CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022225Orig1s000

CHEMISTRY REVIEW(S)

CHEMISTRY REVIEW

NDA 22225

Bridion (Sugammadex) for Injection

Merck
(formerly Organon, USA)

Julia C. Pinto, Ph.D.

OPQ/ONDP/Division II

For
Division of Anestheis, Analgesia and Addiction Products

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Chemistry Review Data Sheet

Chemistry Review Sheet

1. NDA 22225

2. REVIEW #: 4

3. REVIEW DATE: November 22, 2015

4. REVIEWER: Julia C. Pinto, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original NDA	30-Oct-2007
CMC Review #1	30-Jan-2008
CMC Review #2	12-Jun-2008
CMC Review 3	03-Aug-2013
Memorandum to CMC Review #2	24-July-2008
Product Quality Microbiology Review #1	20-Feb-2008
FDA Not Approvable Letter	31-Jul-2008
Complete Response	20-Dec-2012
Response to CMC Information Request	22-Feb-2013
Withdrawal of Compatibility Protocol	08-May-2013
Response to CMC Information request	27-Jun-2013
Response to CMC Information request	15-July-2013

6. SUBMISSIONS BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA Resubmission	June 18, 2015

7. NAME AND ADDRESS OF APPLICANT:

Name: Merck and Co., Inc (Merged with Organon USA, previous NDA Sponsor)
Address: One Merck Drive, PO Box 100
Whitehouse Station, NJ 08889

8. Product Drug Code and Name:
   a) Proprietary Name: Bridion®
   b) Non-Properitary Name (USAN): Sugammadex Sodium for Injection

9. LEGAL BASIS FOR SUBMISSION: N/A

Chemistry Review Data Sheet

10. PHARMACOLOGICAL CATEGORY: Reversal of Neuomuscular Blocking Agents

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 100mg/ml

13. ROUTE OF ADMINSITRATION: Intravenous Infusion

14. Rx/OTC DISPENSED: __√__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM:
_____SPOTS product – Form Completed

__x___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

See Review #1

17. RELATED/SUPPORTED DOCUMENTS:

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
none		

18. Status

OPQ:

CONSULTS/ CMC RELATED REVIEWS	**RECOMMENDATION**	**DATE**	**REVIEWER**
Biometrics	NA		
OPF-Facilities	Acceptable	July 15, 2015	OPQ/OPF
Pharm/Tox	Review #1		
Biopharm	Review #1		
LNC	NA		
Methods Validation	NA		
DMET/DDMAC	NA		
EA	Review #1		
Microbiology	Review #1		

The Chemistry Review for NDA 22-356

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

In the last review cycle, (August 2013), this NDA submission was recommended as a Complete Response, from the CMC perspective, pending an adequate evaluation from Office of Compliance. Currently, the Office of Process and Facilities, has recommended all facilities as adequate. The CMC data remains the same as that reviewed in previous cycles. Therefore, from the CMC perspective, this NDA is recommended for approval. The drug product has an acceptable expiry of 36 months when stored at 25°C.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable-

No Post Approval commitments are required.

II. Summary of Chemistry Assessment

A. Description of Drug Substance and Drug Product:

The drug substance (Org 25969 or sugammadex sodium) is the octasodium salt, of a modified γ-cyclodextrin. The drug product is a sterile parenteral solution for intravenous administration, prepared as a 100mg/ml solution and contained in 2ml and 5ml vial presentations. The container closure system is type I glass vials with a (b) (4) rubber closure and an aluminum flip off cap.

Description of How the drug is intended to be used:

The drug product is intended for reversal of neuromuscular block by rocuronium or vecuronium, through the formation of complexes between the cyclodextrin drug and the neuromuscular blocking agents.

C. Basis for Approvability Recommendation

The CMC data remains the same as that reviewed in previous cycles. The Office of Process and Facilities, has recommended all facilities as adequate, (July 15, 2015). CMC Labeling adjustments, demonstrating the compatability of the drug product with intravenous fluids, and the incompatibility with several co-administered drug products, is satisfactory. The drug product has an acceptable expiry of 36 months when stored at 25°C. Therefore, from the CMC perspective, this NDA is recommended for approval.

III. Administrative

A. Reviewer's Signature

Julia C. Pinto, Ph.D.

B. Endorsement Block

C. CC Block

CHEMISTRY ASSESSMENT

I. Review of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body of Data

DRUG SUBSTANCE

For a complete review of the Drug Substance for this NDA, See Reviews #1 to 3, by Alan Schroeder, Ph.D. and Yong Hu, Ph.D.

P . DRUG PRODUCT:

For Complete review of the Drug Product, See Reviews #1 to 3, by Alan Schroeder, Ph.D. and Yong Hu, Ph.D.

In the current submission, data to support compatibility of the drug product, in intravenous solutions, including the frequently used, 5% Dextrose, Saline and Lactated Ringer solutions, is provided.

Table 4: Infusion Fluids used for the compatibility study

Code	Infusion Fluid	Supplier	Lot Number.	Exp. date	Appearance	Clarity	Particles
SC	0.9% Sodium Chloride	(b) (4)	03J2261	08-2006	Colorless liquid	Clear	Practically free from particles
DE	5% Dextrose		040820H42 1018	07-2006	Colorless liquid	Clear	Practically free from particles
(b) (4)							(b) (4)
SCDE	0.45% Sodium chloride, 2.5% Dextrose		040113H41 3275	12-2005	Colorless liquid	Clear	Practically free from particles
RLS	Ringers lactate solution (Hartmann's solution)		050226H42 2172	1-2007	Colorless liquid	Clear	Practically free from particles
RS	Ringers solution		04F02A	5-2007	Colorless liquid	Clear	Practically free from particles
(b) (4)							(b) (4)
DESC	5% Dextrose, 0.9% Sodium Chloride						
IPD	Isolyte P with 5% Dextrose		J5J579	1-2008	Colorless liquid	Clear	Practically free from particles

End of Sponsor Material

Data for the drug product, in all the fluids listed in the table above, when stored at (b) (4) 25C, (b) (4) demonstrates the drug product remains stable.

Further, compatibility report, also provides data, to demonstrate the compatability of the Sugamadex Drug product when co-administered with other drug products

Table 10: Co-medication used for the compatibility study

Code	Co-medication	Trade name	Conc.	Supplier	Lot Number.	Exp. date	Appearance	Clarity	particles	pH
FEN	Fentanyl	Fentanyl	50 µg/mL	(b) (4)	343069	10-2008	(b) (4)	Clear	(b) (4)	(b) (4)
MID	Midazolam	Midazolam	1 mg/mL		03A09FBA	01-2006		Clear		
MOR	Morphine	Morphine	20 mg/mL		03K08H	11-2006		Clear		
REM	Remifentanil	Ultiva	2 mg/vial		C097355	10-2005		Clear		
ATR	Atropine	Atropine Sulfate	1 mg/ mL		02J24Y802917	10-2007		Clear		
EPP	Epinephrine	Adrenaline	1 mg/mL		02J23Z802910	10-2005		Clear		
ESM	Esmolol	Brevibloc®	10 mg/mL		304220A	08-2005		Clear		
NOR	Norepinephrine	Norepinephrine	1 mg/mL		03H23D	08-2006		Clear		
OND	Ondansetron HCl dehydrate	Zofran®	2 mg/mL		3F03	06-2006		Clear		
PRF	Propofol	Diprivan	10 mg/mL		X5042A	09-2006		-		
RAN	Rantidine HCl	Zantac®	25 mg/mL		3G04	07-2006		Clear		
THS	Thiopental sodium	Pentothal	25 mg/mL		32034TF01	08-2007		Clear		
VER	Verapamil HCl	Isoptin®	2.5 mg/mL		306196	08-2008		Clear		

[1] soln: solution

[2] conform: practically free from particles

Pharm. dev. compatibility

End of Sponsor Material

The data demonstrates that possible precipitation ("particle formation") can occur with Ondansetron, Rantidine and Verapamil, when co-administered with the drug product.
Therefore a warning to not mix Sugammadex with these products, is added to the Package Insert.

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

Carton Labeling

Examples of the Container labels are shown below. All contain the NDC number, expiry, barcode, storage statement [redacted] (b) (4)

[redacted] (b) (4)

COMPOSITE LABEL
(TOP & BASE LABELS)

Evaluation: Adequate.

Facilities Overall Recommendation as of July 14, 2015 is Approve

(b) (4)

Memo

Date: March 25, 2015
Revised March 29, 2015

From: Fred Mills, Staff Scientist, OBP, Division 4

To: Gerry Feldman, Lab Chief, OBP, Division 4

Tracking number: NDA 022225

Sponsor: Merck

Product: Sugammedex (b) (4)) for reversal of anesthesia from rocuronium or vecuronium (neuromuscular blocking agents)

Subject of Review: Immunogenicity review of binding antibody, IgG, and IgG assays used in the Study P101 for targeted hypersensitivity study submitted in the current (3rd) review cycle for NDA 02225. Consult as requested by the Sugammedex clinical review team in CDER/OND/ODEII/DAAAP.

Comments to the File
Review of the assay validation for the anti-Sugammedex binding antibody assay used for Study P101 indicates that this assay is appropriately validated and suitable for its intended use, with a screening assay sensitivity of 0.28 ng/ ml and a confirmatory assay sensitivity of 0.69 ng/ ml, both which represent a high level of sensitivity. Thus this assay can accurately support the Sponsor's determined incidence of binding antibody formation, which is (b) (4)%.

Review of the assay validation for the anti-Sugammedex IgG assay used in Study P101 indicates that this assay is also appropriately validated. This assay has a sensitivity of 143 ng/ml control antibody, which is adequate to detect antibodies posing the greatest theoretical risk; i.e. those found at moderate to high levels. This assay may not detect antibodies expressed at low levels, however.

Review of the assay validation for the anti-Sugammedex IgE assay used in Study P101 reveals that this assay is not appropriately validated, as its sensitivity has not been defined. Therefore, no conclusions can be drawn regarding the Sponsor's assessment of IgE incidence in this study.

Executive Summary
Sugmammedex is used for reversal of anesthesia from rocuronium or vecuronium (neuromuscular blocking agents). Sugammadex is a modified γ-cyclodextrin, with a lipophilic core and a hydrophilic periphery, allowing it to sequester these anesthetics and neutralize their pharmacological activity. In clinical data provided during the first NDA review cycle in 2008, incidents of hypersensitivity were reported upon Sugammedex administration, even for individuals who had not previously been exposed to the drug. The Sponsor was advised to explore potential mechanisms of hypersensitivity. In response, the Sponsor performed Study P06042 (2009-2010) which included several assessments of basophil function in treated patients, as well skin-prick data, measurement of tryptase, anti-Sugammedex IgG, and anti-Sugammedex

IgE, with these results submitted during a 2nd review cycle. These studies did not provide any definitive mechanism underlying hypersensitivity. Moreover, the IgG and IgE data were difficult to interpret because the sensitivity of these antibody assays was not determined.
To address deficiencies in Study P06042, the Sponsor performed a dedicated hypersensitivity Study, designated P101, with study results submitted in a 3rd review cycle. In P101, there were 375 healthy subjects, who were assigned to one of three parallel arms for treatment with 3 successive single doses of one of the following treatments in a 2:2:1 ratio: 4 mg/kg sugammadex, 16 mg/kg sugammadex or placebo (151, 148 and 76 subjects respectively).Validation of the binding antibody, IgG, and IgE assays used in this study is the subject of this review, as requested by the Sugammedex clinical review team in CDER/OND/ODEII/DAAAP.

The binding antibody assay uses a sensitive ECL-based methodology. The Sponsor has appropriately set screening and confirmatory assay CutPoints from normal serum samples, and has determined that the screening CutPoint corresponds to the assay signal resulting from 0.28 ng/ml control antibody and the confirmatory CutPoitn corresponds to 0.69 ng/ ml control antibody. Therefore, this binding antibody assay can accurately support the determined incidence of binding antibody formation of approximately 10%.

The IgG and IgE assays use an ELISA based antibody capture format. The IgG assay has a sensitivity at the CutPoint corresponding to 143 ng/ml control antibody. This should be adequate to detect antibodies posing the greatest theoretical risk; i.e. those found at moderate to high levels, although antibodies present at low levels may not be detected. For the IgE assay, the Sponsor only confirmed reactivity of anti-human IgE detection antibody with ELISA wells coated with human IgE, and sensitivity was not determined due to lack of an control anti-Sugammedex IgE antibody. Therefore, the Sponsor's determined incidence of no IgE antibody formation is not reliable.

In Study P101, There was a binding antibody incidence of approximately 10%. Assays for the presence of anti-Sugammadex IgG and IgE were carried out at baseline and ~4-5 weeks after each dose (subjects who completed all 3 dosing periods were tested 4 times) in all subjects with adjudicated hypersensitivity (n=25), subjects referred to the Adjuication Committee (AC) but without adjudicated hypersensitivity (n=69), and in a set of control subjects (n=91) who did not have findings of potential hypersensitivity and were not referred to the AC. There were 2 subjects with adjudicated hypersensitivity with measurable anti-Sugammadex IgG. The first subject had been treated with 4 mg/ kg Sugammedex, and had anti-Sugammadex IgG at baseline, but did not have measurable anti-Sugammadex IgG after the 1st, 2nd and 3rd doses. The second subject was treated with 14 mg/ kg Sugammedex, and was negative at baseline, but then had anti-Sugamadex IgG in samples drawn after each dose. The Sponsor states that there were no IgE positives, but this conclusion is unreliable because the sensitivity of the IgE assay is unknown.

Comments to the Sponsor

Your anti-Sugammedex binding antibody assay has been appropriately validated and has adequate sensitivity for analysis of clinical samples. Similarly, your anti-Sugammedex IgG assay is appropriately validated and has sensitivity (143 ng/ ml control antibody) adequate for measurement of antibodies in the moderate to high range, where there is greatest concern. However, we note that this assay may not be able to detect low concentration IgG antibodies. You did not determine sensitivity for your anti-Sugammedex IgE assay, and thus we find that determination of IgE incidence with this assay is unreliable.

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Background

Sugammedex is an agent for reversal of anesthesia from rocuronium or vecuronium (neuromuscular blocking agents). NMB are used in anesthesiology to induce muscle relaxation during surgery. Sugammadex is designed to work by inactivating rocuronium or vecuronium molecules directly by encapsulation

Mechanism of Action

Sugammadex is a modified γ-cyclodextrin, with a lipophilic core and a hydrophilic periphery. This gamma cyclodextrin has been modified from its natural state by placing (b) (4)

(b) (4)

Clinical Studies relevant to immunogenicity

Study P06042

8/24/2009-4/13/2010

n.b. StudyP06042 was reviewed during the 2nd Sugammedex review cycle, and is not the subject of this review, which discusses immunogenicity assays and data submitted in the current (3rd) review cycle. A summary of P06042 is provided for background.

This was a parallel-group design study to evaluate the potential for hypersensitivity signs/symptoms and anaphylaxis at the time of initial exposure to sugammadex and upon repeat exposure in a healthy subject population. Sugammadex 4 mg/kg and 16 mg/kg were chosen as the 2 experimental arms of interest because these doses represent the highest routinely used (4 mg/kg) and maximally recommended (16 mg/kg) doses for clinical practice. Placebo (normal saline) was included as a control arm against which to compare the response in the Sugammadex arms. Treatment was by IV bolus at days 8, 36, and 78. There was a 1-week post-treatment follow-up for all subjects and/or a 2- and 4-week extra follow-up after onset of symptoms for subjects with suspected

hypersensitivity. A total of 450 subjects (150 per treatment arm) were to be randomized as this was considered a sufficient sample size to obtain an indication of the number and percentage of subjects with adjudicated hypersensitivity signs/symptoms for each dose of Sugammadex (4 and 16 mg/kg) and placebo.

