 125422  
Product Name: Jetrea (ocriplasmin) Intravitreal Injection, 2.5 mg/mL

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PMC/PMR Description: Validate (b) (4) with sufficient controls for  
PMC #19 use with the LAL endotoxin assay using 3 lots of Ocriplasmin Drug substance /Drug product samples.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>03/29/2013</u>
	Other: _____	<u>MM/DD/YYYY</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: Improvement to the method

(b) (4)

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.”

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

*If not a PMR, skip to 4.*

- **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:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- 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?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC 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?

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**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.*

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## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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NDA/BLA # 125422  
Product Name: Jetrea (ocriplasmin) Intravitreal Injection, 2.5 mg/mL

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PMC/PMR Description: Validate yeast and mold recovery in TSA and demonstrate the comparability to the traditional compendial method or requalify the method suitability using SDA plates for mold & yeast incubated at 30-35°C for ≤ 5 days as per USP<61> with 3 lots of in process samples.  
PMC # 20

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PMR/PMC Schedule Milestones: Final Protocol Submission: MM/DD/YYYY  
Study/Trial Completion: MM/DD/YYYY  
Final Report Submission: 03/29/2013  
Other: \_\_\_\_\_ MM/DD/YYYY

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
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- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other: Improvement to the method

Currently, for bioburden testing TSA is used for both bacteria and yeast and mold (b) (4) USP <61> Bioburden method qualification recommends TSA for bacteria incubated for ≤ 3 days at 30-35°C and SDA for mold & yeast incubated for ≤ 5 days at 30-35°C and for bioburden testing, TSA plates incubated for a minimum of 3 days and SDA for a minimum of 5 days.

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.”

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

*If not a PMR, skip to 4.*

- **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:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- 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?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC 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?
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**PMR/PMC Development Coordinator:**

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/s/  
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LAKSHMI RANI NARASIMHAN  
10/12/2012

PATRICIA F HUGHES TROOST  
10/15/2012

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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NDA/BLA # 125422  
Product Name: Jetrea (ocriplasmin) Intravitreal Injection, 2.5 mg/mL  
PMC/PMR Description (Microbial Quality Review of Drug Substance): Submit new limits for bioburden (action limit (b) (4) and endotoxin (action limit (b) (4) alert limit (b) (4) in (b) (4) We request that you submit the new limits as a CBE-0.  
PMC #21

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PMR/PMC Schedule Milestones: Final Protocol Submission: MM/DD/YYYY  
Study/Trial Completion: MM/DD/YYYY  
Final Report Submission: MM/DD/YYYY  
Other: Submission of new action limits 03/30/2013

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 (b) (4)  
 Other

The (b) (4) has no endotoxin limits and (b) (4) bioburden limits (b) (4) (b) (4). The sponsor agreed to match the microbial quality action limits (bioburden and endotoxin) of the (b) (4). The sponsor will amend the BLA to include the new limits.

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.”

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

*If not a PMR, skip to 4.*

- **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:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- 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?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC 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?

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**PMR/PMC Development Coordinator:**

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## PMR/PMC Development Template

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NDA/BLA #	125422
Product Name:	Jetrea (ocriplasmin) Intravitreal Injection, 2.5 mg/mL
PMC/PMR Description (Microbial Quality Review of Drug Substance): PMC #22	Qualify bioburden and endotoxin methods for (b) (4) and (b) (4) and establish bioburden and endotoxin specifications based on an assessment of risk to ocriplasmin product quality. We request that you submit the outcome of the risk assessment and the bioburden and endotoxin specifications as a CBE-0.
PMR/PMC Schedule Milestones:	Final Protocol Submission: <u>MM/DD/YYYY</u> Study/Trial Completion: <u>MM/DD/YYYY</u> Final Report Submission: <u>03/30/2013</u> Other: <u>Submission of new Specifications</u> <u>03/30/2013</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

(b) (4) are complex raw materials used in the manufacture of ocriplasmin drug substance without bioburden and endotoxin specifications. The sponsor agreed to establish methods to measure bioburden and endotoxin in these raw materials. In addition, the sponsor will assess raw material bioburden and endotoxin risk to product quality. Based on the risk assessment, the sponsor will set bioburden and endotoxin specifications for (b) (4) and (b) (4) and will amend the BLA to include new specifications.

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.”

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

*If not a PMR, skip to 4.*

- **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:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- 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?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC 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?

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**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.*

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## PMR/PMC Development Template

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NDA/BLA #	125422
Product Name:	Jetrea (ocriplasmin) Intravitreal Injection, 2.5 mg/mL
PMC/PMR Description (Microbial Quality Review of Drug Substance):	Investigate the use of (b)(4) for endotoxin measurements of in-process samples (b)(4) and revise the endotoxin methods accordingly. We request that you submit any changes to the in-process endotoxin methods as a CBE-0.
PMC #23	

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>03/30/2013</u>
	Other: <u>Submission of new Specifications</u>	<u>MM/DD/YYYY</u>

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- 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

Endotoxin measurement of in-process samples of ocriplasmin drug substance (b)(4). The sponsor will measure endotoxin in the presence of (b)(4) to provide a more accurate endotoxin measurement (b)(4). The sponsor will submit a report with the results of those studies and will amend the BLA if endotoxin methods are changed.

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.”

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

*If not a PMR, skip to 4.*

- **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:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- 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?  
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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.

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Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
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  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
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- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
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5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
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## PMR/PMC Development Template

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NDA/BLA # 125422  
Product Name: Jetrea (ocriplasmin) Intravitreal Injection, 2.5 mg/mL  
PMC/PMR Description (Microbial Quality Review of Drug Substance): Validate the efficacy of the (b) (4) and submit a protocol with pre-established acceptance criteria. We request that you submit the protocol as a CBE-0. Fulfillment of acceptance criteria at the (b) (4) should be filed in subsequent Annual Reports.  
PMC # 24

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>03/30/2013</u>
	Other: <u>Submission of new Specifications</u>	<u>MM/DD/YYYY</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

Efficacy (b) (4) has not been validated at the (b) (4) manufacture of ocriplasmin drug substance. Validation will be conducted at the (b) (4) as a worst case scenario for (b) (4) and a report with the results will be submitted to the Agency.

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.”

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

*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
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- **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?
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*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- 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?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC 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?

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**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.*

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## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

---

NDA/BLA # 125422  
Product Name: Jetrea (ocriplasmin) Intravitreal Injection, 2.5 mg/mL  
PMC/PMR Description (Microbial Quality Review of Drug Substance): Evaluate the effects of freezing on endotoxin recovery from ocriplasmin drug substance. These studies will include (b) (4) as appropriate. We request that you submit any changes to the in-process endotoxin methods as a CBE-0.  
PMC #25

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PMR/PMC Schedule Milestones: Final Protocol Submission: MM/DD/YYYY  
Study/Trial Completion: MM/DD/YYYY  
Final Report Submission: 03/30/2013  
Other: Submission of new Specifications MM/DD/YYYY

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

(b) (4) of ocriplasmin drug substance are (b) (4) for endotoxin testing. However, the effects of freeze-thaw on endotoxin recovery have not been studied and an evaluation is requested. The sponsor is currently investigating the effects of (b) (4) in endotoxin measurements of ocriplasmin drug substance and drug product. Therefore, (b) (4) may be included in the evaluations of freeze-thaw on endotoxin recovery. The sponsor will submit a report summarizing the results of the freeze-thaw study and will amend the BLA in case of changes to the endotoxin method.

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.”

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

*If not a PMR, skip to 4.*

- **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:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- 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?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC 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?

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**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.*

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## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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NDA/BLA # 125422  
Product Name: Jetrea (ocriplasmin) Intravitreal Injection, 2.5 mg/mL  
PMC/PMR Description (Microbial Quality Review of Drug Substance): Qualify the bioburden method for (b) (4) and submit a report. We request that you submit the report as a CBE-0.  
PMC #26

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PMR/PMC Schedule Milestones: Final Protocol Submission: MM/DD/YYYY  
Study/Trial Completion: MM/DD/YYYY  
Final Report Submission: 03/30/2013  
Other: Submission of new Specifications MM/DD/YYYY

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

Qualification of the (b) (4) bioburden detection method is requested to ensure suitability of the method for testing. The sponsor will qualify the method and will send a summary report to the Agency.

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.”

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

*If not a PMR, skip to 4.*

- **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:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- 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?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC 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?

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**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.*

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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REYES CANDAU-CHACON  
10/12/2012

PATRICIA F HUGHES TROOST  
10/15/2012

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

---

NDA/BLA #                      STN 125422  
Product Name:                 Jetrea (ocriplasmin)

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PMR/PMC Description:      To perform a feasibility study to adjust the drug product final fill volume or concentration to reduce the likelihood that more than one patient could be dosed from the same single use vial due to excess reconstituted drug product remaining in the vial after the initial dosing.  
PMC #2

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PMR/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>Feasibility Data Findings</u>	<u>03/2013</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

For the current drug product presentation, there is a potential to withdraw and administer a minimum of 2 doses from a single use vial that contains no preservatives. This is not an approvability issue since all the quality data for proposed dosage of 125 µg do not indicate a safety issue and the package insert and labeling indicate that the vial is use for single-use only for the indicated dosage.

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.”

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

*If not a PMR, skip to 4.*

- **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:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- 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?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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.

Thrombogenics should perform additional studies to determine the feasibility of reducing the fill volume or change in the concentration (b) (4).

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)  
Feasibility study to adjust the drug product final fill volume or concentration
  - Other
- 

5. Is the PMR/PMC 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.*

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## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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NDA/BLA #                      STN 125422  
Product Name:                 Jetrea™ (Ocriplasmin)

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PMR/PMC Description:        To revise the acceptance criteria for the drug substance and drug product release and stability specifications for low pH CEX-HPLC, RP-HPLC, and low pH SEC-HPLC to include “No new peaks above the limit of quantitation” and for non-reduced SDS-PAGE “No new bands greater than the limit of quantitation.”  
PMC #3

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Interim Report Submission:	<u>12/2012</u>
	Final Report Submission:	<u>MM/DD/YYYY</u>
	Other: <u>Assay Development Findings</u>	<u>04/2013</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 release and stability acceptance criteria do not adequately capture “total other bands” or “total other peaks” for uncharacterized bands (SDS-PAGE) and peaks (chromatographic methods), respectively. The release and stability specifications for the low pH SEC-HPLC, low pH CEX-HPLC, and RP-HPLC methods should be revised to include an acceptance criterion for the test samples that states “no new peaks above the LOQ”. Similarly, for non-reduced SDS-PAGE, the acceptance criterion should include “no new bands above the LOQ”.

