

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022225Orig1s000**

**MICROBIOLOGY / VIROLOGY REVIEW(S)**

# Product Quality Microbiology Review

5/10/2013

**NDA: 022225**

**Drug Product Name**

**Proprietary:** Bridion

**Non-proprietary:** sugammadex sodium

**Review Number:** 2

**Dates of Submission(s) Covered by this Review**

<b>Submit</b>	<b>Received</b>	<b>Review Request</b>	<b>Assigned to Reviewer</b>
12/19/2012	12/20/2012	1/02/2013	1/11/2013
5/08/2013	5/10/2013	N/A	N/A

**Submission History (for amendments only)**

<b>Submit Date(s)</b>	<b>Microbiology Review #</b>	<b>Review Date(s)</b>
10/30/2007	10/30/2007	12/06/2007

**Applicant/Sponsor**

**Name:** Organon USA Inc.

**Address:** One Merck Drive

**P.O.Box** 100, Whitehouse Station, NJ 08889

**Representative:** Dori L. Glassner, Director Reg. Affairs

**Telephone:** 732 594-2735

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

**Conclusion:** Recommended for Approval

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## Product Quality Microbiology Data Sheet

- A.**
- 1. TYPE OF SUBMISSION:** NDA Resubmission
  - 2. SUBMISSION PROVIDES FOR:** New drug product and addressing deficiencies in Complete Response Letter (dated July 31, 2008).
  - 3. MANUFACTURING SITE:** Organon (Ireland) Limited, a subsidiary of Merck & Co., Inc., Drynam Road, Swords, Co. Dublin, Ireland
  - 4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Injection, IV, 100 mg/ml; 2 ml and 5 ml single dose glass vial
  - 5. METHOD(S) OF STERILIZATION:** (b) (4)
  - 6. PHARMACOLOGICAL CATEGORY:** Selective Relaxant Binding Agent
- B. SUPPORTING/RELATED DOCUMENTS:** None
- C. REMARKS:** This is a resubmission to provide Merck's response to the Not Approvable letter received by the applicant July 31, 2008 for NDA 022225. The responses are provided in Module 1.11.2 for the nonclinical response and Module 1.11.4 for the clinical response, in the 12/19/2012 submission. No product quality microbiology deficiencies are identified in the Not Approvable letter. The previous Product Quality Microbiology review for NDA 22225 is dated February 20, 2008 and recommended the NDA for approval. The 12/19/2012 submission also included a (b) (4)
- 

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**Executive Summary****I. Recommendations**

- A. Recommendation on Approvability –**  
NDA 022225 is recommended for approval.
- 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**  
No product quality microbiology deficiencies were identified based upon the information provided.
- C. Assessment of Risk Due to Microbiology Deficiencies -**  
N/A
- D. Contains Potential Precedent Decision(s)-**  Yes  No

**III. Administrative**

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

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## **Product Quality Microbiology Assessment**

### **1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q)**

#### **MODULE 3.2: BODY OF DATA**

There are no Product Quality Microbiology deficiencies to be addressed in the resubmission of 12/19/2012; the applicant states that there are no changes to the manufacturing process of the drug substance and drug product or to their composition. Consequently, the quality of sugammadex drug product in the original NDA and the NDA resubmission is unchanged. The applicant does identify some informational changes in the Overall Quality Summary which are listed below:

- The product vials are [REDACTED] (b) (4)
- The rubber stoppers for Org 25969 Solution for Injection 100 mg/ml will be [REDACTED] (b) (4). The validation results are included in section 4.2 (QOS, Sec. 4.2).
- The container closure integrity test has been re-validated but there has been no change to the container or closure.
- The text in section 5 on "Procedures and specifications for [REDACTED] (b) (4) has been removed and replaced with the text [REDACTED] (b) (4)
- The facility floor plan in section 14.1 has been updated.
- Stability data from two different manufacturing locations have been updated. Neither of these locations include the alternate facility proposed in the comparability protocol.

The above changes are not considered critical for a [REDACTED] (b) (4) and will not be considered in this review.

A critical change that has been identified in the Quality Overall Summary of the 12/19/2013 submission (pg. 10) is the inclusion of [REDACTED] (b) (4) in Section 3.2.R.