Hypersensitivity in Study P06042

Based on an extensive list of pre-defined possible hypersensitivity signs/symptoms, 68 cases of suspected hypersensitivity in 49 subjects (10.9% of overall treated subjects; 23.3% of Sugammadex 16 mg/kg treated subjects [35 subjects]; 6.8% of Sugammadex 4 mg/kg treated subjects [10 subjects]; and 2.7% of placebo treated subjects [4 subjects]) were sent to the Adjudication Committee for review, as identified by the investigator or after Sponsor review of all signs and symptoms. The constellation of hypersensitivity signs/symptoms of a total of 8 subjects (1.8% of All Treated Subjects) were classified as hypersensitivity by the Adjudication Committee. Seven of these 8 subjects received Sugammadex 16 mg/kg, and the other subject received Sugammadex 4 mg/kg. One subject experienced anaphylaxis which was confirmed by the Adjudication Committee to meet the definition of anaphylaxis according to the Sampson criteria. The same subject was confirmed by the Adjudication Committee to have experienced anaphylaxis, meeting the Rüggeberg definition at level 1 (highest) certainty. Two additional subjects were confirmed by the Adjudication Committee to have experienced anaphylaxis meeting the Rüggeberg definition at level 2 certainty.

The Sponsor stated that IgG- and IgE-specific anti-Sugammadex antibody evaluations did not support an immunoglobulin mediated mechanism as an etiology for the hypersensitivity reactions of the 8 subjects with adjudicated hypersensitivity.

None of the washed whole blood samples containing IgE-intact basophils of the 6 tested subjects with adjudicated hypersensitivity who responded to the positive control showed significant histamine release after challenge with a therapeutic relevant range of Sugammadex concentrations. This finding was further supported by the IgE stripping of basophils and passive sensitization experiments.

The Sponsor states that is unlikely that the hypersensitivity reactions were caused by a mast cell response, as no relevant increases in tryptase were observed, the skin prick test results were all negative, and only the subject with the anaphylactic shock SAE had a positive intradermal test result at a high Sugammadex concentration (a 1:10 dilution, 10 mg/mL). Ex vivo/in vitro basophil results suggest the absence of a direct non-IgE mediated histamine release from basophils.

Results of the additional hypersensitivity parameters evaluated for this study did not suggest that contact system activation, complement activation, potential predisposition regarding contact system activation, neutrophil and/or cytokine activation could explain the potential relationship between sugammadex and hypersensitivity reactions. Subjects were tested with an ECL-based screening antibody assay, followed by an ECL (PC control competition) confirmatory assay. Samples positive in the confirmatory assay were tested for IgG and IgE in and ELISA assay.

At the time of this study, which was submitted during the 2nd review cycle for this NDA, screening assay sensitivity was assessed as 35 ng/ml control antibody. IgG and IgE assay sensitivity was not established, as the Sponsor only confirmed IgG or IgE reactivity established by coating wells with human IgG or human IgE.

Study P06402 antibody testing results

Non- HS

	subjects	**binding Ab positive**	
Placebo	39	5.1% baseline -- 2nd dose	2.6 % 3rd dose
4 mg/ kg	34	2.9% baseline -- 3rd dose	
16 mg/kg	21	4.8% baseline – 3rd dose	

Adjudicated HS

subjects	**binding Ab positive**
8	2 positives both in 16 mg/kg arm

No Adjudicated HS were IgG, IgE positive

Reviewer comments

The Sponsor's binding antibody results are based upon an ECL assay that has appropriate sensitivity. These data indicate a low, but significant binding antibody incidence, which may be higher in subjects with adjudicated hypersensitivity, although the numbers are small (2 positive subjects out of 8 total). However, the Sponsor's statement that no adjudicated hypersensitive subjects were IgG or IgE positive cannot be confirmed, as the sensitivity of these assays was not established.

Study P101: dedicated Hypersensitivity Study in Healthy Subjects (01/07/2014-08/01/2014)

This study was designed to address the deficiencies in Study P06402.

A total of 375 healthy subjects were randomized in P101 to one of three parallel arms assigned to treatment with 3 successive single doses of one of the following treatments in a 2:2:1 ratio: 4 mg/kg sugammadex, 16 mg/kg sugammadex or placebo (151, 148 and 76 subjects respectively). Dosing periods were spaced apart by approximately 5 weeks to allow potential sensitization to develop. Each subject was examined after each dose at least three times for signs and/or symptoms of hypersensitivity (at 0.5, 4 and 24 hours after each dose administration) with a standardized Targeted Hypersensitivity Assessment (THA). Of the 375 treated subjects, 334 (89.1%) completed the study and received all 3 doses of the assigned treatment.

A total of 94 subjects (45, 35 and 14 subjects in the 16 mg/kg Sugammadex, the 4 mg/kg Sugammadex and the placebo treatment groups, respectively) were referred to the AC for evaluation. Among these 94 subjects, the Adjudication Committee (AC) identified 25 subjects with adjudicatedhypersensitivity after receiving at least one dose of study medication. The incidence of adjudicated hypersensitivity was 6.6% (10 of 151 subjects) in the 4 mg/kg Sugammadex

treatment group, 9.6% (14 of 148 subjects) in the 16 mg/kg Sugammadex treatment group, and 1.3% (1 of 76 subjects) in the placebo treatment group. Only one case was adjudicated as anaphylaxis, and that individual was in the Sugammadex 16 mg/kg group, which corresponds to an incidence of 0.7% (95% CI [0.0%, 3.7%]; AN 5020 had adjudicated anaphylaxis by definition of Sampson (Criterion 1) on the first dosing occasion. No subject in either the 4 mg/kg sugammadex treatment group or the placebo treatment group had adjudicated anaphylaxis, which corresponds to an incidence of 0.0% (95% CI [0.0%, 2.4%]) for 4 mg/kg sugammadex and 0.0% (95% CI [0.0%, 4.7%]) for placebo.

The incidence of adjudicated hypersensitivity in all treatments of P101 was higher than those observed in the corresponding treatments of P06042. Incidences of adjudicated hypersensitivity in P101 and P06042 , as tabulated below:

Table 2.5: 2 Incidence of Adjudicated Hypersensitivity is Higher in P101 (Left Panel) Than in P06042 (Right Panel)

P101 Adjudicated Hypersensitivity		
Treatment	**Number of Subjects**	**%, (n) [95% CI]**
Placebo	76	1.3, (1) [0.0, 7.1]
4 mg/kg Sugammadex	151	6.6, (10) [3.2, 11.8]
16 mg/kg Sugammadex	148	9.5, (14) [5.3, 15.4]

P06042 Adjudicated Hypersensitivity		
Treatment	**Number of Subjects**	**%, (n) [95% CI]**
Placebo	148	0, (0) [0.0, 2.4]
4 mg/kg Sugammadex	150	0.7, (1) [0.0, 3.7]
16 mg/kg Sugammadex	150	4.7, (7) [1.9, 9.3]

CI=Confidence Interval
Source: [Ref. 5.3.5.4: P101] Table 11-1; [Ref. 5.3.5.4: P06042-194117]

P101 antibody testing results

In P101, was an approximate 10% binding antibody incidence. Assays for the presence of anti-Sugammadex IgG and IgE were carried out at baseline and ~4-5 weeks after each dose (subjects who completed all 3 dosing periods were tested 4 times) in all subjects with adjudicated hypersensitivity (n=25), subjects referred to the AC but without adjudicated hypersensitivity (n=69), and in a set of control subjects (n=91) who did not have findings of potential hypersensitivity and were not referred to the AC. There were 2 subjects with adjudicated hypersensitivity with measurable anti-Sugammadex IgG. The first subject had been treated with 4 mg/ kg Sugammedex, and had anti-Sugammadex IgG at baseline, but did not have measurable anti-Sugammadex IgG after the 1st, 2nd and 3rd doses. The second subject was treated with 14 mg/ kg Sugammedex, and was negative at baseline, but then had anti-Sugamadex IgG in samples drawn after each dose. The Sponsor states that there were no IgE positives, but this cannot be confirmed because the sensitivity of the IgE assay is unknown.

Reviewer comments
Given an ~10% binding antibody incidence, there were two IgG positives, both of whom were adjudicated hypersensitive subjects. It may difficult to assign an IgG incidence rate, however, because of the small numbers (2 positives out of 8 adjudicated subjects). The Sponsor's statement that there were no IgE positives cannot be confirmed, because the sensitivity of the IgE assay was not established.

P101 ECL binding antibody assay Validation Report BT00097 (04/23/2014)

An assay for the detection of human anti-Sugammadex antibodies was developed to characterize any potential hypersensitivity reactions observed in human volunteers or patients treated with Sugammadex. An affinity-purified rabbit polyclonal anti-Sugammadex antibody is available. This antibody was made by first conjugating Sugammadex to keyhole limpet hemocyanin (KLH) and hyperimmunizing rabbits. An ELISA screen utilizing Sugammadex conjugated to BSA (Sugammadex-BSA) was used to identify rabbit sera that were specific to Sugammadex.

This binding antibody assay is an ECL-based assay in which an antibody bridge is formed between anti-Sugammadex Ab in the test sample or controls and Sugammadex-BSA labeled in one of two ways: either with biotin or with trisbipryidine chelate (TAG). An immune complex is formed between the anti-drugAb, the TAG-labeled Sugammadex-BSA and the biotinylated Sugammadex-BSA. In the presence of the assay read buffer, a light signal is produced in proportion to the amount of anti-sugammadex antibody in the test specimen. An assay cutpoint was established, above which samples are considered as putatively positive. A confirmatory assay, where putative positives are incubated with excess free Sugammadex and evaluated for abrogation of the ECL signal, is utilized to ensure that reactive samples are specific for Sugammadex. Any positive sample is then characterized further in a separate isotyping assay (ELISA –based) to establish if the response is IgG, lgE or both. In the ECL assay, serum samples are diluted 1/2.

Reviewer comment

The low serum dilution (1:2) should help ensure that potential antibody signals are not dilutied below the detection range of the assays.

Cutpoint determination

Screening Cutpoint

The Screening Cutpoint was determined at a 95% confidence level by performing 5 assay runs employing two different analysts, with each run assessing the ECL signals from the same set of 50 individual human serum samples. These values have been provided in tabulated form as S/N (ECL Signal/ ECL Noise). From this data set of 250 values, 7 values were excluded as outliers by Tukey's outlier test. As per FDA Guidance for Industry-Assay Development for Immunogenicity Testing for Therapeutic Proteins (2009), a Cut Point was calculated by adding the mean response of serum sample to 1.645 times the standard deviation; i.e.

Cut Point= Mean (all NHS)+ 1.645 *SD (Standard Deviation)

Taking all the NHS serum values expressed as S/N, this CutPoint was found to correspond to

1.19 + mean NSB (Non-Specific Background).

Using this formula, as expected twelve non-confirmed positive responses of the 243 acceptable responses were still above the cut point factor, yielding a putative false positive rate of 5%.

Therefore, the formula 1.19 + NSB was used as the criterion for calling patient samples positive or negative in routine assay runs. This CutPoint corresponds to 0.28 ng/ ml positive control.

Reviewer Comments

The Sponsor has used standard practice as per Guidance to establish a Screening Cutpoint. There were only a modest number of outlier values, indicating reproducibility of the assay. The CutPoint corresponds to 0.28ng/ml positive control antibody (see discussion of Sensitivity- below), supporting the view that this CutPoint is set so as to detect low levels of antibody. For these reasons, I find that the Screening CutPoint is validated and set appropriately.

Confirmatory Cutpoint

In parallel with the Screening Cutpoint validation, the Sponsor established a Confirmatory Cutpoint, analyzing the same set of 50 normal serum samples in 5 separate validation runs performed by two analysts. For the confirmatory assay, unlabeled MK-8616 (Sugammedex) is added to labeled reagent solution containing Biotin - MK-8616 and Tag-MK-8616 to a final concentration 3.3 μg/ ml. Five of the 250 measurements were classified as outliers. Calculating a 99% confidence rate, the Sponsor found this corresponded to a 53.5% binding assay inhibition; i.e. samples must show ≥ 53.5% inhibition to be confirmed positive. This corresponds to 0.69 ng/ml positive control antibody.

Again the Sponsor used standard practice as per Guidance to establish a Confirmatory Cutpoint. There were only 5 outlier values out of 250, indicating reproducibility of the assay. The CutPoint corresponds to 0.69 ng/ml positive control antibody, so like the Screening Cutpoint, the Confirmatory CutPoint is set so as to detect low levels of antibody. Requiring a 53.5% inhibition of assay signal still leaves 46.5% of the assay signal, which should allow adequate detection by ECL. For these reasons, I find that the Confirmatory CutPoint is validated and set appropriately.

Screening Assay Sensitivity and Selection of Low Positive Control

As shown below in Table 6, sensitivity was determined using data from 6 runs of dilutions of positive control antibody to interpolate a control antibody value at the CutPoint (CP). A seventh run was not used because a Signal/Noise value could not be interpolated. From the mean of these interpolated values (Mean Concentration), sensitivity was defined at a 95% confidence level as defined as

Sensitivity=Mean Concentration +1.645 SD
=0.28 ng/ ml
Meaning that there is 95% confidence that control antibody levels ≥ 0.28 ng/ ml can be detected
In order to provide high assurance that the Low Positive Control (LPC) could be detected in routine assay runs, the LPC value was set at a 99% confidence level above the Mean Concentration as 0.4 ng/ ml control antibody

Table 6. Determination of anti-MK-8616 relative assay sensitivity (screening) and LPC concentration for Human Serum

Date and Analyst:	10Mar2014 LY	11Mar2014 LL	12Mar2014 CALM	12Mar2014 LL	13Mar2014 LY	13Mar2014 CALM	14Mar2014 CALM
Concentration ng/mL	S/N	S/N	S/N	S/N	S/N	S/N	S/N
250	496.61	370.52	424.86	456.13	400.62	316.14	323.63
62.5	115.03	85.19	104.62	120.27	85.98	79.7	76.52
15.6	27.76	23.51	26.82	31.33	20.45	20.3	20.17
3.91	7.55	7.18	7.43	9.97	5.45	5.88	5.67
0.977	2.48	2.65	2.55	3.92	2.03	2.02	2.07
0.244	1.35	1.49	1.45	2.05	1.21	1.18	1.29
0.061	1.04	1.15	1.14	1.56	0.93	1.01	1.02
0.015	1.00	1.08	1.06	1.43	0.96	0.99	0.98
Concentration (ng/mL) at Cut Point [a]	0.15	0.08	0.09	ND	0.23	0.25	0.18
Mean Concentration	0.16						
SD	0.07						
n	6						
Sensitivity [b]	0.28						
(sLPC) Screening Low Positive Control in ng/mL [c]	0.40						
Final rounded concentration of Screening LPC in ng/mL	0.40						

a: Cut Point Factor = 1.19

b: Sensitivity = Mean Concentration + (1.645 SD)

c: Low Positive control = Mean concentration + ($t_{0.99}$ SD)
ND: Not Detrmined, S/NC could not be interpolated at the cut point

Reviewer Comments

The Sponsor has found that there is 95% confidence that their binding antibody assay has a sensitivity of 0.28 ng/ml positive control antibody. This represents high sensitivity, as would be expected for an ECL assay. The Sponsor has set their Low Positive Control (LPC) at a concentration of 0.4 ng to ensure a 99% probability of detection in routine assay use. This sensitivity and LPC concentration indicate that the screening assay can detect even low concentration antibodies, and thus the sensitivity and LPC are appropriate.