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.”

The goal of this study is revise the acceptance criteria for both drug substance and drug product release and stability specifications for the indicated chromatographic methods as well as for non-reduced SDS-PAGE for better control of unidentified (new) peaks or bands.

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

*If not a PMR, skip to 4.*

- **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:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- 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?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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.

Thrombogenics should revise the system suitability criteria for the above-mentioned methods to include an acceptance criteria for controlling new peaks or bands.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC 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?

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**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.*

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Thrombogenics should establish an upper limit for (b) (4) potency.

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

***If not a PMR, skip to 4.***

- **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:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- 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?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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.

Thrombogenics should perform additional validation studies to establish an upper limit for (b) (4) potency.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC 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?

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**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.*

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The goal of this study is to evaluate additional data from sufficient number of lots and revise accordingly the acceptance criteria for release specifications for drug substance.

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

*If not a PMR, skip to 4.*

- **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:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- 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?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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.

Thrombogenics should evaluate data from at least thirty lots, representing current manufacturing process, to revise and update release specification acceptance criteria for drug substance.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC 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?

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**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.*

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(signature line for BLAs)



The goal of this study is to evaluate additional data from sufficient number of lots and revise accordingly the acceptance criteria for release specifications for drug product.

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

*If not a PMR, skip to 4.*

- **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:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- 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?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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.

Thrombogenics should evaluate data from at least thirty lots, representing current manufacturing process, to revise and update release specification acceptance criteria for drug product.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC 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?

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**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.*

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(signature line for BLAs)

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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NDA/BLA #                      STN 125422  
Product Name:                 Jetrea™ (Ocriplasmin)

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PMR/PMC Description:        To revise the system suitability criteria for RP-HPLC drug  
   substance and drug product release and stability method to ensure  
PMC #7                             adequate column performance.

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PMR/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>Assay Development Findings</u>	<u>03/2013</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 system suitability criteria for RP-HPLC are not adequate. The system suitability lacks evaluation of resolution (R), symmetry factor ( $A_s$ ) and theoretical plates (N). These parameters measure adequate separation, symmetry of peaks and column efficiency and thus are necessary to verify that the chromatography system is adequate for the intended analysis. The sponsor should include these parameters in the system suitability. This is not an approvability issue because there are other system suitability measures also in place to monitor assay performance.

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.”

The goal of this study is to revise and update the system suitability criteria for the RP-HPLC method.

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

*If not a PMR, skip to 4.*

- **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:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- 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?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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.

Thrombogenics should perform an additional validation study to revise and update system suitability criteria for RP-HPLC release and stability methods.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC 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?

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**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.*

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(signature line for BLAs)

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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NDA/BLA #                      STN 125422  
Product Name:                 Jetrea™ (Ocriplasmin)

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PMR/PMC Description:        To revise the system suitability criteria for the SDS-PAGE the drug  
   substance and drug product release and stability methods to  
PMC #8                             establish an acceptance criterion for the (b) (4).

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PMR/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>Assay Development Findings</u>	<u>03/2013</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

(b) (4) for system suitability testing of both reduced as well as non-reduced SDS-PAGE. However, the sponsor did not establish an acceptance criterion for (b) (4). This is not an approvability issue as this method is validated for its intended purpose to determine the quantity of Ocriplasmin's size variants.

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."

The goal of this study is revise the system suitability criteria of reduced and non-reduced SDS-PAGE to establish an acceptance criterion (b) (4)

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

*If not a PMR, skip to 4.*

- **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:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- 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?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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.

Thrombogenics should perform additional validation studies to revise and update system suitability to establish an acceptance criterion for (b) (4)

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC 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?

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**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.*

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(signature line for BLAs)



The goal of this study is to establish a limit of quantitation for RP-HPLC and SDS-PAGE specifications.

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

*If not a PMR, skip to 4.*

- **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:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- 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?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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.

Thrombogenics should perform additional validation studies to establish a LOQ value for SDS-PAGE and RP-HPLC methods.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC 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?

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**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.*

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(signature line for BLAs)



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

***If not a PMR, skip to 4.***

- **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:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- 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?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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.

Thrombogenics should perform a study to verify the modified sampling methodology for USP <789> monograph.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC 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?

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**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.*

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(signature line for BLAs)

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA # STN 125422  
Product Name: Jetrea™ (Ocriplasmin)

PMR/PMC Description: To develop release and stability method(s) to detect all types of  
PMC # 11 aggregates observed [redacted] (b) (4) in your drug  
product.

PMR/PMC Schedule Milestones: Final Protocol Submission: MM/DD/YYYY  
Study/Trial Completion: MM/DD/YYYY  
Final Report Submission: MM/DD/YYYY  
Other: Assay Development Findings 08/2013

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

1. Thrombogenics provided AUC data demonstrating that [redacted] (b) (4) detected in their drug product. Their current low-pH SEC-HPLC assay does not detect the [redacted] (b) (4). Therefore the sponsor will need to develop an assay which can detect the [redacted] (b) (4)

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.”

The goal of this study is to develop a method that can detect (b) (4)

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

*If not a PMR, skip to 4.*

- **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:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- 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?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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.

Thrombogenics should develop and validate a method to detect (b) (4)

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other  
develop and validate an orthogonal method for aggregate detection
- 

5. Is the PMR/PMC 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?

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**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.*

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(signature line for BLAs)

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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NDA/BLA # STN 125422  
Product Name: Jetrea™ (Ocriplasmin)

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PMR/PMC Description: To provide the results of the study conducted to evaluate the  
PMC #12 discrepancy in copy number results between the (b) (4) assay  
and the (b) (4) assay.

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PMR/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>Assay Development Findings</u>	<u>03/2013</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

Thrombogenic's quality information amendment (SN#0012, submitted on August 15, 2012) on plasmid copy number analysis of (b) (4) show very different results compared to the those performed by (b) (4). The reason for this discrepancy in (b) (4) number should be evaluated. This is not an approvability issue given the totality of evidence supporting the quality and usability of Ocriplasmin cell banks.

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."

The goal of this study is to evaluate the reason(s) for discrepancy in (b) (4) copy number of (b) (4)

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

*If not a PMR, skip to 4.*

- **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:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- 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?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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.

Thrombogenics should evaluate the assays and provide a justification for the discrepancy.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC 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?

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**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.*

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(signature line for BLAs)



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.”

The goal of this study is establish sensitivity of the [REDACTED] (b) (4) using a 2D SDS-PAGE.

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

*If not a PMR, skip to 4.*

- **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:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- 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?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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.

Thrombogenics should perform 2D SDS-PAGE to determine the sensitivity of [REDACTED] (b) (4) antiserum used in HCP assay, by evaluating the number or percentage of [REDACTED] (b) (4).

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- 
- Other
- 

5. Is the PMR/PMC 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?

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**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.*

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(signature line for BLAs)

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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NDA/BLA #                      STN 125422  
Product Name:                 Jetrea™ (Ocriplasmin)

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PMR/PMC Description:        To submit a reference (standard) material qualification protocol for  
new primary and secondary reference materials which contains  
PMC#14                            characterization testing and more stringent acceptance criteria for  
release assays performed as part of the qualification of the new  
reference materials.

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PMR/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>Assay Development Findings</u>	<u>03/2013</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

Thrombogenics has not established a two-tiered reference material system. As per ICH Q6B recommendations, the sponsor should establish a two-tiered reference material system and should submit a new reference material qualification protocol to the agency requesting for approval. This is not an approvability issue since the current reference material (RS-003-B2436-009) represents commercial manufacturing process and is deemed comparable to the clinical material used in Phase 3 clinical trials.

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.”

The goal of this post-marketing commitment is to establish a two-tiered reference material system and to submit a new reference standard qualification protocol.

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

*If not a PMR, skip to 4.*

- **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:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- 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?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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.

Thrombogenics should establish a two-tiered reference standard system per ICH Q6B recommendations.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC 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?

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**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.*

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(signature line for BLAs)

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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NDA/BLA #                      STN 125422  
Product Name:                 Jetrea™ (Ocriplasmin)

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PMR/PMC Description:        To conduct an extractable study for the (b) (4)  
   rubber stoppers used for the drug product container closure (b) (4)  
PMC #15                         (b) (4) This information should be used in the risk  
   assessment conducted for drug product final container closure  
   system leachable study.

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PMR/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>Assay Development Findings</u>	<u>12/2012</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

USP <381> recommends for elastomeric closures further processed by the end user should be subjected to extractable studies after processing. In this case the rubber stoppers (b) (4) the sponsor should conduct an extractable study for the rubber stopper (b) (4) and use this data to determine which potential extractables should be assessed as part of the long-term drug product leachable study. This is not an approvability issue because the drug product is stored frozen and will have limited contact with the rubber stopper.

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.”

The goal of this study is to determine the extractable profile of the rubber stoppers (b) (4) used for the drug product container closure.

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

*If not a PMR, skip to 4.*

- **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:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- 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?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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.

Thrombogenics should perform an extractable study and provide a risk analysis on (b) (4) rubber stoppers of the drug product container closure, (b) (4)

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC 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?

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**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.*

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(signature line for BLAs)



The goal of this study is to evaluate any leachates in the drug product under long-term storage, and if there are any, to assess the impact of these leachates on ocriplasmin's product quality.

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

***If not a PMR, skip to 4.***

- **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:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- 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?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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.

Thrombogenics should perform a leachables study on ocriplasmin's drug product, stored under recommended storage conditions, at the end of shelf-life. The final study report should also include a detailed risk analysis of the impact of any leachates on the product quality of Ocriplasmin.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC 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?

