

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204958Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)

Product Quality Microbiology Review

1/03/2014

NDA: 204958

Drug Product Name

Proprietary: (b) (4)

Non-proprietary: Cangrelor for Injection

Review Number: 1

Dates of Submission(s) Covered by this Review

| Submit | Received | Review Request | Assigned to Reviewer |
|---------------|-----------------|-----------------------|-----------------------------|
| 4/30/2013 | 4/30/2013 | 5/02/2013 | 5/02/2013 |
| 8/19/2013 | 8/19/2013 | N/A | N/A |
| 8/30/2013 | 8/30/2013 | N/A | N/A |
| 10/09/2013 | 10/09/2013 | N/A | N/A |

Submission History (for 2nd Reviews or higher)

None

Applicant/Sponsor

Name: The Medicines Company

Address: 8 Sylvan Way, Parsippany, NJ 07054

Representative: Stephen Sherman, Sr. Director Global Reg. Affairs

Telephone: 973 290 6300

Name of Reviewer: Steven P. Donald, M.S.

Conclusion: Recommended as Approvable Pending a Complete Response to Microbiology Deficiencies

Product Quality Microbiology Data Sheet

- A. 1. **TYPE OF SUBMISSION:** Original NDA
2. **SUBMISSION PROVIDES FOR:** The manufacture and marketing of a sterile drug product.
3. **MANUFACTURING SITE:** [REDACTED] (b) (4)
4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Lyophilized powder for reconstitution and injection, IV, 50 mg, in a single dose glass vial.
5. **METHOD(S) OF STERILIZATION:** [REDACTED] (b) (4)
6. **PHARMACOLOGICAL CATEGORY:** Anti Coagulant
- B. **SUPPORTING/RELATED DOCUMENTS:** DMF [REDACTED] (b) (4) for [REDACTED] (b) (4)
- C. **REMARKS:** Partial responses to the 8/02/201 information request were received on 8/19/2013 and 8/30/2013.

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Executive Summary

I. Recommendations

- A. Recommendation on Approvability** - Recommended as Approvable Pending a Complete Response to Microbiology Deficiencies.
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – N/A

II. Summary of Microbiology Assessments

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** –  (b) (4)
- B. Brief Description of Microbiology Deficiencies** – Product labeling does not reflect the conclusions of the post constitution hold time study.
- C. Assessment of Risk Due to Microbiology Deficiencies** – Failure to address the product quality microbiology deficiency could result in a significant risk to the sterility assurance of the reconstituted and diluted drug product.
- D. Contains Potential Precedent Decision(s)**- Yes No

III. Administrative

- A. Reviewer's Signature** _____
Steven P. Donald, M.S.
Microbiology Reviewer
- B. Endorsement Block** _____
Stephen Langille, Ph.D.
Senior Microbiology Reviewer
- C. CC Block**
N/A

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/s/

STEVEN P DONALD
01/06/2014

STEPHEN E LANGILLE
01/06/2014

PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 204958

Applicant: The Medicines
Company

Letter Date: 4/30/2013

Drug Name: Cangrelor for
Injection

NDA Type: 505 (b)(1)

Stamp Date: 4/30/2013

The following are necessary to initiate a review of the NDA application:

| | Content Parameter | Yes | No | Comments |
|----|---|------------|-----------|--|
| 1 | Is the product quality microbiology information described in the NDA and organized in a manner to allow substantive review to begin? Is it legible, indexed, and/or paginated adequately? | X | | Submission is in eCTD format |
| 2 | Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product? | X | | See 3.2.P.3.3 |
| 3 | Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product? | X | | See 3.2.P.3.5 |
| 4 | Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review? | X | | English versions are available when necessary |
| 5 | Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies? | X | | See 3.2.P.2.5 and Report CC167.12 |
| 6 | Has the applicant submitted microbiological specifications for the drug product and a description of the test methods? | X | | See 3.2.P.5.1 |
| 7 | Has the applicant submitted the results of analytical method verification studies? | X | | See 3.2.P.5.3 |
| 8 | Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions? | | | N/A |
| 9 | If sterile, are extended post-constitution and/or post-dilution hold times in the draft labeling supported by microbiological data? | X | | Testing is limited and may not support post reconstitution and dilution hold times. Further review will be required. See stability.summary.pdf, pg. 29 and 54. |
| 10 | Is this NDA fileable? If not, then describe why. | X | | |

Additional Comments:

(b) (4) is intended for IV administration only after reconstitution and dilution. (b) (4) is administered as a 30 ug/kg IV bolus followed by 4 ug/kg/minute IV infusion. Sterile Water for Injection is used for reconstitution; dilution is performed in Sodium Chloride Injection 0.9% USP or 5% Dextrose Injection USP. In some cases, IV administration may occur over a (b) (4) period. Reconstituted and diluted (b) (4) may be stored at USP Controlled Room Temperature for up to 24 hours. Any remaining unused portion in the vial is discarded.

A request will be made for the sponsor to submit microbiological data to demonstrate that the reconstituted and diluted product solution will not support microbial growth during the proposed storage and administration period.

| | |
|---|-----------|
| Steven P. Donald CDER/OPS/NDMS | 5/14/2013 |
| Reviewing Microbiologist | Date |
| Stephen Langille CDER/OPS/NDMS | 5/14/2013 |
| Microbiology Secondary Reviewer/Team Leader | Date |

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/s/

STEVEN P DONALD
06/04/2013

STEPHEN E LANGILLE
06/04/2013