Confirmatory Assay Sensitivity and Low Positive Control Selection

Using a similar procedure to that followed for determining screening assay CP and LPC, the Confirmatory Assay used data from 7 runs of dilutions of positive control antibody (data not shown in the interests of brevity) to interpolate a control antibody value at the CutPoint (CP). From the mean of these interpolated values (Mean Concentration), sensitivity was defined at a 99% confidence level as

Sensitivity=Mean Concentration +2.326*SD
= 0.32 ng/ml + 2.326*0.16 ng/ ml
=0.69 ng/ml

So there is a 99% confidence that control antibody levels $\geq$ 0.69 ng/ ml can be detected
In order to provide high assurance that the Low Positive Control (LPC) could be detected in routine assay runs, the LPC value was set at a 99% confidence level above the Mean Concentration as 0.89 ng/ ml control antibody

Reviewer Comments

The Sponsor has found that there is 99% confidence that their confirmatory binding antibody assay has a sensitivity of 0.69 ng/ml positive control antibody. The Sponsor set their Low Positive Control (LPC) at a concentration of 0.89 ng to ensure a 99% probability of LPC detection in routine assay use. This sensitivity and LPC concentration indicate that the Sponsor's assay can confirm even low concentration antibodies, and thus the sensitivity and LPC are appropriate.

Screening Assay Precision

The Sponsor performed 6 assay runs using the High Positive Control (HPC), Screening Low Positive Control sLPC, and Confirmatory LPC (cLPC), and determined the following variability values:

	%CV
HPC: Intra-Assay Precision	6.6%
HPC: Inter-Assay Precisions	16.2%
sLPC: Intra-Assay Precision	9.2%
sLPC: Inter-Assay Precision	12.3%
cLPC: Intra-Assay Precision	2.2%
cLPC: Inter-Assay Precision	11 .7%

Reviewer comments

Inspection of the Sponsor's tabulated data indicates that their statements regarding precision are accurate. Both the intra-assay and inter assay % CVs are modest, and should support reproducible performance of the assay. Significantly, the %CVs for the LPCs are slightly better than those for the HPC, allowing accurate assignments of antibody status. Therefore, the Screening Assay Precision validation is acceptable.

Confirmatory Assay Precision

The Sponsor performed 6 assay runs using the High Positive Control (HPC), Screening Low Positive Control sLPC, and Confirmatory LPC (cLPC), and determined the following variability in the % inhibition of the assay by Sugammedex:

HPC: Intra-Assay Precision 0.1%
HPC: Inter-Assay Precision 0.0%
sLPC: Intra-Assay Precision 6.5%
sLPC: Inter-Assay Precision 6.9%
cLPC: Intra-Assay Precision 1.9%
cLPC: Inter-Assay Precision 4.0%

Reviewer comments

Inspection of the Sponsor's tabulated data indicates that their statements regarding Confirmatory Assay precision are accurate. Both the intra-assay and inter assay % CVs are modest, and should support reproducible performance of the assay. Therefore, Confirmatory Assay Precision validation is acceptable.

Matrix selectivity

Matrix selectivity of anti-MK-8616 antibodies serum obtained from normal donors. All samples tested were potentially positive or reactive in the screening assay with samples spiked at the HPC having higher responses than those spiked at the sLPC. Samples with hemolysis level at grade C (140 mg/dl) and beyond showed an inconsistent positive rate for the sLPC. Therefore, hemolyzed clinical samples may show potential false negative results

Reviewer comment

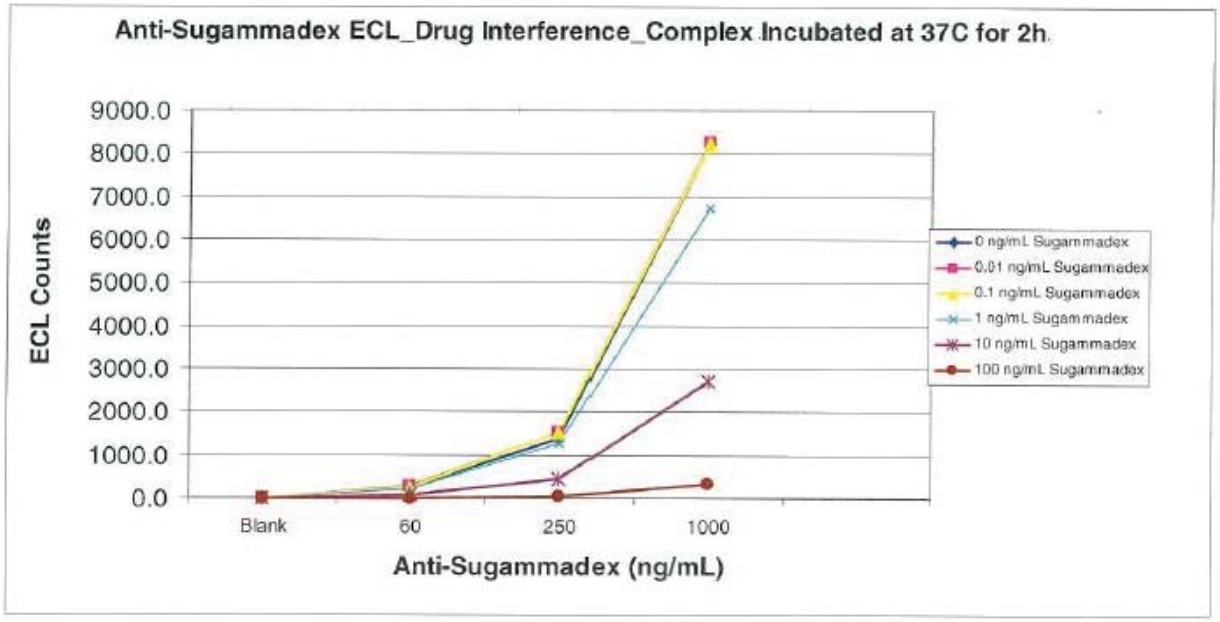
In actual study of patient sera, only 2 out > 1000 samples had hemolysis at a level ≥ 140 mg/dl, so this concern did not significantly affect the Sponsor's results

If pre-dose samples are reactive in-study, a post/pre ratio will be calculated and if it is greater than or equal to 1.19 it will be called reactive and move on to the confirmatory test. If post-dose samples are less than 1.19 the sample will be considered negative for drug-induced antibodies.

Reviewer comment

The Sponsor needed to have some protocol to handle baseline positive patients. The provision described above appropriately allows for scoring of increasing signal with these patients as antibody positive.

Drug Tolerance

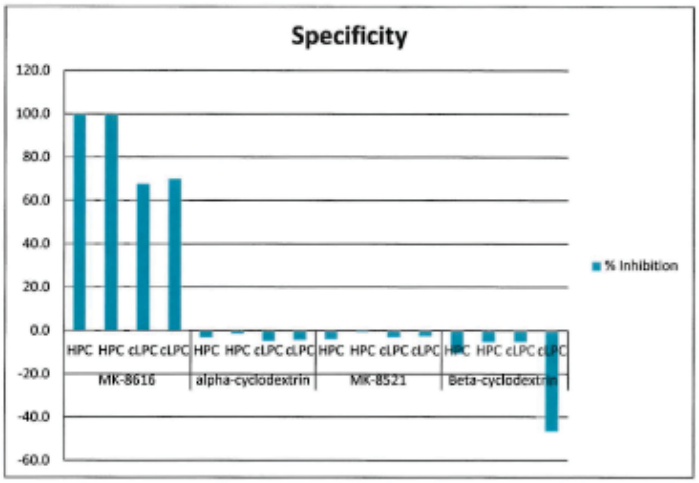


Reviewer comment

The assay is insensitive to on-board Sugammedex in the 0.01 ng/ ml -1 ng/ml range. In any case, sensitivity to on board product is not expected to impact clinical results, since antibody samples are collected pre-dose, doses in Study P101 were administered approximately 5 weeks apart, and Sugammedex serum concentrations become undetectable in <7 days, even in patients with severe renal impairment.

Assay specificity for Anti-MK-8616 (Sugammedex) antibody.

As show below, MK-8616, alpha-cyclodextrin, MK-8521 and beta-cyclodextrin were added to the negative control (NC), low positive control (cLPC) and the high positive control (HPC) samples. Only addition of MK-8616 abrogated the response of the anti-MK-8616 antibody above the confirmatory cut point.



Reviewer comment
The Sponsor as appropriately demonstrated specificity by showing that compared to several other cyclodextrins, only Sugammedex inhibits the binding antibody assay.

Stability of the positive control anti-Sugammedex antibody samples

PC room temperature stability

The Signal/Noise ratio (S/N) for sLPC and HPC remained well within the values for freshly prepared validation samples during storage for 21 hours at room temperature.

PC Freeze Thaw stability

For triplicate stability samples there was only modest variability in the S/N for sLPC and HPC upon 5 freeze-thaw cycles (< 6%), except for a single sLPC sample that dropped slightly below the CP (1.18 vs CP of 1.19) at the 3rd freeze-thaw cycle and then returned to within specification on the 4th and 5th cycles.

Stability at 4 ^{0}C.

Triplicate sLPC and HPC were stored at 4 ^{0}C for 7 weeks, and showed only modest variability (0.0- 3.0% CV) as compared to similar variability (0.0-2.6% CV) for samples stored over the same time period frozen.

Stability at -15 ^{0}C and -70 ^{0}C

Triplicate sLPC and HPC were stored at ≤ -15 ^{0}C and ≤ -70 ^{0}C for 1 month, and showed only modest variabitiy for this time period ;i.e

Storage conditions	n	HPC (250 ng/mL) S/N	sLPC (0.40 ng/mL) S/N
one month at -15ºC or colder	1	268.44	1.25
	2	273.19	1.56
	3	284.79	1.54
one month at -70ºC or colder	1	283.56	1.39
	2	291.64	1.43
	3	290.69	1.51

Cut Point Factor = 1.19; Acceptance criteria: S/N>Cutpoint

Reviewer comments
The Sponsor has assessed stability of the sLPC and HPC. There is little variability of these controls upon RT, 4 ^{0}C, -15 ^{0}C and -70 ^{0}C storage, as well as five freeze-thaw cycles. Therefore, the Sponsor has demonstrated acceptable stability of these important assay reagents.

ELISA for IgG and IgE Validation BT00092 (04/28/2014)-used in Study P101

This assay is a typical sandwich ELISA in which Sugammadex conjugated to bovine serum albumin (SGDX-BSA) is coated onto 96-well microtiter plates. Following a blocking step, test samples or controls are added to the plates and incubated. The IgG positve control is a rabbit polyclonal IgG anti-Sugammedex antibody. Because the Sponsor did not develop an anti-Sugammedex IgE positive control antibody, wells coated with human IgE are used as positive controls for the IgE assay. Bound IgG is detected with a protein-G HRP conjugate (IgG assay) while bound IgE is detected with an anti-human IgE specific antibody conjugated to HRP. A chromogenic substrate is added and absorbance read with a plate reader. Serum dilutions are 1:2 for the IgE assay and 1:4 for the IgG assay. Samples are obtained pre-treatment and after washout, so drug interference was not assessed.

Reviewer comment

The low serum dilutions (1:2 for IgG, 1:4 for IgE, should help ensure that potential antibody signals are not dilution below the detection range of the assays.

Cutpoint Factor for the IgG Assay

Fifty normal serum samples were analyzed in 4 independent assay runs. Applying Tukey's outlier test, the Sponsor found 17 outlier data points out of 200. Because this is a 2nd tier, or confirmatory assay, the CutPoint Factor was calculated at a 99% confidence level by simply performing a non-parametric ranking of S/N values from lowest to highest of the S/N values. Since there were 183 S/N values after excluding outliers,

0.99 *183=181

which corresponds to S/N=1.82.

This value is used as a CutPoint factor; i.e. for a given assay run, the mean plate S/N

$CP_{plate}=1.82*S/N_{NC}$

Cutpoint Factor for the IgE Assay

Similarly, for the IgE assay, fifty normal serum samples were analyzed in 4 independent assay runs. Applying Tukey's outlier test, the Sponsor found 2 outlier data points out of 200.

A CutPoint Factor was calculated at a 99% confidence level by simply performing a non-parametric ranking of S/N values from lowest to highest of the S/N values. Since there were 198 S/N values after excluding outliers,

0.99 *198=196

which corresponds to S/N = 1.17

This value is used as a CutPoint factor; i.e. for a given assay run, the mean plate S/N

$CP_{plate}=1.17*S/N_{NC}$

Reviewer comments

As discussed by Shankar et al.2008, J. Pharm. Biomedical Analysis 48, pp 1267-1281, non-parametric ranking to determine a CP can be a robust method, as it does not rely on assumptions of normal data distribution. It is susceptible to outlier values, but the Sponsor has

excluded these before ranking. Therefore, the assignment of IgG and IgE CutPoints by non-parametric ranking is acceptable.

IgG Assay Sensitivity

Sensitivity for the IgG ELISA was determined from 6 independent assay runs using standard procedure to interpolate the anti-Sugammedex positive control signal at the Cutpoint as a Mean Concentration of 100.671 ng/ml antibody. As this is 2nd tier, or confirmatory assay, sensitivity was determined at a 99% confidence level as Mean Concentration +2.326*SD= 143 ng/ ml. An anti-MK-8616 Positive Control concentration of 325 ng/ml was set to lie above the Cutpoint, with this value determined by

PC= [Mean Concentration+ ($t_{0.99}$ *SD)]*2

Table 4. Determination of Anti-MK-8616 Isotyping Assay Sensitivity and Anti-MK-8616 Positive Control Concentration

Date and Analyst:	07Mar2014_KSK	07Mar2014_SW	10Mar2014_KSK	10Mar2014_SW	11Mar2014_KSK	11Mar2014_SW
Anti-MK-8616 ng/mL	Signal/Noise Ratio	Signal/Noise Ratio	Signal/Noise Ratio	Signal/Noise Ratio	Signal/Noise Ratio	Signal/Noise Ratio
1000	12.736	13.879	18.342	11.463	15.432	16.303
500	5.887	6.879	6.395	5.610	7.386	7.030
250	2.943	3.485	3.421	2.927	3.841	3.455
125	1.849	2.091	2.132	1.829	2.364	2.121
62.5	1.321	1.545	1.526	1.463	1.659	1.485
31.3	1.057	1.273	1.211	1.220	1.318	1.242
15.6	0.962	1.273	1.053	1.171	1.205	1.152
Concentration (ng/mL) at Cut Point Factor	121.567	93.979	92.822	123.463	76.773	95.421
Mean Concentration of acceptable results equal to the CPF (ng/mL)	100.671					
SD	18.227					
n	6					
Sensitivity [a] (ng/mL)	143.067					
Positive Control [b] (ng/mL)	324.010					
Final rounded concentration of Positive Control (ng/mL)	325					

Notes:
a: Sensitivity = Mean Concentration + (2.326 SD)
b: Positive control =[Mean concentration + ($t_{0.99}$ SD)]*2

Reviewer comments

The sensitivity of this ELISA assay for anti-Sugammedex IgG is appropriately determined and adequate to detect patient antibodies at concentrations above a moderate range of 143ng/ ml. Therefore the assay can detect antibodies in the range of greatest concern. The assay does not appear suitable for detecting low (<143 ng) concentrations of anti-Sugammedex IgG antibody.