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**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.*

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(signature line for BLAs)

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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NDA/BLA # STN 125422  
Product Name: Jetrea™ (Ocriplasmin)

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PMR/PMC Description: To evaluate drug substance for the presence of (b) (4)  
PMC #17 Provide a risk assessment of the potential impact these (b) (4) impurities may have on the quality, safety and efficacy of ocriplasmin and propose an appropriate control strategy.

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PMR/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: Assay Development Findings	<u>03/2013</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

(b) (4) impurities resulting from Ocriplasmin's drug substance manufacturing process, (b) (4) are measured and controlled during release testing. However, Thrombogenics did not evaluate if (b) (4) impurities (b) (4) are present in the drug substance. Presence of these impurities, if any, without appropriate control strategy can be a concern for immunogenicity. However, this is not an approvability issue since the sponsor has demonstrated adequate clearance of (b) (4) impurities (b) (4) during process validation.

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."

The goal of this study is to evaluate the efficiency of clearance of [REDACTED] (b) (4) during Ocriplasmin drug substance manufacture.

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

***If not a PMR, skip to 4.***

- **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:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- 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?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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.

Thrombogenics should conduct testing of Ocriplasmin drug substance for the presence of [REDACTED] (b) (4) [REDACTED] [REDACTED] If needed, perform and submit a risk assessment in your study report with a control strategy to mitigate the risk.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC 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?

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**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)

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

---

NDA/BLA # STN 125422  
Product Name: Jetrea™ (Ocriplasmin)

---

PMR/PMC Description: To conduct a drug product stability study demonstrating that drug product stored at -70°C for 120 days followed by storage at -20°C up to the expiry (18 months) does not adversely impact product quality.  
PMC #18

---

PMR/PMC Schedule Milestones: Final Protocol Submission: MM/DD/YYYY  
Study/Trial Completion: MM/DD/YYYY  
Final Report Submission: 12/2013  
Other: \_\_\_\_\_ MM/DD/YYYY

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

Thrombogenics submitted stability data for drug product stored at either -70°C or -20°C for up to 18 months. However, the sponsor did not conduct a stability study on the drug product demonstrating that a hold up to 120 days at -70°C followed by -20°C for long term storage does not affect product quality. This is not an approvability issue because the available stability data indicate that the product is stable when stored at -70°C or -20°C for 18 months.

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.”

The goal of this study is evaluate if there is any negative impact on drug product quality due to drug product's transition from the manufacturing site (with a maximum hold time of 120 days when stored at -70°C) to the distribution site where the drug product is stored at -20°C.

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

***If not a PMR, skip to 4.***

- **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:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- 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?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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.

Thrombogenics should perform additional stability studies and provide data that drug product stored at -70°C for 120 days followed by storage at -20°C up to the expiry does not adversely impact product quality.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC 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.*

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(signature line for BLAs)

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/s/  
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RAMESH B POTLA  
10/12/2012

MARY K W LEE  
10/12/2012

MEMORANDUM

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

---

ADDENDUM TO CLINICAL INSPECTION SUMMARY

DATE: October 4, 2012

TO: Jacquelyn Smith, Project Manager  
Jennifer Harris, Medical Officer  
Division of Transplant and Ophthalmology Products

FROM: Kassa Ayalew, M.D.  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

THROUGH: Susan Leibenhaut, M.D.  
Acting Team Leader  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

Susan Thompson, M.D.  
Acting Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigators

SUBJECT: Addendum to Evaluation of Clinical Inspections

BLA: 125422

APPLICANT: ThromboGenics Inc,

DRUG: JETREA™ (ocriplasmin) Intravitreal Injection, 2.5 mg/mL

NME: Yes

THERAPEUTIC CLASSIFICATIONS: Original

INDICATION: Treatment of Symptomatic Vitreomacular Adhesion  
including Macular Holes

CONSULTATION REQUEST DATE: May 29, 2012  
ACTION GOAL DATE: October 3, 2012  
PDUFA DATE: October 17, 2012

## **I. BACKGROUND:**

The CIS Addendum is submitted to supplement the CIS for JETREA™ (ocriplasmin) Intravitreal Injection, 2.5 mg/mL entered into DARRTS on October 1, 2012. The EIR has been reviewed, and there is no change in the OSI assessment and recommendations contained in the CIS dated October 1, 2012. The original CIS for this Application, dated October 1, 2012 contained a preliminary DSI assessment of findings and recommendations for inspections of Drs. Matthew Benz, Carl Baker, and Michael Jumper and Michael Tolentino.

For a complete background discussion, see CIS dated October 1, 2012.

Protocols inspected were Study TG-MV-006 and Study TG-MV-007 both entitled, "A Randomized, Placebo Controlled, Double Masked, Multicenter Trial of Microplasmin Intravitreal Injection for Non Surgical Treatment of Focal Vitreomacular Adhesion." Both studies were the same in design and conduct. However, Study TG-MV-007 had centers that were located in Europe and United States, and Study TG-MV-006 was exclusively conducted in the United States.

The primary efficacy outcome measure for both studies was the proportion of subjects with VMA resolution at Day 28, as determined by masked Central Reading Center (CRC) OCT evaluation. Any subjects who had a creation of an anatomical defect (i.e. retinal hole, retinal detachment) that resulted in loss of vision or that required additional intervention were not counted as successes for this primary endpoint. The safety endpoints of this study were summaries of post-injection complications, including the following: AEs, with special attention to ocular events, worsening VA, worsening macular edema, vitreous hemorrhage, retinal tear or detachments, increase in ocular inflammation, or IOP increases.

Four domestic clinical investigators were selected for inspection, mainly due to enrollment of large numbers of study subjects, high number of INDs, and previous inspectional history. There was no site specific safety or efficacy concern. This BLA submission was for an NME.

**II. RESULTS (by Site):**

<b>Name of CI</b>	<b>Protocol # /Site # and # of Subjects enrolled:</b>	<b>Inspection Date</b>	<b>Classification</b>
<b>Matthew Benz, M.D.</b> Retinal Consultants of Houston 6560 Fannin Street, Ste 750 Houston, TX 77030	TG-MV-006 Site 601 n=20 subjects	June 25 to June 28, 2012	NAI
<b>Carl Baker, M.D.</b> Paducah Retinal Center 1900 Broadway Street, Ste. 2 Paducah, KY 42001, USA	TG-MV-007 Site 764 n=16 subjects	July 16 to July 18, 2012	NAI
<b>J. Michael Jumper, M.D.</b> West Coast Retina Group, Inc 185 Berry Street Suite 130 San Francisco, CA 94107, USA	TG-MV-007 Site 719 n=14 subjects	June 25 to July 9, 2012	NAI
<b>Michael Tolentino, M.D.</b> Center for Retina and Macular Disease 250 Avenue K SW, Suite 200 Winter Haven, FL 33880	TG-MV-006 Site 622 n=18 subjects	July 9 to July 25, 2012	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. Matthew Benz, M.D.**Vitreoretinal Consultants  
6560 Fannin Street, Ste 750  
Houston, TX 77030

- a. **Assessment of data integrity:** The EIR has been reviewed, and there is no change in the OSI assessment and recommendations contained in the CIS dated October 1, 2012. Based on the inspectional findings above, efficacy and safety data obtained from this site can be considered reliable in support of the application.

**2. Carl Baker, M.D.**

Paducah Retinal Center  
1900 Broadway Street, Ste. 2  
Paducah, KY 42001

- a. **Assessment of data integrity:** The EIR has been reviewed, and there is no change in the OSI assessment and recommendations contained in the CIS dated October 1, 2012. All study records were reviewed and there was a single isolated instance of an unreported adverse events and delayed notification of a subject not meeting eligibility criteria. These were considered isolated instances. Based on the inspectional findings above, efficacy and safety data obtained from this site can be considered reliable in support of the application.

**3. J. Michael Jumper, M.D.**

West Coast Retina Group, Inc  
185 Berry Street Suite 130  
San Francisco, CA 94107

- a. **Assessment of data integrity:** The EIR has been reviewed, and there is no change in the OSI assessment and recommendations contained in the CIS dated October 1, 2012. Based on the inspectional findings, efficacy and safety data obtained from this site can be considered reliable in support of the application. :

**4. Michael Tolentino, M.D.**

Center for Retina and Macular Disease  
250 Avenue K SW, Suite 200  
Winter Haven, FL 33880

- a, **Assessment of data integrity:** The EIR has been reviewed, and there is no change in the OSI assessment and recommendations contained in the CIS dated October 1, 2012. In general, the study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication. Although changes made to source documents by the site study coordinator is of concern, there is no evidence that primary safety or efficacy data was impacted. Data derived from Dr. Tolentino's site are considered reliable.

### III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The final classification of the Clinical Investigator inspection of Drs. Matthew Benz, Carl Baker, and Michael Jumper is No Action Indicated (NAI). The final classification of the Clinical Investigator inspection of Dr. Michael Tolentino is Voluntary Action Indicated (VAI). Based on these four inspections, the data appear reliable and can be used in support of this application. The conclusions and recommendations of this addendum have not changed from the original CIS dated October 1, 2012.

*{See appended electronic signature page}*

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

CONCURRENCE:

*{See appended electronic signature page}*

Susan Leibenhaut, M.D.  
Acting Team Leader  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

*{See appended electronic signature page}*

Susan Thompson, M.D.  
Acting Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

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/s/  
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KASSA AYALEW  
10/04/2012

SUSAN LEIBENHAUT  
10/04/2012

SUSAN D THOMPSON  
10/04/2012

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

**Label, Labeling and Packaging Review**

Date: October 2, 2012

Reviewer: Jung Lee, RPh  
Division of Medication Error Prevention and Analysis

Acting Team Leader: Jamie Wilkins Parker, PharmD  
Division of Medication Error Prevention and Analysis

Division Director: Carol Holquist, RPh  
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Jetrea (Ocriplasmin) Injection, 0.5 mg/0.2 mL

Application Type/Number: BLA 125422

Applicant: ThromboGenics, Inc

OSE RCM #: 2012-1097

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

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## 1 INTRODUCTION

This review evaluates the proposed container label, carton and insert labeling for Jetrea (BLA 125422) for areas of vulnerability that could lead to medication errors.