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(b) (4)



**Acceptable**

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/s/  
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STEVEN P DONALD  
05/14/2013

STEPHEN E LANGILLE  
05/15/2013

# Product Quality Microbiology Review

March 17, 2015

**NDA:** 22-225

**Drug Product Name**

**Proprietary:** Bridon

**Non-proprietary:** sugammadex sodium Injection

**Review Number:** 1

**Dates of Submission(s) Covered by this Review**

Submit	Received	Review Request	Assigned to Reviewer
October 22, 2014	October 22, 2014	October 30, 2014	October 30, 2014

**Submission History (for 2<sup>nd</sup> Reviews or higher) – N/A**

Submit Date(s)	Microbiology Review #	Review Date(s)
October 30, 2007	1	March 03, 2008
December 19, 2012	2	May 15, 2013

**Applicant/Sponsor**

**Name:**

**Address:** Organon

56 Livingston Ave. Roseland, NJ 07068

**Representative:** Dori L. Glassner, Director Global Reg. Affairs  
TEL: 732-594-2735

**Name of Reviewer:** Vinayak B. Pawar, Ph.D.

**Conclusion:** Recommend Approval

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## Product Quality Microbiology Data Sheet

- A. 1. **TYPE OF SUBMISSION:** Priority Review, resubmission
2. **SUBMISSION PROVIDES FOR:** Response to Complete Response Letter.
3. **MANUFACTURING SITE:** [REDACTED] (b) (4)  
[REDACTED]
4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Injection, IV, 100 mg/ml; 2 ml and 5 ml single dose glass vial or 200mg/vial and 500mg/vial.
5. **METHOD(S) OF STERILIZATION:** [REDACTED] (b) (4).
6. **PHARMACOLOGICAL CATEGORY:** Reversal of Neuromuscular blockade
- B. **SUPPORTING/RELATED DOCUMENTS:** None
- C. **REMARKS:** The previous Product Quality Microbiology review for NDA 22225 is dated February 20, 2008 and recommended the NDA for approval. However, Merck received a Not Approvable letter for NDA 22225 from the Agency on July 31, 2008. The sponsor responded by providing a resubmission on December 12, 2012 which included [REDACTED] (b) (4). However, a Warning Letter was issued as a result of a site inspection conducted on September 23 through November 25, 2013, Organon, Dublin, Ireland. After review of comparability protocol and subsequent teleconference on April 24, 2013 between the Agency and the applicant, [REDACTED] (b) (4). [REDACTED] The subject resubmission is a response to the deficiencies identified in the CR letter which includes a response to the [REDACTED] (b) (4). [REDACTED]. This is an electronic submission.

**filename:** N022225R2

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## **Executive Summary**

### **I. Recommendations**

- A. Recommendation on Approvability** – Recommend Approval.
- 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** – The drug product is manufactured (b) (4)
- B. Brief Description of Microbiology Deficiencies** – None.
- C. Assessment of Risk Due to Microbiology Deficiencies** – N/A
- D. Contains Potential Precedent Decision(s)** -  Yes  No

### **III. Administrative**

- A. Reviewer's Signature** \_\_\_\_\_  
Vinayak B. Pawar, Ph.D., Sr. Review Microbiologist,  
CDER/OPQ/DMA
- B. Endorsement Block** \_\_\_\_\_  
Stephen E. Langille, Ph.D., Acting Chief Branch III,  
CDER/OPQ/DMA
- C. CC Block**  
N/A

**Product Quality Microbiology Assessment**

**1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA**

**S DRUG SUBSTANCE** - Not the subject of this review.

**P DRUG PRODUCT**

**P.1 Description of the Composition of the Drug Product**

- Description of drug product – Sugammadex (Org 25969) Solution for Injection 100 mg/mL is a clear, colorless to slightly yellow aqueous solution for injection filled in (b) (4) (2 mL solution per vial) or (b) (4) (5 mL solution per vial) glass vials.
- Drug product composition – The composition of Sugammadex (Org 25969) Solution for Injection 100 mg/mL filled in (b) (4) vials (2 mL per vial) or (b) (4) vials (5 mL per vial) is provided in Table 1 (copied from Table 1, Section 2.3.P.1).