IgE assay sensitivity

The Sponsor did not develop an anti-Sugammedex IgE positive control, so the positive control is simply reactivity of anti-human IgE detection antibody with ELISA plate wells coated with human 200 ng/ well human IgE. Therefore the sensitivity of the IgE assay is unknown.

Reviewer comments

Because the Sponsor did not establish sensitivity for the IgE assay, it is not clear if the assay is suitable for its intended purpose, which is detection of anti-Sugammedex IgE, expected to be in the low nanogram range. Therefore the Sponsor's IgE patient data cannot be interpreted.

Precision of the IgG assay

Precision was assed measuring the PC in 7 assay runs.

Table 5. Precision of Anti-MK-8616 Positive Control Samples in Human Serum in the Anti-MK-8616 Isotyping Assay

Control (Conc.)	Assay Date_Analyst (Run No.)	Determination (S/N)			Intra-Assay Precision				Inter-Assay Precision	
		1[a]	2	3	Mean	SD	%CV	n		
PC (325 ng/mL)	21Mar2014_KSK (1)	5.515	5.515	5.515	5.515	0.000	0.0	3	Mean	4.765
	21Mar2014_SW (2)	5.269	5.000	5.308	5.192	0.168	3.2	3	SD	0.568
	25Mar2104_KSK (3)	3.838	3.757	4.000	3.865	0.124	3.2	3	%CV	11.9
	24Apr2014_SW (4)	5.000	4.444	4.815	4.753	0.283	6.0	3	n	7
	26Mar2014_KSK (5)	4.400	4.514	4.429	4.448	0.059	1.3	3		
	25Mar2014_SW (6)	4.833	4.778	4.472	4.694	0.195	4.2	3		
	10Apr2014_SW (7)	4.500	4.133	4.333	4.322	0.184	4.3	3		

Note:
a. First determination of 7 runs was used to calculate inter-assay precision

Reviewer comments

The range of S/N values (3.838-5.515) for the PC are consistent with those seen throughout the validation, with intra-assay % CV (0-6%), and inter-assay % CV of 11.9%, that are modest. These data support the reproducibility of the assay.

Summary of the Analytical performance of the IgG PC

The Sponsor has summarized the S/N values for the 325 ng/ ml IgG positive control, which was assayed in triplicates on each of 11 assay plates used in different phases of the validation, resulting in 33 individual values. These S/N values range from 3.730-5.545, except for a single "high" value of 6.727.

Reviewer comment

The IgG PC signal shows a satisfactory degree of reproducibility for what is a qualitative assay, as discussed further below.

Matrix Selectivity of the IgG Assay

Table 6a. Matrix Selectivity of Anti-MK-8616 antibodies in Normal Human Serum

Individual Serum Samples	Fortified with anti-MK-8616 Ab at 326 ng/mL				Pass (Yes or No)	Unfortified				Pass (Yes or No)
	Mean	SD	%CV	S/N Ratio		Mean	SD	%CV	S/N Ratio	
1	0.191	0.023	12.0	5.788	Yes	0.035	0.001	2.9	1.061	Yes
2	0.202	0.016	7.9	6.121	Yes	0.056	0.002	3.6	1.697	Yes
3	0.225	0.003	1.3	6.818	Yes	0.052	0.002	3.8	1.576	Yes
4	0.190	0.007	3.7	5.758	Yes	0.036	0.001	2.8	1.091	Yes
5	0.238	0.009	3.8	7.212	Yes	0.033	0.003	9.1	1.000	Yes
6	0.167	0.008	4.8	5.061	Yes	0.027	0.001	3.7	0.818	Yes
7	0.168	0.017	10.1	5.091	Yes	0.022	0.001	4.5	0.667	Yes
8	0.168	0.006	3.6	5.091	Yes	0.024	0.001	4.2	0.727	Yes
9	0.203	0.008	3.9	6.152	Yes	0.037	0.000	0.0	1.121	Yes
10	0.191	0.006	3.1	5.788	Yes	0.036	0.001	2.8	1.091	Yes

Note:
IgG CPF = 1.82; Mean IgG NC = 0.033

Reviewer comment

As expected, this validation exercise gives low S/N values in the range 0.667-1.697 for un-spiked serum samples, and ~ 5-7 fold higher values for samples spiked with the positive control (325 ng/ ml). There is considerable individual variability for the S/N values for serum samples spiked with Positive Controls, consistent with the fact that is primarily a qualitative assay, simply indicating the presence of an anti-Sugammedex IgG signal above the CutPoint.

Effect of hemolysis on the IgG assay

One human serum lot was tested at varying degrees of hemolysis (35, 70, 140, 275, 550, 1100 mg/dL-corresponding to samples 1-6 in the following table.

Table 6b. Matrix Selectivity of Anti-MK-8616 antibodies in Hemolyzed Human Serum

Hemolyzed Samples	Fortified with anti-MK-8616 Ab at 326 ng/mL				Pass (Yes or No)	Unfortified				Pass (Yes or No)
	Mean	SD	%CV	S/N Ratio		Mean	SD	%CV	S/N Ratio	
1	0.157	0.006	3.8	4.758	Yes	0.024	0.002	8.3	0.727	Yes
2	0.152	0.023	15.1	4.606	Yes	0.023	0.001	4.3	0.697	Yes
3	0.157	0.000	0.0	4.758	Yes	0.023	0.001	4.3	0.697	Yes
4	0.150	0.006	4.0	4.545	Yes	0.022	0.001	4.5	0.667	Yes
5	0.155	0.005	3.2	4.697	Yes	0.021	0.001	4.8	0.636	Yes
6	0.178	0.008	4.5	5.394	Yes	0.030	0.004	13.3	0.909	Yes

Note:
IgG CPF = 1.82; Mean IgG NC = 0.033

Reviewer comment

Anti-Sugammedex IgG signal from the positive control appears insensitive to hemolysis. In any case, hemolysis is unlikely to have affected the results for patient sera, as only four samples showed appreciable hemolysis.

Cross-Reactivity/Specificity

Table 7. Cross-reactivity/Specificity of Detection Reagents in the Anti-MK-8616 Isotyping Assay

	Mean Signal/Noise Ratio			
	SGDX NC	Anti-MK-8616 Ab	IgG coated wells	IgE coated wells
IgG Detection (Protein G-HRP)	1.034 (Negative)	**4.759 (Positive)**	**10.759 (Positive)**	0.690 (Negative)
IgE Detection (Mouse anti-Human IgE-HRP)	1.156 (Negative)	1.067 (Negative)	0.978 (Negative)	**5.733 (Positive)**
Note: IgG CPF = 1.82, IgE CPF = 1.17				

Reviewer comment

The IgG and IgE detection reagents are not cross reactive, as expected.

IgG depletion efficiency

Table 8. IgG Depletion Efficiency in the Anti-MK-8616 Isotyping Assay

anti-MK-8616 Ab	Untreated or Unprocessed Samples					Treated or Depleted Samples				
	Mean OD	SD	%CV	S/N Ratio	Pass (Yes or No)	Mean OD	SD	%CV	S/N Ratio	Pass (Yes or No)
0 ng/mL 1	0.035	0.003	8.6	1.000	N/A	0.010	0.002	20.0	0.286	Yes
0 ng/mL 2	0.036	0.001	2.8	1.029	N/A	0.010	0.000	0.0	0.286	Yes
500 ng/mL 1	0.226	0.025	11.1	6.457	Yes	0.019	0.000	0.0	0.543	Yes
500 ng/mL 2	0.232	0.005	2.2	6.629	Yes	0.010	0.000	0.0	0.286	Yes
1000 ng/mL 1	0.493	0.012	2.4	14.086	Yes	0.029	0.000	0.0	0.829	Yes
1000 ng/mL 2	0.444	0.004	0.9	12.686	Yes	0.030	0.001	3.3	0.857	Yes
Note: IgG CPF = 1.82, Mean IgG NC = 0.035										

Reviewer comment

Complete competition of the assay signal is observed even at 1 mg/ ml positive control anti-Sugammedex, demonstrating that an IgG assay signal can be confirmed by competition even at high antibody concentrations.

Stability of the anti-Sugammedex IgG PC

Room temperature stability of the anti-Sugammedex positive control (anti-MK-8616 PC)

Room Temperature (24 hours)		
Run Date	Aliquot	Anti-MK-8616 PC (325 ng/mL) S/N
28Mar2014	1	4.237
	2	4.184
	3	4.026
Cut Point Factor = 1.82		

After 24 hours at RT, the PC shows a range of S/N values (4.026-4.237) within those seen in the precision study (3.865-5.151 for inter assay precision)

Stability of coated and blocked ELISA plates

Plate Stability (25 days at 4°C)		
Run Date	Aliquot	Anti-MK-8616 PC (325 ng/mL) S/N
31Mar2014	1	4.471
	2	4.206
	3	4.353
Cut Point Factor = 1.82		

Again, wells coated with PC and stored at 4 ^{0}C for 25 hours show a range of values (4.206-4.353) within those seen for inter assay precision (3.865-5.151)

Freeze Thaw Stability of the anti-MK-8616 PC

No. of Freeze-Thaws	Assay Date	Aliquot	Anti-MK-8616 PC (325 ng/mL) S/N
1	31Mar2014	1	4.364
		2	4.303
		3	4.364
2	31Mar2014	1	4.333
		2	4.333
		3	4.303
3	31Mar2014	1	4.061
		2	4.030
		3	4.333
4	31Mar2014	1	4.303
		2	4.303
		3	4.182
5	31Mar2014	1	4.242
		2	4.091
		3	4.121
6	31Mar2014	1	4.000
		2	3.667
		3	4.212
7	31Mar2014	1	4.333
		2	4.212
		3	4.303
Cut Point Factor = 1.82			

Seven freeze-thaw cycles do not change the ECL values for the PC outside of those determined for inter-assay precision.

Reviewer comment

The Sponsor has demonstrated satisfactory stability of a critical reagent, the anti-Sugammedex PC, upon RT storage, coating in ELISA wells and storage of the plates at 4 ^{0}C, and after 7 freeze thaw cycles.

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/s/

FREDERICK C MILLS
03/30/2015

GERALD M FELDMAN
03/30/2015

NDA 22225

Bridion (sugammadex) Injection

Organon USA Inc.,
a subsidiary of Merck & Co., Inc.

Yong Hu, Ph.D.

Office of Pharmaceutical Quality

For

Division of Anesthesia, Analgesia, and Addiction Products

Table of Contents

Chemistry Review Data Sheet

1. NDA: 22225

2. REVIEW #: 4

3. REVIEW DATE: 3/24/2015

4. REVIEWER: Yong Hu, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original NDA	30-Oct-2007
CMC Review #1	30-Jan-2008
CMC Review #2	12-Jun-2008
Memorandum to CMC Review #2	24-July-2008
Product Quality Microbiology Review #1	20-Feb-2008
FDA Action Letter (Not Approvable)	31-Jul-2008
Complete Response	20-Dec-2012
Response to CMC Information Request	22-Feb-2013
Withdrawal of Compatibility Protocol	08-May-2013
Response to CMC Information request	27-Jun-2013
Response to CMC Information request	15-July-2013
CMC Review #3	06-Aug-2013
Addendum to CMC Review #3	28-Aug-2013
FDA Action Letter (Complete Response)	20-Sept-2013

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Complete Response	22-Oct-2014
Labeling/Container-carton	20-Jan-2015

7. NAME & ADDRESS OF APPLICANT:

Name: Organon USA Inc.

Chemistry Review Data Sheet

Address:	2000 Galloping Hill Rd, Kenilworth, New Jersey 07033
Representative:	Dori L. Glassner
Telephone:	732-594-2735

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Bridion (pending FDA review)
b) Non-Proprietary Name (USAN): Sugammadex Sodium
c) Code Name/# (ONDC only): Org 25969 (SCH900616/MK-8616) and Org 48302
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:

505 (b)(1)

10. PHARMACOL. CATEGORY:

The compound serves as a reversal agent for neuromuscular blocking agents.

11. DOSAGE FORM:

Injection

12. STRENGTH/POTENCY:

100 mg/mL (sugammadex)

13. ROUTE OF ADMINISTRATION:

Intravenous (single bolus injection)

14. Rx/OTC DISPENSED: __x_ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___x___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

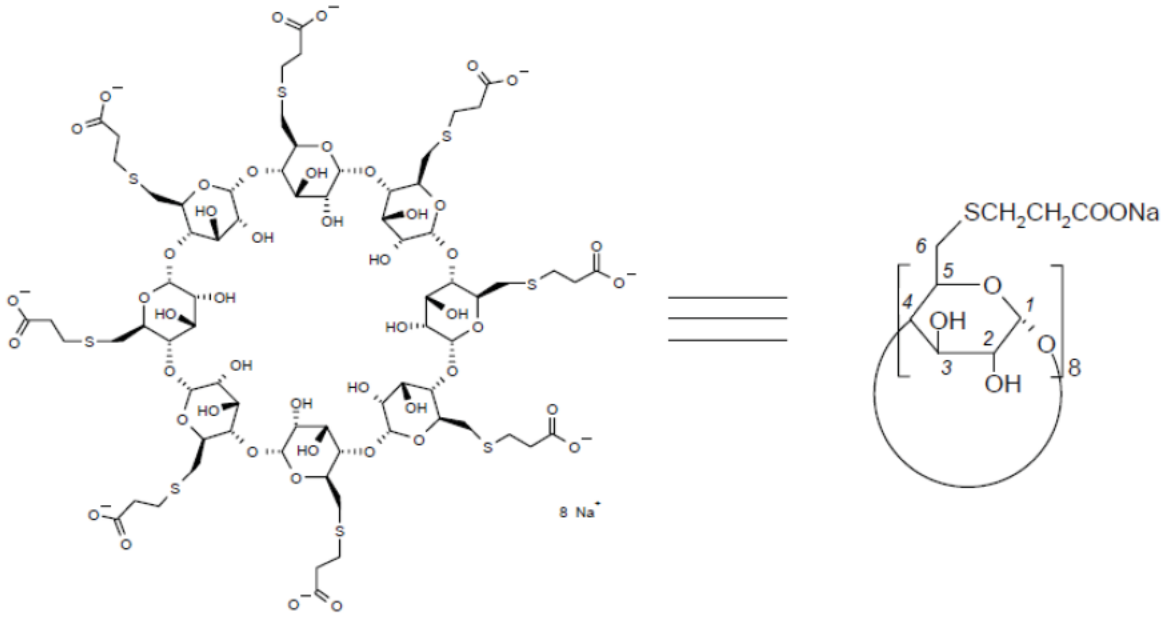
Org 25969 – Sugammadex Sodium:

Chemical name: $6^A, 6^B, 6^C, 6^D, 6^E, 6^F, 6^G, 6^H$ –octakis-S-(2-carboxyethyl) -$6^A, 6^B, 6^C, 6^D, 6^E, 6^F, 6^G, 6^H$ – octathio-γ-cyclodextrin octasodium salt (CA Index name) or octakis(6-S-(2-carboxyethyl)-6-thio)cyclomaltooctaose octasodium salt (IUPAC)

Molecular formula: $C_{72}H_{104}O_{48}S_8Na_8$

Molecular weight: 2178.01

Structural formula:



The drug substance may contain a low percentage (typically (b) (4) w/w) of a related compound Org 48302, which is claimed to have activity and pharmacological profiles similar to Org 25969.