### 1.1 REGULATORY HISTORY

The application was submitted

(b) (4)

BLA 125422 which has been designated as a priority review.

### 1.2 PRODUCT INFORMATION

The following product information is provided in the submission.

- Active Ingredient: Ocriplasmin
- Indication of Use: Treatment of symptomatic vitreomacular adhesion including macular hole
- Route of Administration: Intravitreal injection
- Dosage Form: Injection Solution
- Strength: 0.5 mg/0.2 mL
- Dose and Frequency: Dilute with 0.2 mL of sterile sodium chloride (0.9% w/v) solution for injection into the vial. Administer 0.125 mg (0.1 mL of the diluted solution) by intravitreal injection to the affected eye once as a single dose
- How Supplied: 0.2 mL representing 0.5 mg ocriplasmin in a citric-buffered solution (2.5 mg/mL) in a 2 mL Single-use glass vial
- Storage: Store frozen at or below -20°C (-4°F) until ready to use
- Container and Closure Systems: 2 mL glass vial with a latex free rubber stopper
- Distribution: Controlled distribution and specialty pharmacy network directly to the treating physician clinics and hospitals. In the US, drop shipment deliveries on a 24 hour schedule will be provided.

### 1.3 LABELS AND LABELING

Using the principals of human factors and Failure Mode and Effects Analysis,<sup>1</sup> along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- Container Labels submitted February 2, 2012 (Appendix B)
- Carton Labeling submitted February 2, 2012 (Appendix C)
- Insert Labeling submitted February 2, 2012

#### 1.4 PREVIOUSLY COMPLETED REVIEWS

DMEPA previously reviewed the proprietary name Vitroclar (Ocriplasmin) Injection (OSE #2010-1586). In this review concerns over the safety of the proposed product design were assessed specifically regarding the need for dilution of the product and the excess fill volume of the vial.

As was expressed in the initial review, the proposed packaging configuration introduces safety concerns that may result in over or under dosing and the potential for multiple injections from a single dose vial. Based on the recommended dose of 0.125 mg/0.1 mL, the proposed volume after dilution is 0.4 mL which theoretically provides enough doses for up to four injections. To prevent the potential for multiple injections from this single dose vial or the potential for overdosing, a lower overall volume should be utilized for a single injection product. The recommendation was communicated to the Applicant that the final volume be in accordance with the recommended dose to prevent the potential for multiple dosing or overdosing from the intended one-dose vial.

#### 1.5 CURRENT REVIEW

A drug product volume reduction feasibility study was conducted by the Applicant.

Based on the results of the study, the Applicant stated they will [REDACTED] (b) (4)

[REDACTED] An 18 month long term stability drug product comparability data is currently being gathered [REDACTED] (b) (4). In the meantime, the Applicant has submitted the application for the 0.2 mL (before dilution) fill volume presentation.

## 2 CONCLUSIONS

DMEPA concludes that the proposed vial container label, carton labeling and insert labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product, to mitigate any confusion and to clarify information.

## 3 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this BLA:

### 3.1 COMMENTS TO THE DIVISION

#### A. General Comments

1. Currently the strength is expressed as the [REDACTED] (b) (4) (2.5 mg/mL); however, the proposed vial only contains an approximate fill volume of 0.2 mL. Therefore, the expression of strength should reflect the

vial contents per 0.2 mL. Revise the strength statement throughout the insert labeling to read “0.5 mg/0.2 mL”.

B. Insert Labeling

1. Dosage and Administration (Section 2)

a) The applicant utilizes trailing zeros in section 2.4 (Administration) of the insert labeling. Trailing zeros can lead to 10-fold errors in dosing. DMEPA recommends removing all trailing zeros with the exception of when it is required to demonstrate the level of precision of the value being reported, such as for laboratory results, imaging studies that report size of lesions, or catheter/tube sizes.

b) We recommend adding a unit of measure immediately following all numbers for clarity, as appropriate. (For example, revise “3.5-4.0 mm” to read [REDACTED] (b) (4) in section 2.4.)

c) Under section 2.1 (General Dosing Information), to emphasize the need to dilute the solution before administration, revise the statement “FOR SINGLE-USE OPHTHALMIC INTRAVITRAL INJECTION ONLY” to read [REDACTED] (b) (4)

d) Under section 2.3 (Preparation for Administration), revise statement #1, “Remove the vial (2.5 mg/mL corresponding to 0.5 mg ocriplasmin)” to read [REDACTED] (b) (4)

e) Under section 2.4 (Administration), revise the statement “The injection volume of 0.1 mL is then delivered into the mid-vitreous” to read [REDACTED] (b) (4)

2. Dosage Forms and Strengths (Section 3)

a) Revise the statement [REDACTED] (b) (4)

3. How Supplied (Section 16)

a) [REDACTED] (b) (4)

b) [REDACTED] (b) (4)

### 3.2 COMMENTS TO THE APPLICANT

#### A. Container Label

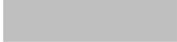
1. Revise the presentation of the proprietary name from all upper case letters “JETREA” to title case “Jetrea” to improve readability. Words set in upper and lower case form recognizable shapes, making them easier to read than the rectangular shape that is formed by words set in all capital letters.
2. The strength statement should be expressed as the total drug content per total volume (see USP, General Chapter 1). For containers holding a volume of less than 1 mL, the strength per fraction of a mL should be the only expression of strength. Therefore, we request you revise the statement of strength to read as follows: (b) (4). Additionally, increase the prominence of the strength statement as this information is important for the proper dosing of the product.
3. The dosage form “Injection” should follow immediately below the established name. The route of administration statement (b) (4) should appear below the statement of strength. Therefore, we request the dosage form "Injection" be added immediately following the established name and the route of administration statement (b) (4) to be relocated to below the statement of strength. The revised label should read:

(b) (4)

4. Include the statement (b) (4) on the principal display panel (PDP) below the route of administration statement.
5. Decrease the prominence of the manufacturer’s statement on the PDP as it is overly prominent and distracts from the most important information on the label, such as the proprietary and established names and the strength.

#### B. Carton Labeling

1. See comment A1 to A2.
2. Remove the circular graphic to the left of the proprietary name statement as it could be misinterpreted as the letter ‘O’.

3. Remove the large circular background graphic in the middle of the principal display panel to ensure there is no intervening matter that distracts from the important information on the label.
4. Ensure that the established name is at least half the size of the proprietary name. Ensure the established name has prominence commensurate with the proprietary name taking into account all pertinent factors including typography, layout, contrast and other printing features per 21 CFR 201.10(g)(2).
5. The dosage form "Injection" should follow immediately below the established name. The route of administration statement "For Intravitreal Injection" should appear below the statement of strength. Therefore, we request the dosage form "Injection" be added immediately following the established name and the route of administration statement "For Intravitreal Injection" to be relocated to below the statement of strength.
6. To further emphasize the importance of using the vial for one time use only, revise the statement on the principal display panel "Single-use vial. Dilute before use. Use immediately after dilution" to read as follows: (b) (4)  
 (b) (4)
7. Revise the statement on the side panel "Dilute before use. Use immediately after dilution" to read as follows: (b) (4)  

8. The manufacturer's name is presented in a red font color which competes with the prominence of the red font color of the storage statement and the white color of the proprietary and established name statements. Revise the font color of the manufacturer's name to black.
9. Relocate the statement "FOR INTRAVITREAL INJECTION AFTER DILUTION ONLY" on the top panel to appear below the statement of strength.

If you have further questions or need clarifications, please contact Karen Townsend, project manager, at 301-796-5413.