**Table 1. Composition of Org 25969 Drug Product**

Component	Reference to quality standard	Function	Quantity per vial (2 mL)	Quantity per vial (5 mL)	Quantity per mL
Sugammadex Sodium (Org 25969) + mono OH-derivative of sugammadex (Org 48302) <sup>†</sup>	In-house standard	active	200 mg	500 mg	100 mg
Sodium Hydroxide <sup>‡</sup>	Ph. Eur., NF	pH adjuster	q.s. to pH 7.5	q.s. to pH 7.5	q.s. to pH 7.5
Hydrochloric Acid <sup>‡</sup>	Ph. Eur., NF	pH adjuster	q.s. to pH 7.5	q.s. to pH 7.5	q.s. to pH 7.5
(b) (4)					
(b) (4)					
<sup>†</sup> Declared amount of 100 mg/mL sugammadex corresponds with 108.8 mg/mL sugammadex sodium salt (Org 25969) which may contain up to 7.2mg/mL of mono OH-derivative of sugammadex (Org 48302)					
(b) (4)					

- Description of container closure system – A description of the glass vial and stopper primary packaging that has been qualified for use is given in Table 2 (copied from Table 2, Section 3.2.P.3.2).

**Table 2. Container Closure Components**

Component	Supplier	Description	Compendial compliance
Vial (b) (4) Vial DMF (b) (4)	(b) (4)	(b) (4) Type I glass container, for injectables, (b) (4) with 13mm neck finish, (b) (4) with 20mm neck finish.	JP <sup>‡</sup> USP Ph. Eur.
Stopper for (b) (4) vial Stopper for (b) (4) vial DMF (b) (4) DMF (b) (4)	(b) (4)	(b) (4) rubber (b) (4) (b) (4) latex free.	JP <sup>‡</sup> USP Ph. Eur.
Cap for (b) (4) vial Cap for (b) (4) vial	(b) (4)	Aluminum crimp cap with (b) (4) flip off button.	None
<sup>‡</sup> when required per the product license <sup>§</sup> for (b) (4)			

**P.2 Pharmaceutical Development**

**P.2.5 Microbiological Attributes**

- Container-Closure and Package integrity – According to the applicant, five hundred (b)(4) units (exposed to maximum F<sub>o</sub> attained for routine production) were subjected to microbial challenge according to Standard Operating Procedures. This test involves inversion and submersion of the test units up to the sealing interface in a suspension of *Escherichia coli* (ATCC 8739), population 10<sup>6</sup> CFU/mL, within a vacuum chamber. The vacuum pressure in the chamber is set at approximately 13" Hg and held for approximately 10 minutes. The vacuum allows inoculum penetration of the crimp to the sealing interface of the vial and stopper where leaks are most likely to occur. The units are then incubated at 30-35°C for 14 days. In a 500-unit test, the results are acceptable if there are no unit failures and at least 50% of the known defectives are positive. Twenty (b)(4) units will be tested annually according to the same microbial challenge for the duration of the test protocol, typically the longest expiry of the product which utilizes the container/closure system plus one year. In a 20-unit test, the results are acceptable if there are no unit failures and at least one (1) of the known defectives is positive. Results of the Microbial Ingress challenge are presented in Table 3 for the (b)(4) vial component combination and Table 4 for the (b)(4) vial component combination (copied from Tables 46 & 47, Section 3.2.P.3.5.2).

**Table 3. Container Closure Integrity (b)(4) vial and 13 mm stopper**

Batch Number	AB5426	Date Filled	01 Oct 2013
Vial:	(b)(4)	(b)(4)	13hrs 41mins
Stopper:	13 mm		13 mm
	<b>Acceptance Criteria</b>	<b>Results</b>	
Microbial Ingress:	(b)(4)	(b)(4) units (b)(4) cycled for each of three runs	
Container Closure Integrity:	All must be positive for inoculated microbial growth.	(b)(4) non-cycled for each of three runs	

**Table 4. Container Closure Integrity (b)(4) vial and 20 mm stopper**

Batch Number	AB3762	Date Filled	25 Oct 2013
Vial:	(b)(4)	(b)(4)	14hrs 36mins
Stopper:	20 mm		20 mm
	<b>Acceptance Criteria</b>	<b>Results</b>	
Microbial Ingress:	(b)(4)	(b)(4) units (b)(4) cycled for each of three runs	
Container Closure Integrity:	All must be positive for inoculated microbial growth.	(b)(4) non-cycled for each of three runs	

- Preservative Effectiveness – N/A

- Justification for not having a microbial limit specification for a non-sterile drug product – N/A

### ADEQUATE

**REVIEWER COMMENT** – The applicant’s verification of container closure integrity is consistent with regulatory expectations for a pharmaceutical product.