Chemical name (b) (4)

Molecular formula: (b) (4)

Molecular weight: 2067.90

Structural formula:

(b) (4)

[redacted]

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	4	N/A		(b) (4) met USP requirements per information in NDA. See Addendum to CMC Review #2
	III			3	Adequate	5/13/2011 (Reviewed by Jesse Wells)	Also see Addendum to CMC Review #2
	III			3	Adequate	6/18/2009 (Reviewed by Zedong Dong)	

[1] Action codes for DMF Table:
1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	68029	Org 25969 Injection

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not requested in this review cycle.		
Facilities (OPF)	Approval.		Juandria Williams
Pharm/Tox	Not requested in this review cycle.		
Biopharm	N.A.		
LNC	N.A.		
Methods Validation	Not requested in this review cycle. No method changes.		
OPDRA	N.A.		
EA	Adequate per CMC Review #2		Alan Schroeder
Microbiology	Approval	3/24/2015	Vinayak Pawar

The Chemistry Review for NDA 22225

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is recommended for Approval from CMC perspective.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance (Org 25969 or sugammadex sodium), an octasodium salt, is a modified γ-cyclodextrin and its mode of action is based on the formation of 1:1 inclusion complexes with rocuronium or vecuronium. The drug substance contains a related compound (b) (4) Org 48302, which the applicant claims to have an activity and pharmacological profile comparable to that of Org 25969, and therefore it is also treated as an active entity. Org 48302 is typically present at (b) (4) in the representative drug substance batches. Dr. Zengjun (Alex) Xu, the Pharmacology/Toxicology reviewer, concurs that the two compounds have comparable activities and pharmacological profiles. The drug product is formulated as an injection solution and therefore, solid state properties of the drug substance such as polymorphism and particle size distribution are not critical for the drug product. The drug substance is highly soluble in water. The drug substance (b) (4) have been extensively characterized/identified/qualified and controlled. The drug substance is manufactured by N.V.Organnon at Oss, The Netherlands.

The drug product is a sterile parenteral solution for intravenous administration. It is prepared by (b) (4) adjusting the pH to 7.5 with sodium hydroxide or hydrochloric acid, (b) (4) 2 mL and 5 mL vials, (b) (4) The strength is 100 mg/mL (expressed as the total amount of Org 25969 and Org 48302 free acids). The level of Org 48302 is typically below 7 mg/mL in the product. The container closure system is type I glass vials with a (b) (4) rubber closure and an aluminum flip off cap.

All 100 mg/mL clinical preparations are considered representative for the market formulation. Batches identified as pivotal clinical batches are indicated to be manufactured by a process and at a scale comparable to the primary stability batches. Critical process steps for the manufacture of the drug product include the following: (b) (4)

The major change in this resubmission is the change of [redacted] As a result, there were some changes to the sterilization process. Three production scale "validation" batches of each strength have been successfully manufactured at [redacted] The batch data supports the process validation at the [redacted] site from chemistry perspective. The microbiology reviewer also deemed that application has met the regulatory expectations for validating the process used for [redacted] of the drug product.

In stability studies, the only trending parameters are as follows: [redacted] The drug product is sensitive to light [redacted] and the applicant proposes that the primary container be exposed to light no longer than for 5 days. [redacted] Photostability data support the 5 day maximum limit on exposure to normal indoor lighting, [redacted].

Six months stability data at the long-term and accelerated conditions were provided in this resubmission for the above "validation" batches manufactured at the [redacted] site. No stability issues are indicated.

B. Description of How the Drug Product is Intended to be Used

The proposed indications are routine reversal of shallow or profound neuromuscular blockade induced by rocuronium or vecuronium, and immediate reversal of neuromuscular blockade at 3 minutes after administration of rocuronium. The recommended doses are 2 mg/kg or 4 mg/kg for routine reversal, and 16 mg/kg for immediate reversal. The injection is to be given as a single bolus dose intravenously. The drug product solution (100 mg/mL), is filled in colorless, [redacted] (2 mL per vial) or [redacted] (5 mL per vial) vials of [redacted] glass, type I, and closed with gray [redacted] rubber closures. The rubber closures are held in position on the glass vials by aluminium crimp-caps with a "flip-off" seal.

A shelf life of 36 months at 25°C is acceptable for the drug product. The supporting stability data include 36 months data of the three primary stability batches manufactured at Oss, The Netherlands and one primary stability batch (pilot scale) manufactured at Swords, Ireland for each presentation, and 36 months data of three production-scale batches manufactured at Swords, Ireland for each presentation. In addition, the six months stability data for the production scale batches manufactured at the new commercial site [redacted] showed that the batches were comparable to the previous production scale batches.

The storage statement in the "How Supplied" section of the draft labeling is the following. " Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) (see USP Controlled Room Temperature) [redacted] protect from light. When not protected from light, the vial should be used within 5 days."

C. Basis for Approvability or Not-Approval Recommendation

The CMC recommendations during the last two review cycles were both "Approval".

In this resubmission, the applicant has changed the commercial manufacturing site for the drug product and made some changes to the sterilization process. The applicant has provided adequate batch analysis data and additional stability data to support the proposed process change at the new site. The microbiology reviewer has recommended approval of this NDA. The facilities reviewer has also recommended approval based on the facilities evaluation. The applicant has adequately addressed the CMC labeling comments raised during the last review cycle.

Chemistry Assessment

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data

CMC recommended "Approval" of this NDA pending the resolution of the labeling issues during the last review cycle. In this resubmission, the applicant made some CMC changes to the NDA. These changes are reviewed below.

S DRUG SUBSTANCE

S.1 General Information

Adequate.

The applicant states that a USAN modified application was filed with the USAN Council for "sugammadex", which is the active moiety of the drug substance. The current USP policy is to designate the strength of drug products according to the neutral, active moiety unless the salt ion contributes substantively to the desired ADME profile. This additional USAN designation will support the expression of drug product strength as the neutral active moiety per the agreement reached between the sponsor and FDA teleconference (Type C Meeting – CMC only) held on June 11, 2014.

S.2 Manufacture

S.2.1 Manufacturers

Adequate.

(b) (4)

N.V. Organon (p/a Kloosterstraat 6) remains in the filing as the analytical testing site.

In summary, the manufacturing sites and responsibilities for sugammadex drug substance are presented in Table 1 below. The overall recommendation for the facilities by the facilities reviewer, Dr. Juandria Williams, is "Approve" in Panorama, with the re-evaluation date 2/14/2016.

Table 1 Manufacturing sites and responsibilities for Sugammadex drug substance (MK-8616/ Org 25969)

Site and address	Responsibilities
(b) (4)	All manufacturing steps and analytical testing
N.V. Organon Oss, The Netherlands Street address: Kloosterstraat 6, 5349 AB, Oss	Analytical testing
(b) (4)	

P DRUG PRODUCT

P.1 Description and Composition of the Drug Product

Adequate.

The names for active components Org 25969 and Org48302 were added to the composition tables (Table 1 and Table 2 below). The footnotes were updated to clarify the declared amount of sugammadex in terms of the salt and mono OH-derivative. There is no change to the composition of the product.

Table 1: Complete composition Org 25969 solution for injection 100 mg/mL (2 mL per vial)

Component	Reference to quality standard	Function(s)	Quantity per vial (2.0 mL˜)	Quantity per mL
Sugammadex Sodium (Org 25969) + mono OH-derivative of sugammadex (Org 48302)†	In-house standard	Active	200 mg	100 mg
Sodium hydroxide‡	Ph. Eur., NF	pH adjuster	q.s. to pH 7.5	q.s. to pH 7.5
Hydrochloric acid‡	Ph. Eur., NF	pH adjuster	q.s. to pH 7.5	q.s. to pH 7.5
(b) (4)	Ph. Eur., USP	(b) (4)		
(b) (4)	Ph. Eur., NF			

† Declared amount of 100 mg/mL sugammadex corresponds with 108.8 mg/mL sugammadex sodium salt (Org 25969) which may contain up to 7 mg/mL of mono OH-derivative of sugammadex (Org 48302).
‡ It concerns (b) (4) of Ph. Eur. and USP quality
§ USP name = (b) (4)

Table 2: Complete composition Org 25969 solution for injection 100 mg/mL (5 mL per vial)

Component	Reference to quality standard	Function(s)	Quantity per vial (5.0 mL˜)	Quantity per mL
Sugammadex Sodium (Org 25969) + mono OH-derivative of sugammadex (Org 48302)†	In-house standard	Active	500 mg	100 mg
Sodium hydroxide‡	Ph. Eur., NF	pH adjuster	q.s. to pH 7.5	q.s. to pH 7.5
Hydrochloric acid‡	Ph. Eur., NF	pH adjuster	q.s. to pH 7.5	q.s. to pH 7.5
(b) (4)	Ph. Eur., USP	(b) (4)		
(b) (4)	Ph. Eur., NF			

† Declared amount of 100 mg/mL sugammadex corresponds with 108.8 mg/mL sugammadex sodium salt (Org 25969) which may contain up to 7 mg/mL of mono OH-derivative of sugammadex (Org 48302).
‡ It concerns (b) (4) of Ph. Eur. and USP quality (b) (4)

P.3 Manufacture

P.3.1 Manufacturers

Adequate.

Organon (Ireland) Ltd, Swords, Ireland has been removed as drug product manufacturing, packaging, release and stability site.

N.V. Organon , Netherlands has been removed as release site.

(b) (4) has been selected as the proposed drug product manufacturing, packaging, release and stability testing site.

Manufacturer	Manufacturing site	Responsibility
(b) (4)		
N.V. Organon	Kloosterstraat 6, 5349 AB Oss, Netherlands	Stability testing - Container Closure Integrity
Merck Sharp & Dohme Corp.	4633 Merck Road Wilson, North Carolina NC 27893 USA	Labeling Secondary packaging
(b) (4)		

The overall recommendation for the facilities by the facilities reviewer, Dr. Juandria Williams, is "Approve" in Panorama, with the re-evaluation date 2/14/2016.

P.3.2 Batch Formula

Adequate.

Due to the change of the drug product manufacturer, the proposed commercial batch size for the 200 mg strength (b) (4) vial) has (b) (4) vials) and the batch size for the 500 mg strength (b) (4) vial) has (b) (4) vials). No changes have been made to the product composition. The (b) (4) Manufacturing facility in (b) (4) has validated batch sizes of (b) (4) and (b) (4) for the 200 mg and 500 mg presentations, respectively.

Table 1 Batch formula for a (b) (4) batch Org 25969 Solution for Injection 100 mg/mL (2 mL per vial)

Component	Reference to quality standard	Quantity per vial (2.0 mL*)	Quantity per batch (b) (4)
Sugammadex Sodium (Org 25969) + mono OH-derivative of sugammadex (Org 48302)	In-house standard	200 mg†	(b) (4)
Sodium hydroxide and/or Hydrochloric acid‡	Ph. Eur., NF	q.s. to pH 7.5	q.s. to pH 7.5
(b) (4)	Ph. Eur., USP	(b) (4)	(b) (4)
	Ph. Eur., NF	-	-¶
(b) (4)			

(b) (4)

Table 2. Batch formula for a (b) (4) batch of Org 25969 Solution for injection 100 mg/mL (5 mL per vial)

Component	Reference to quality standard	Quantity per vial (5.0 mL*)	Quantity per batch (b) (4)
Sugammadex Sodium (Org 25969) + mono OH-derivative of sugammadex (Org 48302)	In-house standard	500 mg†	
Sodium hydroxide and/or Hydrochloric acid‡	Ph. Eur., NF	q.s. to pH 7.5	q.s. to pH 7.5
(b) (4)	Ph. Eur., USP	(b) (4)	(b) (4)
	Ph. Eur., NF	-	-¶
			(b) (4)

P.3.3 Description of Manufacturing Process and Process Controls

Adequate.

The section was updated to reflect the process at the [redacted] (b) (4) facility in [redacted] (b) (4)

The manufacturing process steps and process controls at this contract facility in [redacted] (b) (4) align with the process previously presented in 2012 NDA for the facility at Swords, Ireland with the exception of the [redacted] (b) (4)

The manufacturing process flow chart and a detailed manufacturing process description are presented below.

Figure 1 Manufacturing Process Flow Diagram

(b) (4)

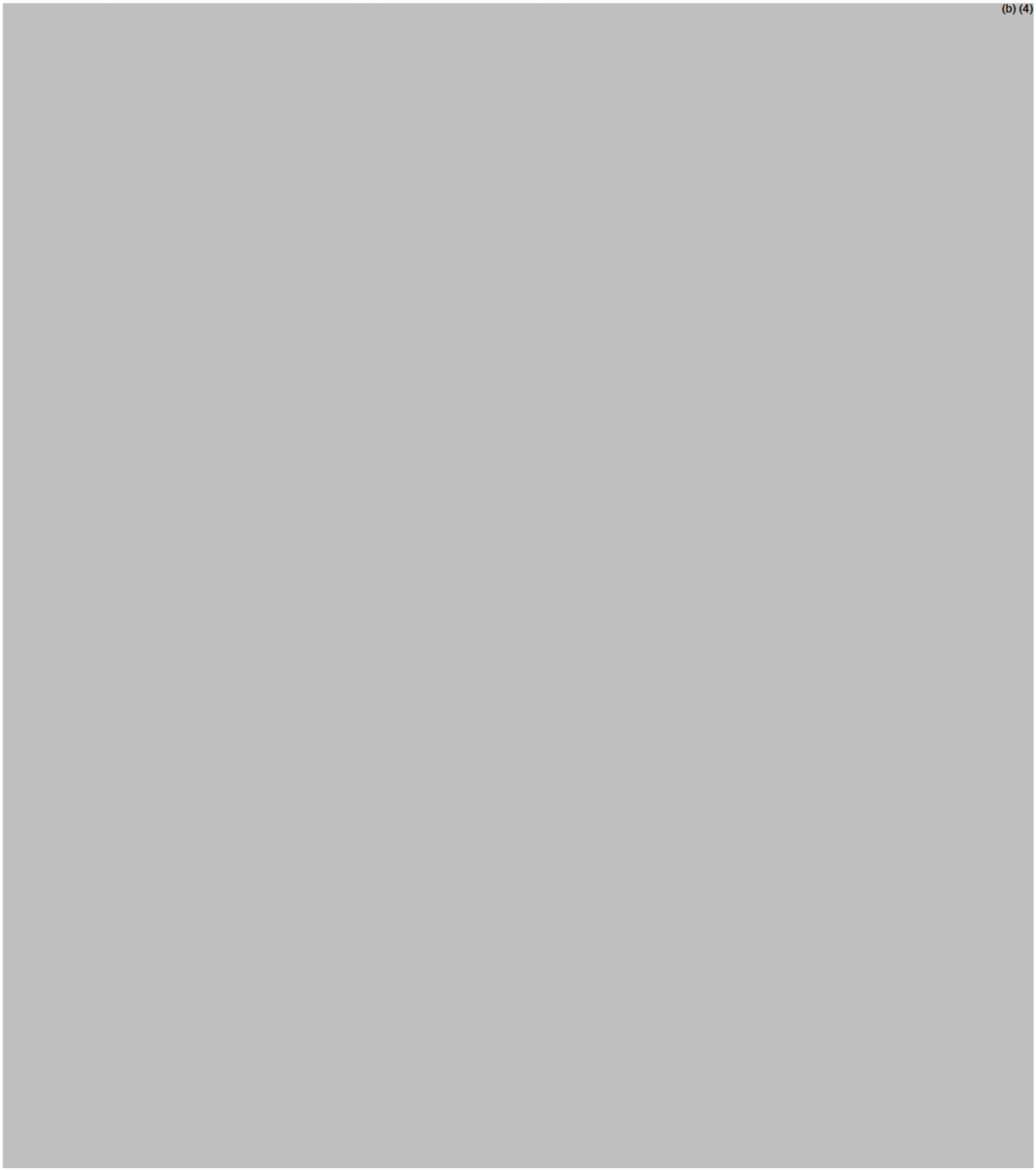


Table 1 Narrative description of the proposed commercial production process

Process step	Narrative description
	(b) (4)
	(b) (4)

The process information provided is adequate from chemistry perspective. The microbiology reviewer, Dr. Vinayak Pawar, has also determined that process information is acceptable from his perspective.