## APPENDICES

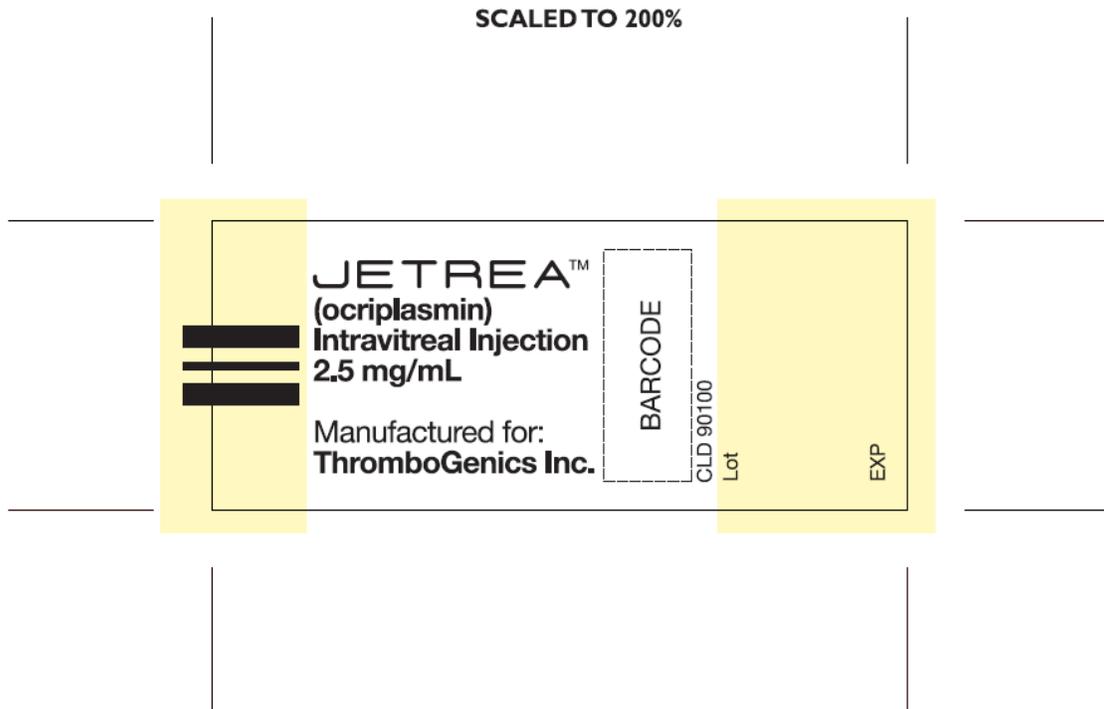
### APPENDIX A. DATABASE DESCRIPTIONS

#### Adverse Event Reporting System (AERS)

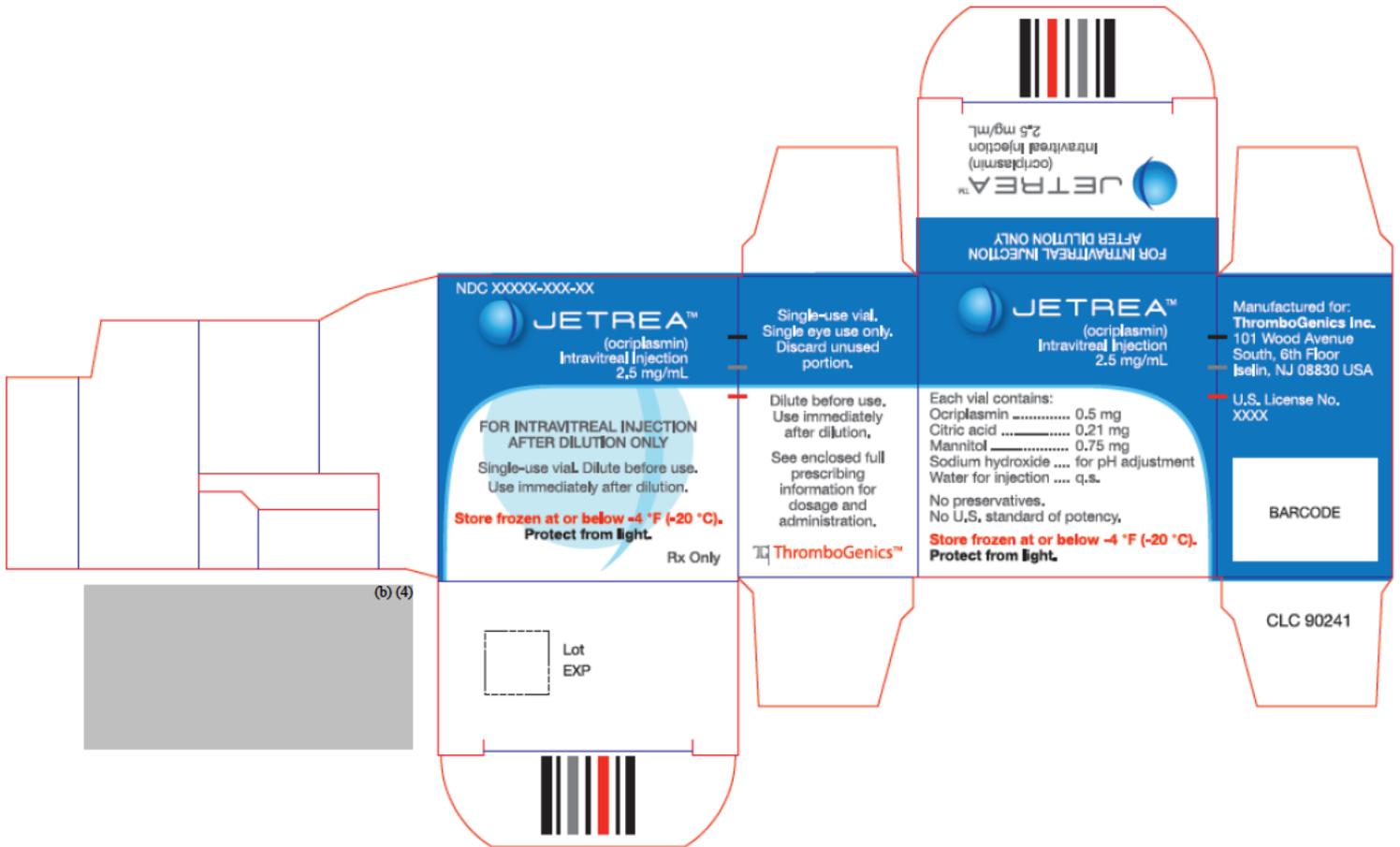
The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance (ICH E2B) issued by the International Conference on Harmonisation. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

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

#### Appendix B: Container Label



**Appendix C: Carton Labeling**



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/s/  
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JUNG E LEE  
10/02/2012

CAROL A HOLQUIST on behalf of JAMIE C WILKINS PARKER  
10/02/2012  
signing on behalf of Jamie Wilkens-Parket

CAROL A HOLQUIST  
10/02/2012

MEMORANDUM

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

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CLINICAL INSPECTION SUMMARY

DATE: September 28, 2012

TO: Jacquelyn Smith, Project Manager  
Jennifer Harris, Medical Officer  
Division of Transplant and Ophthalmology Products

FROM: Kassa Ayalew, M.D.  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

THROUGH: Susan Leibenhaut, M.D.  
Acting Team Leader  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

Susan Thompson, M.D.  
Acting Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigators

SUBJECT: Evaluation of Clinical Inspections

BLA: 125422

APPLICANT: ThromboGenics Inc,

DRUG: JETREA™ (ocriplasmin) Intravitreal Injection, 2.5 mg/mL

NME: Yes

THERAPEUTIC CLASSIFICATIONS: Original

INDICATION: Treatment of Symptomatic Vitreomacular Adhesion  
including Macular Holes

CONSULTATION REQUEST DATE: May 29, 2012

ACTION GOAL DATE: October 3, 2012

PDUFA DATE: October 17, 2012

## I. BACKGROUND:

The sponsor, ThromboGenics Inc. is submitting a new Biologics License Application (BLA) to support JETREA™ (ocriplasmin) Intravitreal Injection, 2.5 mg/mL for the treatment of symptomatic vitreomacular adhesion including macular hole. The product JETREA™ (ocriplasmin) is a recombinant truncated form of human plasmin with retained protease activity produced using recombinant DNA technology from the yeast *Pichia pastoris*.

To support the approval of JETREA™ (ocriplasmin) for the treatment of patients with symptomatic vitreomacular adhesion including macular hole, the sponsor provided Clinical Study Reports for Study TG-MV-006 and Study TG-MV-007 both entitled, "A Randomized, Placebo Controlled, Double Masked, Multicenter Trial of Microplasmin Intravitreal Injection for Non Surgical Treatment of Focal Vitreomacular Adhesion." Both studies were similar in design and conduct. However, Study TG-MV-007 had centers that were located in Europe and United States, and Study TG-MV-006 was exclusively conducted in the United States.

Study TG-MV-006 was conducted at 42 centers in the United States and had a total of 326 subjects who were randomized into the study (107 placebo; 219 ocriplasmin). To be enrolled into the study, subjects had to be male or female subjects aged  $\geq 18$  years with symptomatic vitreomacular adhesion or VMA (i.e. focal VMA leading to symptoms) on optical coherence tomography (OCT) and best corrected visual acuity (BCVA) of 20/25 or worse in the study eye. Exclusion criteria included proliferative retinopathy, full thickness macular hole (FTMH) diameter  $>400$   $\mu\text{m}$ , high myopia, prior retinal detachment, or a history of macular laser or vitrectomy in the study eye. All subjects had to provide written informed consent prior to inclusion into the study. Study TG-MV-006 was a 6 month study with a total of 7 visits: Baseline, Injection Day (Day 0), Post-Injection Day 7, Post-Injection Day 14, Post-Injection Day 28, Post-Injection Month 3, and Post-Injection Month 6. Baseline and Injection Day visits were combined at the Investigator's discretion. The Baseline visit had to be performed within two weeks of the Injection Day visit.

Study TG-MV-007 had the same design, population studied, inclusion and exclusion criteria, treatment groups, treatment schedules, study assessments, and primary and secondary efficacy measures as Study TG-MV-006. The study enrolled a total of 326 subjects (81 placebo; 245 ocriplasmin) in Europe (179) and the U.S. (147).

The primary efficacy outcome measure for both studies was the proportion of subjects with VMA resolution at Day 28, as determined by masked Central Reading Center (CRC) OCT evaluation. Any subjects who had a creation of an anatomical defect (i.e. retinal hole, retinal detachment) that resulted in loss of vision or that required additional intervention were not counted as successes for this primary endpoint. The safety endpoints of this study were summaries of post-injection complications, including the following: AEs, with special attention to ocular events, worsening VA, worsening macular edema, vitreous hemorrhage, retinal tear or detachments, increase in ocular inflammation, or IOP increases.

Four domestic clinical investigators were selected for inspection, mainly due to enrollment of large numbers of study subjects, high number of INDs, and previous inspectional history. There was no site specific safety or efficacy concern. This BLA submission was for an NME.

## II. RESULTS (by Site):

Name of CI	Protocol # /Site # and # of Subjects enrolled:	Inspection Date	Classification
<b>Matthew Benz, M.D.</b> Vitreoretinal Consultants 6560 Fannin Street, Ste 750 Houston, TX 77030	TG-MV-006 Site 601 n=20 subjects	June 25 to June 28, 2012	Pending (Preliminary Classification NAI)
<b>Carl Baker, M.D.</b> Paducah Retinal Center 1900 Broadway Street, Ste. 2 Paducah, KY 42001, USA	TG-MV-007 Site 764 n=16 subjects	July 16 to July 18, 2012	Pending (Preliminary Classification NAI)
<b>J. Michael Jumper, M.D.</b> West Coast Retina Group, Inc 185 Berry Street Suite 130 San Francisco, CA 94107, USA	TG-MV-007 Site 719 n=14 subjects	June 25 to July 9, 2012	Pending (Preliminary Classification NAI)
<b>Michael Tolentino, M.D.</b> Center for Retina and Macular Disease 250 Avenue K SW, Suite 200 Winter Haven, FL 33880	TG-MV-006 Site 622 n=18 subjects	July 9 to July 25, 2012	Pending (Preliminary 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. **Matthew Benz, M.D.**

Vitreoretinal Consultants  
6560 Fannin Street, Ste 750  
Houston, TX 77030

- a. **What was inspected:** This inspection was conducted in accordance with Compliance Program 7348.811 between June 25 and June 28, 2012. There were six INDs associated with the inspected entity in CDER's database, and the CI had no prior inspection history.