#### **P.3 Manufacture**

**P.3.1 Manufacturers:** [REDACTED] (b) (4)

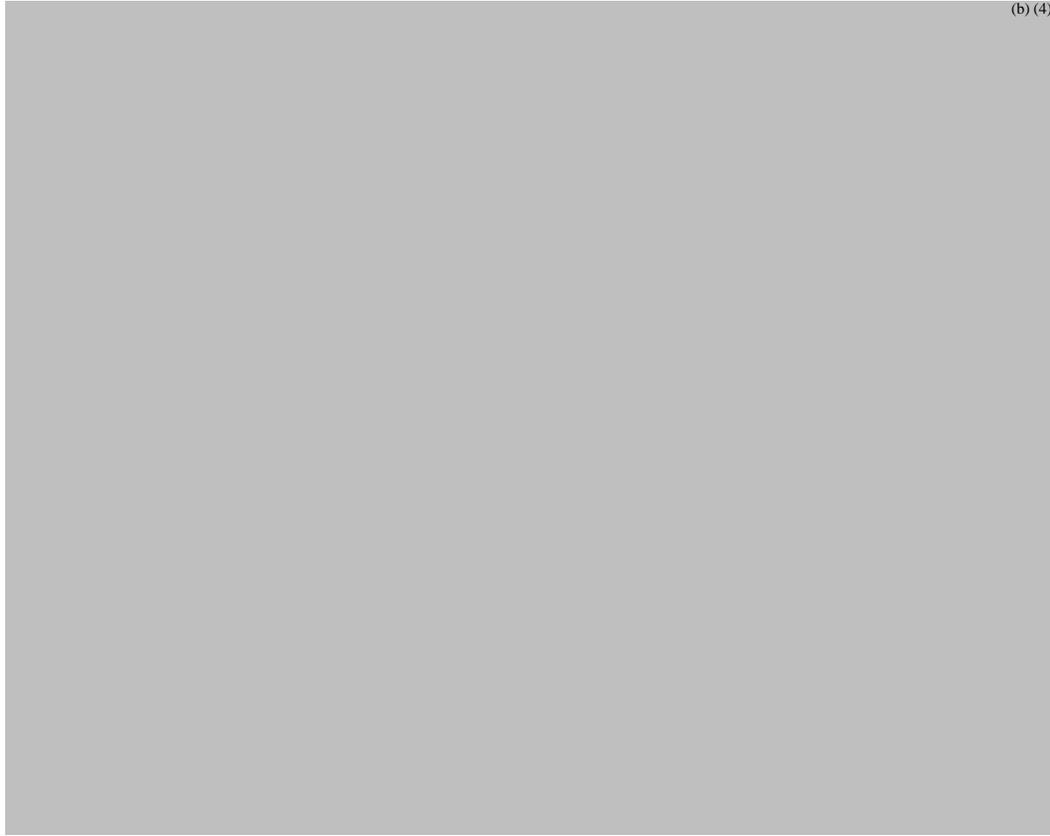
#### **P.3.3 Description of the Manufacturing Process and Process Controls**

The manufacturing process flow chart and a detailed manufacturing process description for the [REDACTED] (b) (4) drug product are presented in Figure 1 (copied from Figure 1, Section 3.2.P.3.3). All manufacturing is conducted according to current Good Manufacturing Practices.

#### **Figure 1 Manufacturing Process Flow Diagram**



(b) (4)



### ADEQUATE

**REVIEWER COMMENT** – The applicant has met regulatory expectations for validating the process used for [redacted] (b) (4) of the drug product.

#### **P.5 Control of Drug Product**

**P.5.1 Specifications** – See the following Section P.5.2.

#### **P.5.2 Analytical Procedures**

Sugammadex Solution for Injection 100 mg/mL is tested at release on sterility and bacterial endotoxins.