P.3.4 Controls of Critical Steps and Intermediates

Adequate

(b) (4)

The microbiology reviewer, Dr. Vinayak Pawar, has deemed that the process controls are acceptable from his perspective.

P.3.5 Process Validation and/or Evaluation

Adequate.

The proposed commercial manufacturing of Sugammadex Solution for Injection 100 mg/mL, 200 mg/vial & 500 mg/vial, (b) (4) respectively, have been validated by the (b) (4) facility located in (b) (4)

A summary of the process validation batches is provided in Table 1. The lots were manufactured according to the manufacturing process description and batch formulas detailed in Sec. 3.2.P.3.3 and Sec. 3.2.P.3.2

Table 1 Relevant batch data process validation batches

Product Presentation	Vial Size	Batch No.	Batch Size (kg)	Batch Size (L)	Drug substance batch number	Manufacturing Date
Sugammadex 2ml Fill (200 mg/vial)	(b) (4)	AB9061		(b) (4)	L00036388	14-Dec-2013
		AB9062			L00036388	16-Dec-2013
		AB9063			L00036388	13-Jan-2014
Sugammadex 5ml Fill (500 mg/vial)		AC0756			L00036388	17-Jan-2014
		AC0757			L00036388/ L00036399	23-Jan-2014
		AC0758			L00036399	26-Jan-2014

Table 5 below shows the process parameters for the six validation batches.

4 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

Table 11 Finished Product – Sugammadex 200 mg/vial and 500 mg/vial Validation Results, end of process (Cont.)

Process Stage	Sample Collection	Sample	Expected Results [*,+]	Test	AB9061	AB9062	AB9063	AC0756	AC0757	AC0758
[redacted]										

(b) (4)

The final product release testing showed that all batches meet the specifications (see data in P.5.4).

Therefore, from chemistry perspective, the in-process and final batch data support the process validation at the commercial manufacturing site [redacted] (b) (4).

P.5 Control of Drug Product [name, dosage form]

P.5.1 Specification(s)

Adequate.

No changes have been proposed for the specification in this resubmission, as compared to the last cycle.

The drug product specification is reproduced below (from 2.3.P.5.1).

It should be noted that most of the acceptance criteria for the impurities are now more stringent than what were proposed in the original application, which Dr. Alan Schroeder, the CMC reviewer in the first cycle, recommended for approval. These acceptance criteria were revised/tightened in the last resubmission and no changes have been made in this resubmission. According to our conversations, Dr. Alex Xu, the Pharmacology/Toxicology reviewer, confirmed that the original impurity limits were considered qualified from safety perspective and the current limits are of no safety concerns as they are mostly lower than the original ones.

Table 15 Specification for Org 25969 drug product

Test	Method principle	Acceptance criterion	
		Shelf life	Release
Description			
Appearance	Visual	Aqueous liquid	
Color	Ph. Eur. (+VIS)	(b) (4)	
Identification			
Active ingredient identical with standard	HPLC	Org 25969 and Org 48302 present	
Active ingredient identical with reference spectrum (UV-DAD)	HPLC	Org 25969 and Org 48302 present	
Assay			
(b) (4)	HPLC	(b) (4)	
	HPLC		
	HPLC		
Impurities			

Table 15 Specification for Org 25969 drug product

Test	Method principle	Acceptance criterion	
		Shelf life	Release
Degradation products Specified identified: (b) (4) Specified unidentified: (b) (4) Unspecified (others): Each individual Total degradation products	HPLC	(b) (4)	
Pharmaceutical technical tests			
Extractable volume	Ph. Eur., USP	For 2.0 mL: individual volume (b) (4) mL per vial For 5.0 mL: individual volume (b) (4) mL per vial	
pH	Ph. Eur., USP	7.0 to 8.0	
Osmolality	Ph. Eur., USP	300 to 500 mOsm/kg	
Clarity	Ph. Eur.	Clear	
Visible particles	Ph. Eur.	Practically free from particles	
Particulate matter (b) (4) m m	Ph. Eur., USP	(b) (4)	
Microbial tests			
Bacterial endotoxins	Ph. Eur., USP	(b) (4) endotoxin units per mL	
Sterility	Ph. Eur., USP	Sterile	
Container closure integrity	Closure integrity	(b) (4) per vial	Not tested

[a] Expressed as active entity, 100 mg/mL of the active entity corresponds to 108.8 mg/mL of the Org 25969 (=sodium salt) (b) (4)
(b) (4)

P.5.4 Batch Analyses

Adequate.

The batch data for the following batches have been added:

- Three (b) (4) validation batches manufactured at (b) (4)
- Three (b) (4) validation batches manufactured at (b) (4)
- One clinical (b) (4) batch manufactured at NV Organon, Netherland, and used in Protocol Number 101.

All batches are within the specifications deemed adequate in the previous review cycles. The data support the process validation at the new manufacturing site – (b) (4).

Table 1 Batch Analysis for (b) (4) vials (2 mL/vial; 200 mg/vial)

Batch No. Acceptance Criteria	AB9061A	AB9062A	AB9063A
Batch Size	(b) (4)		
Manufacturing Site			
Manufacturing Date			
Drug Substance Batch No.			
Studies Used In			
Analytical Procedure			
Appearance			
Color			
Identity			
Composite Assay			
Org 25969 + Org 48302			
Org 25969			
Org 48302			
Degradation products			
Specified identified: (b) (4) **Specified unidentified:** (b) (4) **Unspecified (others):** Each individual Total degradation products			

Table 1 Batch Analysis for (b) (4) vials (2 mL/vial; 200 mg/vial)

	Batch No. Acceptance Criteria	AB9061A	AB9062A	AB9063A
Extractable volume	Minimum 2.0 mL/vial			(b) (4)
pH	7.0 – 8.0			
Osmolality	300 to 500 mOsm/kg			
Clarity	Clear			
Visible Particles	Practically free from particles			
Particulate Matter (b) (4) µm (4) µm	(b) (4) particles per vial particles per vial			
Bacterial Endotoxins	(b) (4) EU/mL			
Sterility	Sterile			

Table 2 Batch Analysis for (b) (4) vials (5 mL/vial; 500 mg/vial)

	Batch No. Acceptance Criteria	AC0756A	AC0757A	AC0758A
Batch Size	-			(b) (4)
Manufacturing Site	-			
Manufacturing Date	-			
Drug Substance Batch No.	-			
Studies Used In	-			
Analytical Procedure	(b) (4)			
Appearance				
Color				
Identity				
Composite Assay				
Org 25969 + Org 48302				
Org 25969				
Org 48302	≤ 7.0 mg/mL			
Degradation products				
Specified identified: (b) (4) **Specified unidentified:** (b) (4) **Unspecified (others):** Each individual Total degradation products				(b) (4)

Table 2 Batch Analysis for (b) (4) vials (5 mL/vial; 500 mg/vial)

	Batch No. Acceptance Criteria	AC0756A	AC0757A	AC0758A
Extractable volume	Minimum 5.0 mL/vial			(b) (4)
pH	7.0 – 8.0			
Osmolality	300 to 500 mOsm/kg			
Clarity	Clear			
Visible Particles	Practically free from particles			
Particulate Matter (b) (4) µm (4) µm	(b) (4) particles per vial particles per vial			
Bacterial Endotoxins	(b) (4) EU/mL			
Sterility	Sterile			

Table 3 Batch Analysis for (b) (4) vials (5 mL/vial; 500 mg/vial) used in Clinical Study PN101

Lot Number	547299	
Bulk Batch Number	417891001	
Manufacturing Site	NV Organon, Netherlands	
Manufacturing Date	15-May-2013	
Studies Used In	Clinical – PN101	
Analytical Procedure	**Acceptance Criteria**	**Results**
Appearance	Aqueous Liquid	Conforms
Color	(b) (4)	
Identity		
Composite Assay: Org 25969 + Org 48302 Org 25969 Org 48302		
Degradation Products **Specified identified:** (b) (4) **Specified unidentified:** (b) (4) **Unspecified (others):** Each individual Total degradation products		
Extractable volume	Minimum 5.0 mL/vial	Conforms
pH	7.0 – 8.0	7.5
Osmolality	300 to 500 mOsm/kg	434
Clarity	Clear	Conforms
Visible Particles	Practically free from particles	Conforms
Particulate Matter (b) (4) µm µm	(b) (4) particles per vial particles per vial	(b) (4)
Bacterial Endotoxins	(b) (4) EU/mL	
Sterility	Sterile	Conforms

P.7 Container Closure System [name, dosage form]

Adequate.

The applicant states that [redacted] will utilize the same packaging components and vendors as were used at the previously proposed commercial manufacturing site at Organon (Ireland) Limited, Swords, Ireland and presented in the 2012 NDA.

The only change is that made to the treatment of the [redacted] After receipt of the [redacted] This change is minor and acceptable.

P.8 Stability [name, dosage form]

P.8.1 Stability Summary and Conclusion

Adequate.

The stability data for drug product manufactured at the new manufacturing site, [redacted] in [redacted] have been provided. The data include 6 months at the long term storage condition of 25 °C/60% RH and at the accelerated condition of 40 °C/75% RH.

No significant changes were observed at any storage condition. Based on the data presented, the lots manufactured at the commercial site of manufacturing continue to support the proposed 36 month shelf life for product stored at 25˚C (77˚F); excursions permitted to 15˚C to 30˚C (see USP Controlled Room Temperature), protected from light. When not protected from light, the vial should be used within 5 days.

The data are summarized below.

Description:
Description (appearance and color) was monitored through 6 months for the 100 mg/mL (2 mL) and 100 mg/mL (5 mL) at 25 °C/60% RH and at 40 °C/75% RH. No change in color or appearance was observed at both long term and accelerated conditions.

Assay and Degradation Products:
There are no significant changes in assay for the site stability batches packaged in [redacted] and [redacted] vials through 6 months at 25 °C/60% RH and through 6 months at the accelerated condition of 40 °C/75% RH. The assay results conform to the specifications as noted in Sec. 3.2.P.5.1. The degradation products [redacted] however, the levels were well below the specification limits. The total degradation products levels were below the proposed acceptance criteria of ≤ [redacted]% at the long term and accelerated conditions.

Extractable Volume, pH, Osmolality, Clarity, Visible Particles and Particulate Matter:
All results conform to the proposed specifications provided in Sec. 3.2.P.5.1.

Microbial Tests: Bacterial Endotoxins, Sterility & Container Closure Integrity:
Bacterial Endotoxins and Sterility were monitored at the initial timepoint for the 100 mg/mL (2 mL) and 100 mg/mL (5 mL) at 25°C/60% RH. All results conform to the proposed specifications

provided in Sec. 3.2.P.5.1. Container closure integrity was monitored at 0, 3 and 6 month timepoints for both the (b) (4) and (b) (4) vials at 25 °C/60% RH and at 40 °C/75% RH. All results conform to the specifications provided in Sec. 3.2.P.5.1.

P.8.2 Postapproval Stability Protocol and Stability Commitment

Adequate.

The following regulatory tests will be monitored in the production stability program:

Test	Code
Description	A
Assay	A
Impurities	A
pH	A
Clarity	A
Visible Particles	A
Particulate Matter	A
Osmolality	B
Extractable Volume	B
Bacterial Endotoxins	C
Sterility	C
Container Closure Integrity	D

An appropriate number of samples have been taken from the validation batches (so-called commitment batches) made at the commercial manufacturing site and placed into the stability program at the long term and accelerated conditions.

The following testing schedule is proposed.

Table 1: Sugammadex Solution for Injection, 100 mg/mL, Commitment Protocol

Stability Condition	Time Intervals (months)							
	0	3	6	9	12	18	24	36
25 ± 2°C/60 ± 5% RH	ABCD	A	A	A	ACD	A	AD	ABCD
40 ± 2°C/75 ± 5% RH	ABD	A	ABD	NS	NS	NS	NS	NS

In order to maintain product contact with the rubber stopper, the vials will be stored in the inverted orientation

NS: Not Scheduled

Thereafter, at least one batch in each container/closure type will be selected on an annual basis and tested for long-term stability to provide additional assurance of the shelf life. The annually

selected batches will be stored at the listed conditions and tested as closely as possible to the schedule listed in Table 2.

Table 2: Sugammadex Solution for Injection, 100 mg/mL, Routine Long-Term Stability Protocol for Annual Production Batches

Long Term Stability Condition	Time Intervals (months)			
	0	12	24	36
25 ± 2°C/60 ± 5% RH	ABCD	AD	AD	ABCD

In order to maintain product contact with the rubber stopper, the vials will be stored in the inverted orientation

Note that, besides the sterility test at the beginning and end of the stability program, the container closure integrity test is also done annually. The microbiology reviewer has deemed the protocol acceptable.

P.8.3 Stability Data

Adequate.