This inspection was performed as a data audit for Protocol # TG-MV-006. At this site, a total of 25 subjects were screened, 20 subjects were randomized, and 18 subjects completed the study. Two subjects were listed as lost to follow-up. There was no evidence of any under reporting of adverse events. An audit of 18 subjects' records was conducted. Study subject files were reviewed for verification of: 1) entry criteria, 2) diagnosis of target disease, 3) efficacy variables, and 4) adequate adverse experience reporting. All primary efficacy endpoint data were compared with the line listings. In addition, drug accountability records, IRB approval and dates, and sponsor monitoring records were reviewed. There were no limitations to the inspection.

- b. **General observations/commentary:** In general, the study was conducted appropriately. There was no evidence of under reporting of adverse events. All primary efficacy endpoint data were verified by comparison of the source documents with the line listings submitted in the NDA. No violations were noted, and no Form FDA 483 was issued at the conclusion of the inspection.
- c. **Assessment of data integrity:** Based on the inspectional findings above, efficacy and safety data obtained from this site can be considered reliable in support of the application.

**Note: Final classification for Dr. Benz's site is pending and will be determined when the final EIR and associated exhibits are received/reviewed and/or finalized. Should the conclusions change upon receipt and review of the Establishment Inspection Report (EIR), an inspection summary addendum will be generated.**

**2. Carl Baker, M.D.**

Paducah Retinal Center  
1900 Broadway Street, Ste. 2  
Paducah, KY 42001

- a. **What was inspected:** This inspection was conducted in accordance with Compliance Program 7348.811 between July 16 to July 18, 2012. There were five INDs associated with the inspected entity in CDER's database, and the CI had no prior inspection history.

This inspection was performed as a data audit for Protocol #TG-MV-007 submitted in support of BLA 125422. At this site, a total of 19 subjects were screened, 16 subjects were randomized, and 16 subjects completed the study. Two subjects were listed as undergoing vitrectomy (Subject 006 & 010) and one subject was deemed not to meet inclusion criteria (sSubject 004). An audit of 16 subjects' records was conducted. Study subject files were reviewed for verification of: 1) entry criteria, 2) diagnosis of target disease, 3) efficacy variables, and 4) adequate adverse experience reporting. All primary efficacy endpoint data were compared with the line listings. In addition, drug accountability records, IRB approval and dates, and sponsor monitoring records were reviewed. There were no limitations to the inspection.

- b. **General observations/commentary:** In general, the study was conducted appropriately. There was evidence of a single instance of an adverse event that was not reported. This

was the presence of “floaters” for Subject 006. All primary efficacy endpoint data were verified by comparison of the source documents with the line listings submitted in the NDA. Subject 764-004 did not meet inclusion criteria according to the Central Reading Center, but this subject remained in the study due to delayed notification to the clinical investigator by the Central Reading Center. No violations were cited, and no Form FDA 483 was issued at the conclusion of the inspection.

- c. **Assessment of data integrity:** All study records were reviewed and there was a single isolated instance of an unreported adverse events and delayed notification of a subject not meeting eligibility criteria. These were considered isolated instances. Based on the inspectional findings above, efficacy and safety data obtained from this site can be considered reliable in support of the application.

**Note: Final classification for Dr. Baker’s site is pending and will be determined when the final EIR and associated exhibits are received/reviewed and/or finalized. Should the conclusions change upon receipt and review of the EIR, an inspection summary addendum will be generated.**

**3. J. Michael Jumper, M.D.**

West Coast Retina Group, Inc  
185 Berry Street Suite 130  
San Francisco, CA 94107

- a. **What was inspected:** This inspection was conducted in accordance with Compliance Program 7348.811 between June 25 and July 9, 2012. There were four INDs associated with the inspected entity in CDER’s database, and the CI had no prior inspection history.

This inspection was performed as a data audit for Protocol #TG-MV-007. At this site, a total of 14 subjects were screened, randomized and enrolled in the study and completed the study. There was no evidence of any under reporting of adverse events. An audit of 14 subjects’ records was conducted. Study subject files were reviewed for verification of: 1) entry criteria, 2) diagnosis of target disease, 3) efficacy variables, and 4) adequate adverse experience reporting. All primary efficacy endpoint data were compared with the line listings. In addition, drug accountability records, IRB approval and dates, and sponsor monitoring records were reviewed. There were no limitations to the inspection.

- b. **General observations/commentary:** In general, the study was conducted appropriately. There was no evidence of under reporting of adverse events. All primary efficacy endpoint data were verified by comparison of the source documents with the line listings submitted in the NDA. No violations were noted, and no Form FDA 483 was issued at the conclusion of the inspection.
- c. **Assessment of data integrity:** Based on the inspectional findings above, efficacy and safety data obtained from this site can be considered reliable in support of the application.

**Note: Final classification for Dr. Jumper’s site is pending and will be determined**

**when the final EIR and associated exhibits are received/reviewed and/or finalized. Should the conclusions change upon receipt and review of the EIR, an inspection summary addendum will be generated.**

**4. Michael Tolentino, M.D.**

Center for Retina and Macular Disease  
250 Avenue K SW, Suite 200  
Winter Haven, FL 33880

- a. **What was inspected:** This inspection was conducted in accordance with Compliance Program 7348.811 between July 9 and July 25, 2012. There were 14 INDs associated with the inspected entity in CDER's database, and the CI had one prior inspection in 2007 that was classified NAI.

This inspection was performed as a data audit for Protocol #TG-MV-006. At this site, 23 subjects were screened. Five (5) subjects did not meet study protocol inclusion/exclusion criteria and were considered screen failures. Eighteen (18) subjects were enrolled and randomized into the study. Three (3) subjects withdrew consent and one subject died. The subject who died was Subject 012, an 85 year-old white female, randomized to the ocriplasmin arm who was diagnosed with lung cancer that was considered unrelated to study drug. A total of 14 subjects completed the study. An audit of 23 subjects' records was conducted.

The inspection included reviews of the following items: 1) entry criteria, 2) diagnosis of target disease, 3) efficacy variables, and 4) adequacy of adverse experience reporting. In addition, drug accountability records, Informed Consents Documents, IRB approval and dates, and sponsor monitoring records were reviewed. All primary efficacy endpoint data were compared with the sponsor supplied line listings. There were no limitations to the inspection.

- b. **General observations/commentary:** In general, the study was conducted appropriately. However, a Form FDA 483, Inspectional Observations, was issued to this investigator for:

- i. Failure to conduct the study in accordance with the signed statement of investigator and investigational plan [21 CFR 312.60]. Specifically,

- a. The review of source document files revealed that two subjects (Subject 014 and 015) had experienced adverse events (nausea and vomiting) during the fluorescein angiography procedures that were not reported on the case report forms.

*OSI Reviewer Comments: Although the clinical investigator failed to report adverse events for the two subjects according to the investigational plan, which is a regulatory violation, due to the isolated nature of the finding it is unlikely that the finding will impact data reliability or subject safety. Dr. Tolentino adequately responded to the inspection findings in a letter dated March 6, 2012*

*and plans to implement corrective actions.*

- b. One subject (Subject 005) had out of window study visits for visits 3 (by 1 day), 4 (by 3 days) & 5 (by 4 days).

*OSI Reviewer Comments: Visit 3 was to occur at 7 days (2± days). Visit 4 was to occur at 14 days (3± days). Visit 5 was to occur at 28 days (3± days), at which time the primary efficacy endpoint data was to be captured. For Subject 005, study visit 5 was out of window by 4 days (occurred on Day 35 versus protocol defined Day 28 ± 3 days). The review division did not feel that this finding would impact efficacy outcome. Although the clinical investigator failed to conduct the study visits according to the protocol specified visit windows for one subject, which is a regulatory violation, given that the finding was isolated, the observed violation should not have significant impact on data reliability, or on the safety and welfare of subjects from the site. Dr. Tolentino adequately responded to the inspection findings in a letter dated March 6, 2012 and has planned to implement corrective actions.*

- ii. Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation [21 CFR 312.62 (b)].

- a. There were discrepancies in data initially recorded on source documents that were later changed to reflect data submitted in the electronic case report forms (eCRF) for 5 subjects (Subjects 004, 005, 006, 008, 015). The changes were not reviewed /approved by the principal clinical investigator and were made without properly documenting the reasons for such changes.

*OSI Reviewer Comments: The clinical investigator failed to maintain adequate and accurate case histories for 5 subjects (Subjects 004, 005, 006, 008, 015) according to the investigational plan. The changes made on the source documents that were initially recorded to reflect data submitted in the electronic case report forms (eCRF) do not appear to impact safety assessment nor assessment of the primary efficacy outcome measure for the study (VMA resolution at Day 28 as determined by masked Central Reading Center (CRC) OCT Evaluation). The EIR states that the study site coordinator dealt with the monitors during the monitoring visit, and the CI allowed the coordinator to make the corrections. On later reflection, he felt that the changes made were not always accurate.*

*The FDA inspector discussed the above findings with the CI during the inspection. The CI acknowledged the violations, provided assurance that he would adequately maintain study records, and, in his written response, noted that the coordinator who made the changes had been terminated from the practice. Dr. Tolentino adequately responded to the inspection findings in a letter dated March 6, 2012 and plans to implement corrective actions.*

- c. **Assessment of data integrity:** In general, the study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication. Although changes made to source documents by the site study coordinator is of concern, there is no evidence that primary safety or efficacy data was impacted. Data derived from Dr. Tolentino's site are considered reliable.

**Note: Final classification for Dr. Tolentino's site is pending and will be determined when the final EIR and associated exhibits are received/reviewed and/or finalized. Should the conclusions change upon receipt and review of the EIR, an inspection summary addendum will be generated.**

### III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The preliminary classification of the Clinical Investigator inspection of Drs. Matthew Benz, Carl Baker, and Michael Jumper is No Action Indicated (NAI). The preliminary classification of the Clinical Investigator inspection of Dr. Michael Tolentino is Voluntary Action Indicated (VAI). Based on these four inspections, the data appear reliable and can be used in support of this application.

**Note:** Final headquarters classifications for all inspections are pending at this time. An addendum to this clinical inspection summary will be forwarded to the review division should there be a change in the final classification or additional observations of clinical and regulatory significance are discovered after reviewing the EIRs.