Endotoxin – Bacterial Endotoxins Test (BET) of Sugammadex Solution for Injection 100 mg/mL is carried out per Ph.Eur. 2.6.14, USP <85> using kinetic turbidimetric method. Sugammadex Solution for Injection 100 mg/mL is tested for BET at release. Vials placed on stability are tested for BET annually and at the end of shelf life. Finished product testing of batches AB9061A, AB9062A, AB9063A (200 mg/vial) & AC0756A, AC0757A, AC0758A (500 mg/vial) tested for endotoxins at < [redacted] (b) (4) EU/mL.

Endotoxin Limit = [redacted] (b) (4)

Endotoxin Limit Conc = [REDACTED] (b) (4)

MVD = [REDACTED] (b) (4)

The compatible test dilution was [REDACTED] (b) (4), i.e. the lowest dilution that demonstrated the least amount of inhibition during the interference screen phase.

- Sterility – Sterility testing of Sugammadex Solution for Injection 100 mg/mL is carried out per Ph.Eur.2.6.1, USP <71> using membrane filtration method. Bacteriostasis and fungistasis testing was provided in Report NL0060383, Section 4.2. Sugammadex Solution for Injection 100 mg/mL is tested for sterility at release. Vials placed on stability are tested for sterility annually and at the end of shelf life. Finished product testing of batches AB9061A, AB9062A, AB9063A (200 mg/vial) & AC0756A, AC0757A, AC0758A (500 mg/vial) all passed sterility test.
- Microbial Limits – N/A

### ADEQUATE

**REVIEWER COMMENT** – The applicant meets regulatory expectations with regard to the test method, acceptance criteria and verification of the suitability of use of the sterility and bacterial endotoxins test that will be performed on the drug product prior to its release.

**P.7 Container Closure System** - See Review Section P.1.

**P.8 Stability**

**P.8.1 Stability Summary and Conclusion**

Bacterial Endotoxins and Sterility were monitored at the initial time point for the 100 mg/mL (2 mL) and 100 mg/mL (5 mL) at 25°C/60%RH as indicated in Review Section P.5.2 above. All results conform to the proposed specifications provided in Sec. 3.2.P.5.1.

**P.8.2 Post-Approval Stability Protocol and Stability Commitment**

Tests are performed on products in market container/closure systems and the program includes both long term and accelerated storage conditions as appropriate. Stability studies are carried out on validation batches (commitment batches) to assure the product stability profile remains unchanged from that exhibited by the research batches. Additional batches of marketed product are selected each year on a continuing basis for examination. Specifications provided in Section 3.2.P.5.1.

Specifications and testing schedule for post-approval stability program:

- Container Closure Integrity – performed at initial, 12, 24 & 36 months
- Endotoxin – performed at initial, 12 & 36 months
- Sterility - performed at initial, 12 & 36 months

**P.8.3 Stability Data** – See Section P.5.2.

**ADEQUATE**

**REVIEWER COMMENT** – The applicant meets the regulatory expectations with regard to the design of the stability program to support the drug product’s microbiological quality throughout its shelf life.

**2. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1**

**A. PACKAGE INSERT** – The drug product is manufactured in a single use vial and there is no manipulation or reconstitution of the product.

**ADEQUATE**

**REVIEWER COMMENT** – The applicant meets the regulatory expectations with regard to the information related to issues of product quality microbiology that is provided in the product labeling.

**3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS: None**

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/s/  
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VINAYAK B PAWAR  
03/24/2015

STEPHEN E LANGILLE  
03/24/2015

# Product Quality Microbiology Review

## Review for HFD-000

20 February 2008

**NDA:** 22-225

**Drug Product Name**

**Proprietary:** Bridion

**Non-proprietary:** sugammadex sodium

**Drug Product Priority Classification:** Priority

**Review Number:** 1

**Dates of Submission(s) Covered by this Review**

Letter	Stamp	Consult Sent	Assigned to Reviewer
October 30, 2007	October 30, 2007	November 13, 2007	December 6, 2007

**Submission History (for amendments only) - NA**

**Applicant/Sponsor**

**Name:** Organon

**Address:** 56 Livingston Ave. Roseland, NJ 07068

**Representative:** June Bray, VP, Regulatory Affairs

**Telephone:** Sabina Rouf: 973-325-5303

**Name of Reviewer:** Vinayak Pawar, Ph. D.

**Conclusion:** The application is recommended for approval from microbiology product quality standpoint.

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## Product Quality Microbiology Data Sheet