Below are the representative stability data for the 2 mL and 5 mL vials. The data are acceptable to support the new manufacturing site at (b) (4)

Table 2 Stability Data Batch AB9061A, 2 mL, 25°C/60%RH

Product Name/Strength:	Sugammadex Soln Inj 100mg/mL	Study Number:	MERCK-P-2013-165	Date Manufactured:	11 Dec 2013
Batch Number:	AB9061A	Storage Conditions:	(b) (4)	Date Packaged:	16 Dec 2013
Batch Size:	Not specified	Purpose of Study:	Process Validation	Date Study Started:	24 Jan 2014
Manufacturer/Packager	(b) (4)	Container/Supplier:	2mL Vial (b) (4) (b) (4)	Drug Substance Manufacturer/Batch:	N.V. Organon AB6066
Proposed Expiration Date	Not specified	Closure/Supplier:	Stopper (b) (4) (b) (4)		

Test	Initial	3 Month	6 Month
Appearance	Conforms	Conforms	Conforms
Clarity	Clear	Clear	Clear
Osmolality (mOsm/kg)	(b) (4)		
pH			
Extractable Volume (mL/vial)			
Color			
Visual Particulate Matter			
Assay of Org 25969+Org 48302 (mg/mL)			
Org 25969 + Org 48302			
Org 25969			
Org 48302			
Degradates of Org 25969 + Org 48302 (%)			
(b) (4)			

Table 2 (cont'd) Stability Data Batch AB9061A, 2 mL, 25°C/60%RH

Test	Initial	3 Month	6 Month
Org (b) (4)			(b) (4)
Org			
(b) (4)			
Each Individual Unspecified			
Total Degradation Products			
Particulate Matter			
(b) (4) m:			
m:			
Bacterial Endotoxins Test (endotoxin units per mL)			
Sterility			
Container Closure Integrity (b) (4) per vial)			

NT = Not Tested

Table 3 Stability Data Batch AB9061A, 2 mL, 40°C/75%RH

Product Name/Strength:	Sugammadex Soln Inj 100mg/mL	Study Number:	MERCK-P-2013-165	Date Manufactured:	11 Dec 2013
Batch Number:	AB9061A	Storage Conditions:	(b) (4)	Date Packaged:	16 Dec 2013
Batch Size:	Not specified	Purpose of Study:	Process Validation	Date Study Started:	24 Jan 2014
Manufacturer/Packager	(b) (4)	Container/Supplier:	2mL Vial (b) (4) (b) (4)	Drug Substance Manufacturer/Batch:	N.V. Organon AB6066
Proposed Expiration Date	Not specified	Closure/Supplier:	Stopper (b) (4) (b) (4)		

Test	Initial	3 Month	6 Month
Appearance	Conforms	Conforms	Conforms
Clarity	Clear	Clear	Clear
Osmolality (mOsm/kg)			(b) (4)
pH			
Extractable Volume (mL/vial)			
Color			
Visual Particulate Matter			
Assay of Org 25969+Org 48302 (mg/mL)			
Org 25969 + Org 48302			
Org 25969			
Org 48302			
Degradates of Org 25969 + Org 48302 (%)			
Org (b) (4)			
Org			
Org			

Table 3 (cont'd) Stability Data Batch AB9061A, 2 mL, 40°C/75%RH

Test	Initial	3 Month	6 Month
Org (b) (4)			(b) (4)
Org			
(b) (4)			
Each Individual Unspecified			
Total Degradation Products			
Particulate Matter			
(b) (4) m:			
m:			
Bacterial Endotoxins Test (endotoxin units per mL)			
Sterility			
Container Closure Integrity (b) (4) per vial)			

NT = Not Tested

Table 6 Stability Data Batch AC0758A, 5 mL, 25°C/60%RH

Product Name/Strength:	Sugammadex Soln Inj 100mg/mL	Study Number:	MERCK-P-2013-175	Date Manufactured:	26 Jan 2014
Batch Number:	AC0758A	Storage Conditions:	(b) (4)	Date Packaged:	27 Jan 2014
Batch Size:	Not specified	Purpose of Study:	Process Validation	Date Study Started:	03 Feb 2014
Manufacturer/Packager	(b) (4)	Container/Supplier:	6mL Vial (b) (4)	Drug Substance Manufacturer/Batch:	N.V. Organon AB6067
Proposed Expiration Date	Not specified	Closure/Supplier:	Stopper (b) (4) (b) (4)		

Test	Initial	3 Month	6 Month
Appearance	Conforms	Conforms	Conforms
Clarity	Clear	Clear	Clear
Osmolality (mOsm/kg)			(b) (4)
pH			
Extractable Volume (mL/vial)			
Color			
Visual Particulate Matter			
Assay of Org 25969+Org 48302 (mg/mL)			
Org 25969 + Org 48302			
Org 25969			
Org 48302			
Degradates of Org 25969 + Org 48302 (%)			
Org (b) (4)			
Org			
Org			

Table 6 (cont'd) Stability Data Batch AC0758A, 5 mL, 25°C/60%RH

Test	Initial	3 Month	6 Month
Org (b) (4)			(b) (4)
Org			
(b) (4)			
Each Individual Unspecified			
Total Degradation Products			
Particulate Matter			
(b) (4) m:			
m:			
Bacterial Endotoxins Test (endotoxin units per mL)			
Sterility			
Container Closure Integrity (b) (4) per vial)			

NT= Not Tested

Table 7 Stability Data Batch AC0758A, 5 mL, 40°C/75%RH

Product Name/Strength:	Sugammadex Soln Inj 100mg/mL	Study Number:	MERCK-P-2013-175	Date Manufactured:	26 Jan 2014
Batch Number:	AC0758A	Storage Conditions:	(b) (4)	Date Packaged:	27 Jan 2014
Batch Size:	Not specified	Purpose of Study:	Process Validation	Date Study Started:	03 Feb 2014
Manufacturer/Packager	(b) (4)	Container/Supplier:	6mL Vial (b) (4)	Drug Substance Manufacturer/Batch:	N.V. Organon AB6067
			Stopper (b) (4)		
Proposed Expiration Date	Not specified	Closure/Supplier:	(b) (4)		

Test	Initial	3 Month	6 Month
Appearance	Conforms	Conforms	Conforms
Clarity	Clear	Clear	Clear
Osmolality (mOsm/kg)	(b) (4)		
pH			
Extractable Volume (mL/vial)			
Color			
Visual Particulate Matter			
Assay of Org 25969+Org 48302 (mg/mL)			
Org 25969 + Org 48302			
Org 25969			
Org 48302			
Degradates of Org 25969 + Org 48302 (%)			
Org (b) (4)			
Org			
Org			

Table 7 (cont'd) Stability Data Batch AC0758A, 5 mL, 40°C/75%RH

Test	Initial	3 Month	6 Month
Org (b) (4)	(b) (4)		
Org			
(b) (4)			
Each Individual Unspecified			
Total Degradation Products			
Particulate Matter			
(b) (4) µm:			
µm:			
Bacterial Endotoxins Test (endotoxin units per mL)			
Sterility			
Container Closure Integrity (b) (4) per vial)			

NT= Not Tested

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

Adequate.

The CMC labeling issues raised during the last review cycle include the following:

1. The current USP policy is to name and designate the strength of drug products according to the neutral, active moiety unless the salt ion contributes substantively to the desired ADME profile. The product name and strength should be [TRADENAME] (sugammadex) Injection, 100 mg/mL (b) (4) .

2. The labeled strength (100 mg/mL) of the product is based on the combined concentration of the free acids of Org 25969 (sugammadex sodium) and Org 48302 (sodium salt). Since the assay accounts for both Org 25969 and Org 48302, the nonproprietary name should reflect the inclusion of Org 48302.
3. When possible, the information about the salt should be included on the side panel. For example, "Each mL contains 100 mg sugammadex, equivalent to 108.8 mg sugammadex sodium."

A teleconference was held on June 11, 2014 between Merck and the CMC review team and the following agreements were reached:

- Merck agreed to label the product as sugammadex injection.
- The information on the mono-OH derivative of sugammadex (Org 48302) will be provided in the "Description" section of the package insert. The USAN (b) (4) does not need to include Org48302.

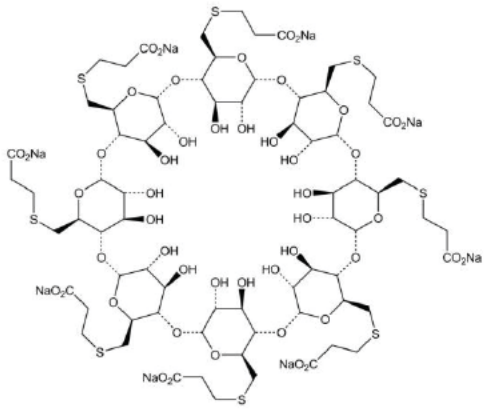
In the updated package insert submitted in this resubmission, the applicant has fulfilled the agreements:

- The product name is updated to [TRADENAME] (sugammadex) Injection.
- The "Description" section has included the information about (b) (4) Org48302 as follows.

11 DESCRIPTION

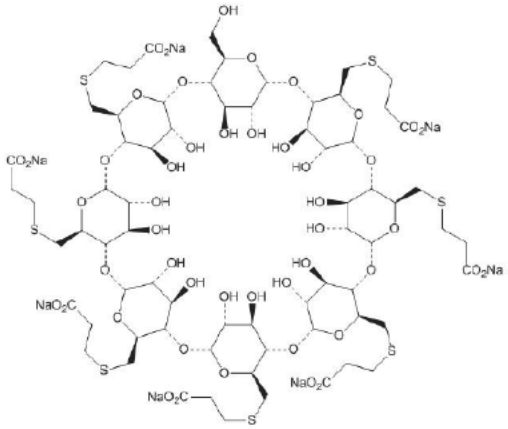
(b) (4)

[TRADENAME] contains sugammadex sodium, a modified gamma cyclodextrin chemically designated as *$6^A,6^B,6^C,6^D,6^E,6^F,6^G,6^H$-Octakis-S-(2-carboxyethyl)-$6^A,6^B,6^C,6^D,6^E,6^F,6^G,6^H$-octathio-γ-cyclodextrin sodium salt (1:8)* with a molecular weight of 2178.01.**[120]** The structural formula is:**[121]**



[TRADENAME] is supplied as a sterile, non-pyrogenic aqueous solution that is clear, colorless to slightly yellow for intravenous injection only. Each mL contains 100 mg sugammadex, which is equivalent to 108.8 mg sugammadex sodium. The aqueous solution is adjusted to a pH of between 7 and 8 with hydrochloric acid and/or sodium hydroxide. The osmolality of the product is between 300 and 500 mOsmol/kg.**[122]**

[TRADENAME] may contain up to 7 mg/mL of the mono OH-derivative of sugammadex**[123]** *[see Clinical Pharmacology (12.2)].* This derivative is chemically designated as *$6^A,6^B,6^C,6^D,6^E,6^F,6^G$-Heptakis-S-(2-carboxyethyl)-$6^A,6^B,6^C,6^D,6^E,6^F,6^G$-heptathio-γ-cyclodextrin sodium salt (1:7)* with a molecular weight of 2067.90. The structural formula is:**[124]**



On the carton labels, the applicant has included the following information:

- Each mL contains 100 mg sugammadex, (b) (4) equivalent to 108.8 mg sugammadex sodium.

Chemistry Assessment Section

Signature Page

Reviewed by: Yong Hu, Ph.D., Office of Pharmaceutical Quality

Yong Hu -S

Digitally signed by Yong Hu -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yong Hu -S, 0.9.2342.19200300.100.1.1=2000336960
Date: 2015.03.24 16:05:29 -04'00'

Concurred by: Julia Pinto, Ph.D., Branch Chief, Office of Pharmaceutical Quality

Julia C. Pinto -A

Digitally signed by Julia C. Pinto -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Julia C. Pinto -A, 0.9.2342.19200300.100.1.1=1300366849
Date: 2015.03.24 16:12:48 -04'00'

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: August 28, 2013

FROM: Yong Hu, Ph.D.

SUBJECT: Addendum to Chemistry Review #3 of NDA 22225 for (b) (4) (sugammadex) Injection
Applicant: Organon USA

TO: NDA 22225 file

This is a follow up to Chemistry Review #3 for the purposes of indicating the Office of Compliance's recommendation in the Establishments Evaluation System (EES) and summarizing the CMC labeling issues.

EES Recommendation:
The Office of Compliance's overall recommendation, made on 27-Aug-2013 in EES, is "Acceptable" for this NDA. See the attachment.

CMC Labeling Issues:
The following comments regarding the carton and container labels were sent to applicant on 15 Aug 2013 and the applicant has not provided a response so far.

1. Label the product name and strength based on the active moiety. The product name and strength should be [TRADENAME] (sugammadex) Injection, 100 mg/mL instead of (b) (4)
2. When possible, the information about the salt should be included on the side panel. For example, "Each mL contains 100 mg sugammadex, equivalent to 108.8 mg sugammadex sodium."

In addition, as recommended in my labeling review in the CMC Review #3, the "Description" section of the Prescriber's Information (PI) should include information about the compound Org 48302, (b) (4), in addition to the information about the principle compound Org 25969 (sugammadex sodium). The rationale is the following:

- The applicant lists both compounds as the active ingredients in the NDA and states that Org 48302 has an activity and pharmacological profile comparable to that of Org 25969. This statement is concurred by the Pharmacology/Toxicology reviewer, Dr. Zengjun (Alex) Xu.

- The phase 1, 2, and 3 clinical trial product batches (CY039, CZ180, and CA 050) contained (b) (4) mg/mL Org 48302.
- The drug product specification sets the acceptance criterion for the assay to be (b) (4) mg/mL (i.e. target 100 mg/mL), based on the sum of Org 25969 and Org 48302 (as the free acids). Therefore the claimed product strength of 100 mg/mL accounts for the content of Org 48302 as well.
- Drug product batch formula targets the product strength of 100 mg/mL based on the combined content of Org 25969 and Org 48302 (as the free acids).

Furthermore, an additional labeling issue came in light during the recent CMC team discussions. (b) (4) It is not appropriate to label the product as sugammadex injection since the USAN entry for sugammadex sodium does not include information about the compound Org 48302.

The CMC team held a teleconference with the applicant on 27 Aug 2013 to communicate about the above labeling issues. The following written comments were also sent to the applicant on the same day.

During the labeling review for NDA 22225, we have identified the following issues that need to be addressed to label your product and be consistent with our current Agency policies. At this time, we do not have recommendations on how to proceed; rather we are alerting you to these issues so that you can propose solutions:

1. *The current USP policy is to name and designate the strength of drug products according to the neutral, active moiety unless the salt ion contributes substantively to the desired ADME profile. In those cases where the salt form contributes to the desired ADME profile, the salt form may be used in the name provided the strength designation matches the salt form.* (b) (4) (b) (4)
2. *The labeled strength (100 mg/mL) of your product is based on the combined concentration of the free acids of Org 25969 (sugammadex sodium) and Org 48302 (sodium salt). Since the assay accounts for both Org 25969 and Org 48302, the nonproprietary name should reflect the inclusion of Org 48302.*
3. (b) (4)
4. *Please update or revise the code names to reflect the correct status of the molecule (neutral species or sodium salt and designate strength accordingly) and current ownership of the application (e.g., Org 25969 to Mrk 25969).*

Recommendation: The NDA is recommended for approval after the labeling issues are resolved.