*{See appended electronic signature page}*

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

CONCURRENCE:

*{See appended electronic signature page}*

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/s/  
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KASSA AYALEW  
10/01/2012

SUSAN LEIBENHAUT  
10/01/2012

SUSAN D THOMPSON  
10/01/2012



Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research

Office of Biotechnology Products

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## FINAL LABEL AND LABELING REVIEW

**Date:** September 19, 2012

**Reviewer:** Kimberly Rains, Pharm.D.  
Office of Biotechnology Products

**Through:** Ramesh Potla, Ph.D.  
Division of Therapeutic Proteins

**Application:** BLA 125422

**Product:** JETREA™ (ocriplasmin)

**Applicant:** ThromboGenics, Inc.

**Submission Date(s):** April 18, 2012

### Executive Summary

The carton and container labels for JETREA™ (ocriplasmin) were reviewed and found to comply most of the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 200.100 and United States Pharmacopeia 8/1/12-11/30/12, USP 35/NF 30. Labeling deficiencies were identified. Comments are listed in the conclusions section.

### Background and Summary Description

JETREA™ (ocriplasmin) is indicated for the treatment of symptomatic vitreous adhesion including macular hole. The product is supplied in a single-use glass vial in a 0.5 mg/ 0.2 mL solution. The product must be diluted before use.

### Materials Reviewed:

Carton and Container labels

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Start of Sponsor Material



End of Sponsor Material

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Subpart G-Labeling Standards  
Subpart A-General Labeling Provisions

## I. Container

### A. 21 CFR 610.60 Container Label

(a) Full label. The following items shall appear on the label affixed to each container of a product capable of bearing a full label:

- (1) The proper name of the product; [see 21 CFR 600.3 (k) and section 351 of the PHS Act]. Conforms
- (2) The name, address, and license number of manufacturer; Conforms.
- (3) The lot number or other lot identification; Conforms
- (4) The expiration date; Conforms
- (5) The recommended individual dose, for multiple dose containers. Single-use vial. Not applicable.
- (6) The statement: “Rx only” for prescription biologicals. **Does not conform.**
- (7) If a Medication Guide is required under part 208 of the chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is

too small, the required statement may be placed on the package label.

(b) Package label information. If the container is not enclosed in a package, all the items required for a package label shall appear on the container label. Not applicable

(c) Partial label. If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label. Not applicable

(d) No container label. If the container is incapable of bearing any label, the items required for a container label may be omitted, provided the container is placed in a package which bears all the items required for a package label. Not applicable

(e) Visual inspection. When the label has been affixed to the container, a sufficient area of the container shall remain uncovered for its full length or circumference to permit inspection of the contents. – **Does not conform.** Information not supplied.

B. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located at the top of the label. [See 21 CFR 207.35]; NDC not present on vial label. **Request NDC presentation at the top of the vial label.**

C. 21 CFR 201.5 Drugs; adequate directions for use; Space limitations. Provided on carton. Conforms.

D. 21 CFR 201.6 Drugs; misleading statements; Conforms

E. 21 CFR 201.10 Drugs; statement of ingredients; [Placement and prominence] Conforms

F. 21 CFR 201.15 Drugs; prominence of required label statements; Conforms

G. 21 CFR 201.17 Drugs; location of expiration date; Conforms

H. 21 CFR 201.25 Bar code; Conforms

I. 21 CFR 201.50 Statement of identity; Conforms

J. 21 CFR 201.51 Declaration of net quantity of contents; **Does not conform**

K. 21 CFR 201.55 Statement of dosage; Conforms

L. 21 CFR 201.100 Prescription drugs for human use; Conforms

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Start of Sponsor Material



End of Sponsor Material

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## **II. Carton**

A. 21 CFR 610.61 Package Label

a) The proper name of the product; [see 21 CFR 600.3 (k) and section 351 of the PHS Act] Conforms

- b) The name, addresses, and license number of manufacturer; Conforms
- c) The lot number or other lot identification; Conforms
- d) The expiration date; Conforms
- e) The preservative used and its concentration, if no preservative is used and the absence of a preservative is a safety factor, the words “no preservative” Conforms
- f) The number of containers, if more than one; Not applicable
- g) The amount of product in the container expressed as (1) the number of doses, (2) the volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable; **Does not conform.**
- h) The recommended storage temperature; Conforms
- i) The words “Do not Freeze” or the equivalent, as well as other instructions, when indicated by the character of the product; Conforms
- j) The recommended individual dose if the enclosed container(s) is a multiple-dose container; Not applicable
- k) The route of administration recommended, or reference to such directions in and enclosed circular; Conforms
- l) Known sensitizing substances, or reference to enclosed circular containing appropriate information; Not applicable
- m) The type and calculated amount of antibiotics added during manufacture; Not applicable
- n) The inactive ingredients when a safety factor, or reference to enclosed circular containing appropriate information; Conforms
- o) The adjuvant, if present; Not applicable
- p) The source of the product when a factor in safe administration; Not applicable

q) The identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation, or reference to an enclosed circular containing appropriate information; Not applicable

r) Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words “No U.S. standard of potency”; Conforms

s) The statement “Rx only” for prescription biologicals; Conforms

B. 21 CFR 610.62 Proper name; package label; legible type [*Note: Per 21 CFR 601.2(c)(1), certain regulation including 21 CFR 610.62 do not apply to the four categories of “specified” biological products listed in 21 CFR 601.2(a)*] Not applicable.

a) Position. The proper name of the product on the package label shall be placed above any trademark or trade name identifying the product and symmetrically arranged with respect to other printing on the label.

b) Prominence. The point size and typeface of the proper name shall be at least as prominent as the point size and typeface used in designating the trademark and trade name. The contrast in color value between the proper name and the background shall be at least as great as the color value between the trademark and trade name and the background. Typography, layout, contrast, and other printing features shall not be used in a manner that will affect adversely the prominence of the proper name.

c) Legible type. All items required to be on the container label and package label shall be in legible type. “Legible type” is type of a size and character which can be read with ease when held in a good light and with normal vision.

C. 21 CFR 610.63 Divided manufacturing responsibility to be shown; Not applicable

D. 21 CFR 610.64 Name and address of distributor

The name and address of the distributor of a product may appear on the label provided that the name, address, and license number of the manufacturer also appears on the label and the name of the distributor is qualified by one of the following phrases: “Manufactured for \_\_\_\_\_”.

“Distributed by \_\_\_\_\_”, “Manufactured by \_\_\_\_\_ for \_\_\_\_\_”, “Manufactured for \_\_\_\_\_ by \_\_\_\_\_”, “Distributor: \_\_\_\_\_”, or “Marketed by \_\_\_\_\_”. The qualifying phrases may be abbreviated. Not applicable.

- E. 21 CFR 610.67 Bar code label requirements  
Biological products must comply with the bar code requirements at §201.25 of this chapter; Conforms
- F. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located on top of the label. [See 21 CFR 207.35] Conforms
- G. 21 CFR 201.5 Drugs; adequate directions for use; Conforms
- H. 21 CFR 201.6 Drugs; misleading statements; Conforms
- I. 21 CFR 201.10 Drugs; statement of ingredients; [Placement and Prominence] Conforms
- J. 21 CFR 201.15 Drugs; prominence of required label statements; Conforms
- K. 21 CFR 201.17 Drugs; location of expiration date; Conforms
- L. 21 CFR 201.25 Bar code label requirements; Conforms
- M. 21 CFR 201.50 Statement of identity; Conforms
- N. 21 CFR 201.51 Declaration of net quantity of contents; **Does not conform**
- O. 21 CFR 201.55 Statement of dosage; Conforms
- P. 21 CFR 201.100 Prescription drugs for human use; Conforms

## Conclusions

- 1. Container
  - a) Add the required statement “Rx Only” per 21 CFR 610.60.
  - b) Please indicate how the label is affixed to the vial and where the visual area of inspection is located per 21 CFR 610.60 (e).
- 2. Container and Carton
  - a) Revise the presentation of the manufacturer from, “Manufactured for:” to [REDACTED]<sup>(b) (4)</sup> to comply with the definition of manufacturer listed in 21 CFR 600.3(t).

- b) Revise the strength presentation from “2.5 mg/mL to (b) (4) [REDACTED] to accurately describe the vial contents per 21 CFR 610.61(g) and 21 CFR 201.51.
3. Vial cap and ferrule
- a) Please comment if there is any text on the ferrule and cap overseal. A revised USP standard will go into effect on December 1, 2013. We refer you to the following link for additional information: <http://www.usp.org/usp-nf/notices/retired-compendial-notices/general-chapter-injections-labeling-ferrules-and-cap-overseals-section>

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KIMBERLY M RAINS  
09/21/2012

RAMESH B POTLA  
09/21/2012

MARY K W LEE  
09/26/2012

**Determining When Pre-License / Pre-Approval Inspections are Necessary  
Inspection Waiver Memorandum**

**Date:** August 28, 2012

**From:** Lakshmi Rani Narasimhan, Ph.D., OC/OMPQ/DGMP/BMAB  
Ramesh Potla, Ph.D., OPS/OBP/DTP  
Jee Chung, Ph.D., OPS/OBP/DTP

**To:** BLA File, STN 125422/0

**Through:** Patricia F. Hughes, Ph.D., Team Leader, CDER/OC/OMPQ/DGMP/BMAB *P/18  
8/29/2012*

**Subject:** Recommendation to waive a pre-license inspection

**Applicant:** ThromboGenics Inc.

**Facility:** [REDACTED] (b) (4)

**Product:** Jetrea™ (ocriplasmin)

**Dosage:** Sterile solution for intravitreal administration containing ocriplasmin at a concentration of 2.5mg/mL

**Indication:** Treatment of Symptomatic vitreomacular adhesion (VMA) including macular hole.

**Waiver Recommendation**

We recommend that the pre-approval inspection of the [REDACTED] (b) (4) be waived for STN 125422/0 (submission dated 17 April 2012). An inspection of the facility was scheduled by GDMAB and conducted (b) (4) on [REDACTED] (b) (4)

**Clearance Routing**

*[Signature]* **CONCUR/NONCONCUR** DATE 9/19/2012  
David Doleski,  
Director, Division of Good Manufacturing Practice Assessment,  
Office of Manufacturing and Product Quality, Office of Compliance, CDER

*[Signature]* **CONCUR/NONCONCUR** DATE 9-11-12  
Amy Rosenberg, M.D.  
Director, Division of Therapeutic Proteins, Office of Biotechnology Products,  
Office of Pharmaceutical Science, CDER

## Summary

BLA 125422/0 is for ocriplasmin (proposed name: Jetrea™) which is used for the treatment of symptomatic vitreomacular adhesion (VMA) including macular hole. Ocriplasmin drug product is supplied as a sterile, clear and colorless solution with no preservatives in a single use glass vial containing 0.5mg of ocriplasmin in 2.5mg/mL solution for intravitreal injection. Prior to administration, ocriplasmin is 1:1 diluted with sodium chloride (0.9% w/v) solution and the recommended dose is 0.125mg (125µg) corresponding to 0.1mL of the diluted solution.