- A.**
- 1. TYPE OF SUBMISSION:** Priority Review, Original NDA
  - 2. SUBMISSION PROVIDES FOR:** New Drug Bridion
  - 3. MANUFACTURING SITE:** Organon, Dublin, Ireland
  - 4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** 100mg/mL, Intravenous injection.
  - 5. METHOD(S) OF STERILIZATION:** (b) (4).
  - 6. PHARMACOLOGICAL CATEGORY:** Reversal of Neuromuscular blockade
- B. SUPPORTING/RELATED DOCUMENTS:** None
- C. REMARKS:** The consult requests a priority review of Original NDA 22-225 for drug product Bridion. The application is submitted as an electronic document for a PDUFA goal date on April 30, 2008. The IQA was filed on 12/27/07 by Parinda Jani.

**filename:** C:\mydocuments\review\NDA\N022225R1

**Executive Summary**

**I. Recommendations**

- A. Recommendation on Approvability** – Based on the sterility assurance of the product the application is recommended for approval from microbiology product quality standpoint.
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable - Na**

**II. Summary of Microbiology Assessments**

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology –** (b) (4)

[Redacted content]

- B. Brief Description of Microbiology Deficiencies -**
- C. Assessment of Risk Due to Microbiology Deficiencies -**

**III. Administrative**

- A. Reviewer's Signature** \_\_\_\_\_  
Vinayak B. Pawar, Ph.D.
- B. Endorsement Block** \_\_\_\_\_  
Stephen Langille, Ph.D.
- C. CC Block**  
N/A

**Product Quality Microbiology Assessment**

**1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q)**

**MODULE 3.2: BODY OF DATA**

**S DRUG SUBSTANCE -**

NA- drug substance not sterile.

**P DRUG PRODUCT**

**P.1 Description of the Composition of the Drug Product**

*Description of drug product/Drug product composition* – Organon’s Bridion Solution for Injection 100 mg/mL is filled in (b) (4) vials (2 mL per vial, batch size (b) (4), approximately (b) (4) vials) in Table 1a or (b) (4) vials (5 mL per vial, batch size (b) (4), approximately (b) (4) vials) in Table 1b.

**Table 1a. Batch Formula 100mg/mL (2mL per vial).**

Component	Reference to quality standard	Quantity per vial (2.0 mL)	Quantity per batch (b) (4)
Org 25969 + Org 483022	In-house standard	200 mg	(b) (4)
Sodium hydroxide and/or Hydrochloric acid3	Ph. Eur., NF, JP	q.s. to pH 7.5	q.s. to pH 7.5

(b) (4)

(b) (4)

Declared amount of 100 mg/mL drug substance corresponds with 108.8 mg/mL Org 25969 (sodium salt) (b) (4)

(b) (4)

(b) (4)

**Table 1b. Batch Formula 100mg/mL (5mL per vial).**

Component	Reference to quality standard	Quantity per vial (5.0 mL)	Quantity per batch (b) (4)
Org 25969 + Org 483022	In-house standard	500 mg	(b) (4)
Sodium hydroxide and/or Hydrochloric acid3	Ph. Eur., NF, JP	q.s. to pH 7.5	q.s. to pH 7.5

(b) (4)

(b) (4)

<sup>2</sup> Declared amount of 100 mg/mL drug substance corresponds with 108.8 mg/mL Org 25969 (sodium salt) (b) (4)

(b) (4)

(b) (4)

(b) (4)

**er closure system –**

Org Bridion drug product is filled in colorless (b) (4) (2 mL per vial) or (b) (4) (5 mL per vial) vials of (b) (4) glass, type I, that are closed with grey (b) (4) rubber closures (code (b) (4)) with a diameter of 13 mm (b) (4) or 20 mm (b) (4). The rubber closures are held in position on the glass vials by aluminum crimp-caps with a flip-off seal. For secondary packaging, 10 vials are placed together in a folding carton; (b) (4)

## P.2 Pharmaceutical Development

### P.2.5 Microbiological Attributes

- Container-Closure and Package integrity - The closure integrity testing forms part of the stability studies of both 2 ml and 5 ml presentations of the drug product. The results demonstrate that the closure integrity of all batches tested thus far remains within specifications during shelf-life and the results of the sterility testing of the batches (as part of finished product testing and the stability studies) confirm that there is no issue with respect to container closure integrity.
- Preservative Effectiveness – NA