Ocriplasmin is a recombinant truncated form of human plasmin produced in a *Pichia pastoris* expression system by recombinant DNA technology. (b) (4)

(b) (4) Drug substance is manufactured by Fujifilm Diosynth Biotechnologies UK Ltd. and drug product is filled and finished at (b) (4)

## Facility Information



## Supporting Information

The following information is provided in support of waiving the pre-approval inspection:

1. *The manufacturer does not hold an active U.S. license, or in the case of a contract manufacturer, is not approved for use in manufacturing a licensed product.*
  - a. (b) (4) will manufacture ocriplasmin drug product which is the subject of BLA 125422 that is currently under review at the Agency. (b) (4)
  - b. (b) (4)

2. FDA has not inspected the establishment in the last 2 years.

(b) (4)

A comprehensive cGMP and Pre-approval inspection for BLA STN 125422 was conducted on (b) (4)

3. The previous inspection revealed significant GMP deficiencies in areas related to the processes in the submission (similar processes) or systematic problems, such as QC/QA oversight.

(b) (4)

(b) (4) However, the facility is recommended for the approval of BLA STN #125422.

4.

(b) (4)

5.

(b) (4)

Signed:

Lakshmi Rani Narasimhan, Ph.D  
Microbiologist  
OC/OMPQ/DGMP/BMAB

Lakshmi Rani Narasimhan Date 28 Aug 12

Ramesh Potla, Ph.D  
Staff Fellow  
OPS/OBP/DTP

Ramesh Potla Date 09/10/2012

Jee Chung, Ph.D  
Biologist  
OPS/OBP/DTP

Jee Chung Date 9/10/12

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/s/  
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LAKSHMI RANI NARASIMHAN  
09/19/2012

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information		
NDA # BLA# 125422/0	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Jetrea Established/Proper Name: ocriplasmin Dosage Form: Intravitreal Injection Strengths: 2.5 mg/mL		
Applicant: ThromboGenics Inc. Agent for Applicant (if applicable):		
Date of Application: April 16, 2012 Date of Receipt: April 17, 2012 Date clock started after UN:		
PDUFA Goal Date: October 17, 2012	Action Goal Date (if different):	
Filing Date: June 16, 2012	Date of Filing Meeting: May 29, 2012	
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): Treatment of Symptomatic Vitreomacular Adhesion including macular Hole		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i><b>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a> and refer to Appendix A for further information.</b></i>		
Review Classification:  <i><b>If the application includes a complete response to pediatric WR, review classification is Priority.</b></i>  <i><b>If a tropical disease priority review voucher was submitted, review classification is Priority.</b></i>	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input checked="" type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>  <i><b>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</b></i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input checked="" type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): 100370				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>		X		
<b>If yes, explain in comment column.</b>				
<b>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</b>				
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<b>User Fee Status</b> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>		Payment for this application: <input checked="" type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<b>Comment: Paid prior to exemption being approved.</b>					
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>		Payment of other user fees: <input type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<b>505(b)(2)</b>		<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>(NDAs/NDA Efficacy Supplements only)</b>					
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?				X	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].				X	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?				X	
<i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i>					
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? <i>Check the Electronic Orange Book at:</i> <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a>				X	
If yes, please list below:					
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i>					
<b>Exclusivity</b>		<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i> <a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a>			X		

<p><b>If another product has orphan exclusivity</b>, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>			X	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p><b>If yes, # years requested:</b></p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>		X		
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		X		
<p><b>If yes</b>, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>			X	

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p><b>If mixed (paper/electronic) submission</b>, which parts of the application are submitted in electronic format?</p>				
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>If electronic submission</b>, does it follow the eCTD guidance?<sup>1</sup>  <b>If not</b>, explain (e.g., waiver granted).</p>	X			
<p><b>Index:</b> Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	X			

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only)				
<b>If no, explain.</b>				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?			<b>X</b>	
<b>If yes, BLA #</b>				
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, <b>paper</b> forms and certifications with hand-written signatures must be included. <b>Forms</b> include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); <b>Certifications</b> include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?				
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with authorized signature?	X			

<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <b>both</b> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&amp;C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>				
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	

<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	

<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b><u>PREA</u></b></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			
<p><b>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</b></p>	X			

<sup>2</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<b>If studies or full waiver not included</b> , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?  <i>If no, request in 74-day letter</i>			X	
<b>If a request for full waiver/partial waiver/deferral is included</b> , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?  <i>If no, request in 74-day letter</i>	X			
<b><u>BPCA</u> (NDAs/NDA efficacy supplements only):</b>  Is this submission a complete response to a pediatric Written Request?  <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>			X	
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>		X		
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? <sup>4</sup>				

<sup>3</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

<sup>4</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>	X			
Are annotated specifications submitted for all stock keeping units (SKUs)?  <i>If no, request in 74-day letter.</i>	X			
If representative labeling is submitted, are all represented SKUs defined?  <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?			X	
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)  <i>If yes, specify consult(s) and date(s) sent:</i>			X	
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s) <b>Date(s):</b> 12/15/10, 9/26/08, 9/24/08  <i>If yes, distribute minutes before filing meeting</i>	X			

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> 9/21/11  <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b>  <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		X		

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** May 29, 2012

**BLA/NDA/Supp #:** 125422/0

**PROPRIETARY NAME:** JETREA

**ESTABLISHED/PROPER NAME:** ocriplasmin intravitreal injection

**DOSAGE FORM/STRENGTH:** 2.5 mg/mL

**APPLICANT:** ThromboGenics, Inc.

**PROPOSED INDICATION:** symptomatic vitreomacular adhesion

**BACKGROUND:** BLA received April 17, 2012

**REVIEW TEAM:**

<b>Discipline/Organization</b>	<b>Names</b>		<b>Present at filing meeting? (Y or N)</b>
Regulatory Project Management	RPM:	Jacquelyn Smith	Y
	CPMS/TL:	Diana Willard	Y
Cross-Discipline Team Leader (CDTL)	William Boyd		N
Clinical	Reviewer:	Jennifer Harris	Y
	TL:	William Boyd	N
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:	N/A	N/A
	TL:	N/A	N/A
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:	N/A	N/A
	TL:	N/A	N/A

Clinical Pharmacology	Reviewer:	Yoriko Harigaya	Y
	TL:	Philip Ccolangelo	Y
Biostatistics	Reviewer:	Yunfan Deng	Y
	TL:	Yan Wang	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Maria Rivera	N
	TL:	Lori Kotch	Y
Statistics (carcinogenicity)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Product Quality (CMC)	Reviewer:	Ramesh Potla	Y
	TL:	Jee Chung	Y
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:	Maria C. & Lakshmi N.	Y
	TL:	Patricia Hughes	Y
CMC Labeling Review	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Facility Review/Inspection	Reviewer:	Maria C. & Lakshmi N.	Y
	TL:	Patrica Hughes	Y
OSE/DMEPA (proprietary name)	Reviewer:	Jung Lee	Y
	TL:	Alice Tu	Y
OSE/DRISK (REMS)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
OC/OSI/DSC/PMSB (REMS)	Reviewer:	Kassa Ayalew	Y
	TL:	Susan Thompson	N

Bioresearch Monitoring (OSI)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Controlled Substance Staff (CSS)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Other reviewers	N/A		N/A
Other attendees	N/A		N/A

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>• 505(b)(2) filing issues?</li> </ul> <p><b>If yes, list issues:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable
<p><b>CLINICAL</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li>○ <i>this drug/biologic is not the first in its class</i></li> <li>○ <i>the clinical study design was acceptable</i></li> </ul>	<input checked="" type="checkbox"/> YES Date if known: July 26, 2012 <input type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<ul style="list-style-type: none"> <li>○ <i>the application did not raise significant safety or efficacy issues</i></li> <li>○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	
<ul style="list-style-type: none"> <li>• Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input checked="" type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter

<p><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>PRODUCT QUALITY (CMC)</b></p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p style="padding-left: 40px;">If no, was a complete EA submitted?</p> <p style="padding-left: 40px;">If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</li> </ul> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ?</li> </ul> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<b><u>CMC Labeling Review</u></b>	
<b>Comments:</b>	<input type="checkbox"/> Review issues for 74-day letter
<b>REGULATORY PROJECT MANAGEMENT</b>	
<b>Signatory Authority:</b>	
<b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):	
<b>Comments:</b>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing.  <u>Review Issues:</u>  <input type="checkbox"/> No review issues have been identified for the 74-day letter.  <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):  <u>Review Classification:</u>  <input type="checkbox"/> Standard Review  <input checked="" type="checkbox"/> Priority Review
<b>ACTIONS ITEMS</b>	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input checked="" type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input checked="" type="checkbox"/>	If priority review: <ul style="list-style-type: none"> <li>notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li> </ul>

<input type="checkbox"/>	<ul style="list-style-type: none"> <li>notify OMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input checked="" type="checkbox"/>	<p>BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at:</p> <p><a href="http://erom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f">http://erom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f</a>]</p>
<input type="checkbox"/>	Other

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JACQUELYN E SMITH  
06/20/2012

DIANA M WILLARD  
06/20/2012