## P.3 Manufacture

### P.3.1 Manufacturers

The product will be Manufactured at Organon (Ireland) Ltd., Drynam Road, Swords, Co. Dublin, Ireland. Primary packaging Release testing and release of drug product Stability testing will be also performed at this facility. Release testing Stability testing could also be performed at N.V. Organon, Kloosterstraat 6, 5349 AB Oss, Netherlands and at Organon Development GmbH, Im Wirrigen 25, 45731 Waltrop, Germany.

### P.3.3 Description of the Manufacturing Process and Process Controls

*Manufacturing Process:*

(b) (4)

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**P.5 Control of Drug Product****P.5.1 Specifications****P.5.2 Analytical Procedures**

- **Endotoxin** – The LAL test is used for the detection of bacterial endotoxins at < (b) (4) EU per mL based on intravenous injection (K= (b) (4) EU/kg) and a maximum daily dose of 16 mg/kg. For inhibition/enhancement testing a dilution of 1:100 in Lysate Reagent Water (1 mg/mL) was chosen. The MVD was (b) (4). The results of the inhibition/enhancement tests were within specification. The validation of the LAL test for the drug product was performed according to Ph. Eur., USP, JP
- **Sterility** – Validated and performed according to Ph. Eur., USP, JP sterile
- **Microbial Limits** – Validated test is performed according to Ph. Eur., USP, JP and the bulk material bioburden must be ≤ (b) (4) CFU/mL.

**P.7 Container Closure System and Integrity –**

Approximately 3,000 vials that were visually inspected were randomly selected from each of the three (b) (4) batches. These were (b) (4)

(b) (4) the vials were dry leak tested under a vacuum of -0.8 bar for 15 minutes. This test is to ascertain that the seals, caps and stoppers are tightly sealed. The vials were subsequently visually inspected for leaks and faulty seals determined by the loss of broth from the vials. The acceptance criterion was met as none of 2871, 3340 and 2967 vials from three lots (422525, 422527 & 422534 respectively) demonstrated any leaks or faulty seals.

**Acceptable**

**P.8 Stability****P.8.1 Stability Summary and Conclusion****MAINTENANCE OF MICROBIOLOGICAL CONTROL AND QUALITY: STABILITY CONSIDERATIONS**

Long term and accelerated stability data, from stability studies conducted under identical storage conditions and time points according to ICH Guidelines, have been generated from primary and supporting stability batches manufactured at both sites. Since the manufacturing processes at Oss and Swords are very similar and the quality of the drug product manufactured at these sites are equivalent, a shelf life of 36 months at (b) (4) °C is also proposed for the drug product based primarily on the 24 months stability data of the supporting batches and 18 months data of the primary stability batches manufactured at Oss as well as the statistical evaluation of the results.

**P.8.2 Post-Approval Stability Protocol and Stability Commitment**

The long-term stability study of the primary stability batches manufactured in Oss and Swords will be conducted for up to 3 years of storage. Three production scale batches manufactured at Swords will be placed on long term stability for 3 years and on accelerated stability studies for 6 months. Thereafter, one batch of drug product manufactured at Swords will be placed on stability annually. Samples will be stored at 25°C/60%RH storage condition and tested at initial, 6, 12, 24, and 36 months and at the actual end of shelf life of the batch under study.

Container Closure integrity – For development purposes,

(b) (4)

**Acceptable**

- P.8.3 Stability Data:** Sterility and bacterial endotoxin results were acceptable for initial and 12 month stability time point.
- A APPENDICES - NA**
- R REGIONAL INFORMATION - NA**
- 2. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q)**
- MODULE 1**
- A. PACKAGE INSERT**  
Org 25969 Solution for Injection 100 mg/mL (2 mL per vial) and Org 25969 Solution for injection 100 mg/mL (5 mL per vial).
- 3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:**  
None

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/s/

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Vinayak Pawar  
3/3/2008 12:02:52 PM  
MICROBIOLOGIST

The application is recommended for approval from microbiology product  
quality standpoint.

Stephen Langille  
3/3/2008 02:04:32 PM  
MICROBIOLOGIST