Attachment

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 22225/000	**Sponsor:**	(b) (4) [redacted]
Org. Code:	170		
Priority:	1P		
Stamp Date:	31-OCT-2007	**Brand Name:**	
PDUFA Date:	20-SEP-2013	**Estab. Name:**	
Action Goal:		**Generic Name:**	SUGAMMADEX SODIUM INJECTION
District Goal:	22-JUL-2013	**Product Number; Dosage Form; Ingredient; Strengths**	001; SOLUTION, INJECTION; SUGAMMADEX SODIUM; 100MG

FDA Contacts:	Y. HU	Prod Qual Reviewer		3017965031
	S. DONALD	Micro Reviewer	(HFD-805)	3017960586
	L. RIVERA	Product Quality PM		3017964013
	D. WALKER	Regulatory Project Mgr	(HFD-170)	3017964029
	D. CHRISTODOULOU	Team Leader		3017961342

Overall Recommendation:	ACCEPTABLE	on 27-AUG-2013	by J. WILLIAMS	()	3017964196
	PENDING	on 16-AUG-2013	by EES_PROD		
	PENDING	on 16-AUG-2013	by EES_PROD		
	PENDING	on 16-AUG-2013	by EES_PROD		
	PENDING	on 08-AUG-2013	by EES_PROD		
	PENDING	on 08-AUG-2013	by EES_PROD		
	PENDING	on 08-AUG-2013	by EES_PROD		
	PENDING	on 03-JAN-2013	by EES_PROD		
	PENDING	on 02-JAN-2013	by EES_PROD		
	PENDING	on 02-JAN-2013	by EES_PROD		
	ACCEPTABLE	on 24-JUL-2008	by ADAMSS		

Establishment:	**CFN:** 1036761 **FEI:** 1036761 MERCK SHARP & DOHME, WILSON FACILITY WILSON, , UNITED STATES 278939613		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE LABELER		
Profile:	(b) (4) [redacted]	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	21-AUG-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	**CFN:** 9610343 **FEI:** 3002806821		
	NV ORGANON KLOOSTERSTRAAT 6 / VEERSEMEER 4		
	OSS, NOORD-BRABANT, NETHERLANDS		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
	DRUG SUBSTANCE RELEASE TESTER		
	DRUG SUBSTANCE STABILITY TESTER		
	FINISHED DOSAGE RELEASE TESTER		
	FINISHED DOSAGE STABILITY TESTER		
Profile:	NON-STERILE API BY CHEMICAL SYNTHESIS	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	27-AUG-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	**CFN:** 9612716 **FEI:** 3002807818		
	ORGANON IRELAND LTD		
	SWORDS, CO. DUBLIN, , IRELAND		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE MANUFACTURER		
	FINISHED DOSAGE PACKAGER		
	FINISHED DOSAGE RELEASE TESTER		
	FINISHED DOSAGE STABILITY TESTER		
Profile:	(b) (4)	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	21-AUG-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

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

/s/

YONG HU
08/28/2013

PRASAD PERI
08/28/2013
I concur

NDA 22225

[redacted] (sugammadex) Injection

Organon USA Inc.

Yong Hu, Ph.D.

Office of New Drug Quality Assessment

For

Division of Anesthesia, Analgesia, and Addiction Products

Table of Contents

Chemistry Review Data Sheet

1. NDA: 22225

2. REVIEW #: 3

3. REVIEW DATE: 6-Aug-2013

4. REVIEWER: Yong Hu, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original NDA	30-Oct-2007
CMC Review #1	30-Jan-2008
CMC Review #2	12-Jun-2008
Memorandum to CMC Review #2	24-July-2008
Product Quality Microbiology Review #1	20-Feb-2008
FDA Not Approvable Letter	31-Jul-2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Complete Response	20-Dec-2012
Response to CMC Information Request	22-Feb-2013
Withdrawal of Compatibility Protocol	08-May-2013
Response to CMC Information request	27-Jun-2013
Response to CMC Information request	15-July-2013

7. NAME & ADDRESS OF APPLICANT:

Name:	Organon USA Inc.
Address:	One Merck Drive, P.O.Box 100, Whitehouse Station, NJ 08889
Representative:	Dori L. Glassner

Telephone: 732-594-2735

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Bridion (b) (4) (pending FDA review)
b) Non-Proprietary Name (USAN): Sugammadex Sodium
c) Code Name/# (ONDC only): Org 25969 and Org 48302
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:

505 B(1)

10. PHARMACOL. CATEGORY:

The Pharmacological Class is pending Pharmacology/Toxicology review. The compound serves as a reversal agent for neuromuscular blocking agents.

11. DOSAGE FORM:

Injection

12. STRENGTH/POTENCY:

100 mg/mL (expressed as sugammadex – the active entity or free acid)

13. ROUTE OF ADMINISTRATION:

Intravenous (single bolus injection)

14. Rx/OTC DISPENSED: __x_ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___x___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

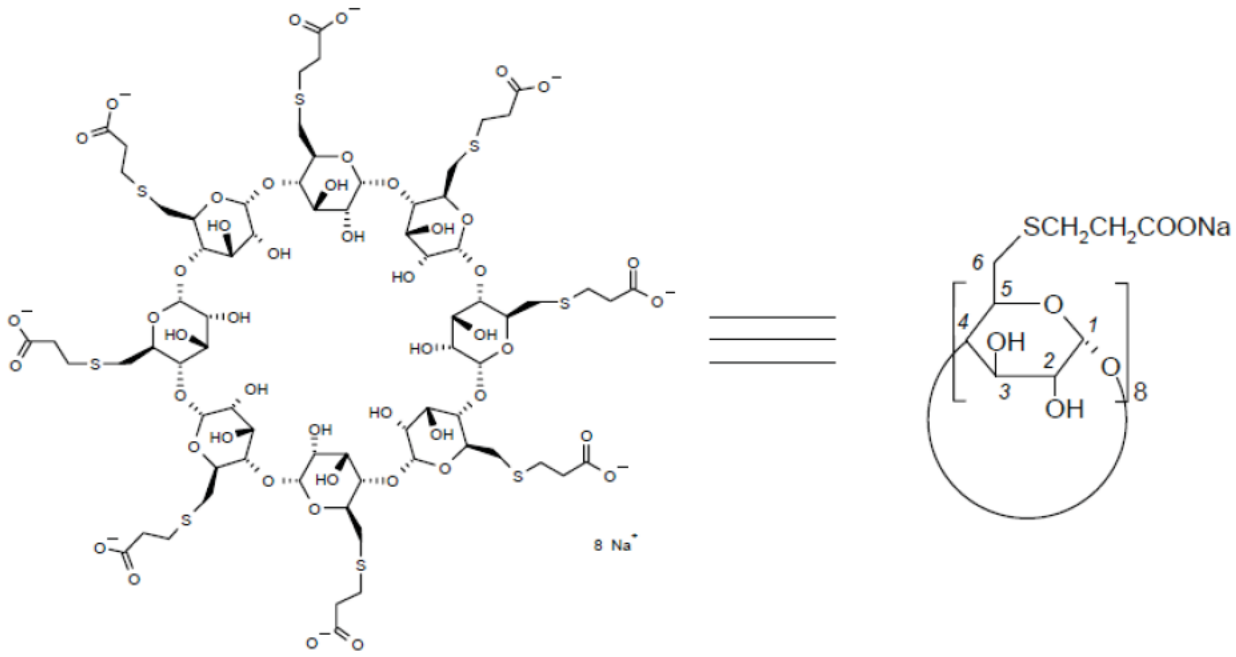
Org 25969 – Sugammadex Sodium:

Chemical name: 6^A, 6^B, 6^C, 6^D, 6^E, 6^F, 6^G, 6^H –octakis-S-(2-carboxyethyl) -6^A, 6^B, 6^C, 6^D, 6^E, 6^F, 6^G, 6^H – octathio-γ-cyclodextrin octasodium salt (CA Index name) or octakis(6-S-(2-carboxyethyl)-6-thio)cyclomaltooctaose octasodium salt (IUPAC)

Molecular formula: $C_{72}H_{104}O_{48}S_8Na_8$

Molecular weight: 2178.01

Structural formula:



The drug substance may contain a low percentage (typically (b) (4)% w/w) of a related compound Org 48302, which is claimed to have activity and pharmacological profiles similar to Org 25969.

Chemical name: (b) (4)

Molecular formula: (b) (4)

Molecular weight: 2067.90

Structural formula:

(b) (4)

[redacted]

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	4	N/A		(b) (4) met USP requirements per information in NDA. See Addendum to CMC Review #2
	III			3	Adequate	5/13/2011 (Reviewed by Jesse Wells)	Also see Addendum to CMC Review #2
	III			3	Adequate	6/18/2009 (Reviewed by Zedong Dong)	

[1] Action codes for DMF Table:

1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	68029	Org 25969 Injection

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not requested in this review cycle.		
EES	Pending.		
Pharm/Tox	The tightened impurity specifications for the DS and DP are acceptable as Pharm/Tox did not have concerns with the original wider specifications during the last review cycle.	Email communications	Zengjun (Alex) Xu
Biopharm	N.A.		
LNC	N.A.		
Methods Validation	Not requested in this review cycle. No method changes.		
OPDRA	N.A.		
EA	Adequate per CMC Review #2		Alan Schroeder
Microbiology	Approval	5/10/13	Steve Donald

The Chemistry Review for NDA 22225

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is recommended for approval pending overall "Acceptable" recommendation in EES from the Office of Compliance and satisfactory labeling revision by the applicant.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

The applicant has fulfilled the following agreements in this resubmission.

- An agreement to revisit the impurity specifications for the drug substance once the applicant has manufactured drug substance at full scale using at least 10 different production lots of the (b) (4)
- An agreement to revisit the specifications for degradants in the drug product following additional experience with the commercial manufacturing process.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance (Org 25969 or sugammadex sodium), an octasodium salt, is a modified γ-cyclodextrin and its mode of action is based on the formation of 1:1 inclusion complexes with rocuronium or vecuronium. The drug substance contains a related compound (b) (4) Org 48302, which the applicant claims to have an activity and pharmacological profile comparable to that of Org 25969, and therefore it is treated as an active entity. Org 48302 is typically present at (b) (4) (b) (4) in the representative drug substance batches. The CMC team had some internal discussions on whether the two identified active entities would make the product a combination drug product. Since the two compounds have comparable activities and pharmacological profiles, as concurred by the Pharmacology/Toxicology reviewer, Dr. Zengjun (Alex) Xu, the drug product does not fall into the combination drug product category. The drug product is formulated as an injection solution and therefore, solid state properties of the drug substance such as polymorphism and particle size distribution are not critical for the drug product. The drug substance is highly soluble in water; it is highly hygroscopic and its hygroscopicity is managed by controlling manufacturing and storage conditions. The drug substance (b) (4)

[redacted] have been extensively investigated, characterized/identified and controlled. The drug substance is manufactured by N.V.Organnon at Oss, The Netherlands.

The drug product is a sterile parenteral solution for intravenous administration. It is prepared by [redacted] adjusting the pH to 7.5 with sodium hydroxide or hydrochloric acid, [redacted] 2 mL and 5 mL vials, [redacted] The strength is 100 mg/mL (expressed as the free acids of Org 25969 and Org 48302). The level of Org 48302 is typically below 7 mg/mL in the product. The container closure system is type I glass vials with a [redacted] rubber closure and an aluminum flip off cap.

The drug product is intended for reversal of neuromuscular block by rocuronium or vecuronium, through the formation of complexes between the cyclodextrin drug and the neuromuscular blocking agents.

All 100 mg/mL clinical preparations are considered representative for the market formulation. Batches identified as pivotal clinical batches are indicated to be manufactured by a process and at a scale comparable to the primary stability batches. Critical process steps for the manufacture of the drug product include the following: [redacted] In stability studies, the only trending parameters are as follows: [redacted] The drug product is sensitive to light [redacted] and the applicant proposes that the [redacted] container be exposed to light no longer than for 5 days. [redacted] . Photostability data support the 5 day maximum limit on exposure to normal indoor lighting. [redacted] The drug product will be manufactured by Organon (Ireland) Limited at Swords, Ireland.

B. Description of How the Drug Product is Intended to be Used

The proposed indications are routine reversal of shallow or profound neuromuscular blockade induced by rocuronium or vecuronium, and immediate reversal of neuromuscular blockade at 3 minutes after administration of rocuronium. The recommended doses are 2 mg/kg or 4 mg/kg for routine reversal, and 16 mg/kg for immediate reversal. The injection is to be given as a single bolus dose intravenously. The drug product solution (100 mg/mL expressed as the free acids of Org 25969 and Org 48302), is filled in colorless, [redacted] (2 mL per vial) or [redacted] (5 mL per vial) vials of [redacted] glass, type I, and closed with gray [redacted] rubber closures. The rubber closures are held in position on the glass vials by aluminium crimp-caps with a "flip-off" seal.

A shelf life of 36 months at 25°C is acceptable for the drug product. The supporting stability data include 36 months data of the three primary stability batches manufactured at Oss, The Netherlands and one primary stability batch (pilot scale) manufactured at Swords, Ireland for each presentation, and 36 months data of three production-scale batches manufactured at Swords, Ireland for each presentation.

The storage statement in the "How Supplied" section of the draft labeling is the following. " Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) (see USP Controlled Room

Temperature). [redacted] (b) (4) protect from light. When not protected from light, the vial should be used within 5 days."

C. Basis for Approvability or Not-Approval Recommendation

The CMC recommendation during the last review cycle was "Approval".

In this resubmission, the applicant has fulfilled the agreements to revisit the impurity and degradant specifications for the drug substance and drug product. Some of the specifications have been tightened as a result of the analysis of more batch data.

The applicant has not made significant changes in the manufacturing and controls of the drug substance and drug product. The applicant has provided additional stability data to support the proposed re-test period for the drug substance and the shelf life for the drug product.

[redacted] (b) (4)

The New Drug Microbiology Staff reviewer has recommended approval of this NDA.

III. Administrative

A. Reviewer's Signature

See DARRTS.

B. Endorsement Block

See DARRTS.

C. CC Block

See DARRTS.

Chemistry Assessment

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data

S DRUG SUBSTANCE [Name, Manufacturer]

The previous CMC reviewer considered the drug substance information in the original NDA adequate to support the NDA approval. In the resubmission, the applicant made some changes and updates to the drug substance information. This review pertains to the changes and updates only.

S.2 Manufacture [name, manufacturer]

S.2.1 Manufacturers

Adequate.

The applicant has updated the Table 1 below.

Table 1: Names of manufacturers, including addresses and responsibilities

Manufacturer	Manufacturing site	Responsibility
N.V. Organon[1]	Oss, the Netherlands Street addresses[2]: - Kloosterstraat 6, 5349 AB Oss - Veersemeer 4, 5347 JN Oss	API manufacture, Release testing, Stability testing

[1] FEI number: 3002806821

[2] Both manufacturing site addresses are consolidated by agreement with FDA

The facilities at Kloosterstraat 6, Oss, The Netherlands and Veersemeer 4, Oss, The Netherlands are consolidated under one establishment name – N.V. Organon. The establishment information for N.V. Organon in the FDA's EES system reflects the two addresses. The recommendation from the Office of Compliance for this establishment is "Acceptable" with a recommendation date of 2/1/2013.

The applicant has removed Organon Development GmbH (in Waltrop, Germany) as stability testing site. The applicant states that "For commercial drug substance production this site is not needed as stability testing site."

S.2.2 Description of Manufacturing Process and Process Controls

Adequate.

The applicant [redacted] (b) (4)
The applicant states that [redacted] (b) (4)
of the reaction temperature range, it is acceptable.

A minor rewording in the reprocessing section has been implemented: [redacted] (b) (4)

S.2.3 Control of Materials

Adequate.

For the reagent [redacted] (b) (4) which is used in manufacturing step B, the following acceptance criteria have been tightened. The original acceptance criteria were acceptable according to the previous CMC reviews. The tightened acceptance criteria are thus acceptable as well.

Test	Acceptance criterion	
	Original NDA	NDA resubmission
Purity	[redacted] (b) (4)	
[redacted] (b) (4)		
[redacted] (b) (4)		
Total organic impurities		

The updated specification for [redacted] (b) (4) is reproduced below.

Table 3: Specification for [redacted]

Test	Method principle	Acceptance criterion
[redacted]	*Step b*	
Description		
Appearance	Visual	Liquid
Color	Visual	Colorless to light yellow
Clarity	Visual	Clear
Identification		
IR-spectrum	Ph. Eur , USP, JP [11]	Identical with reference spectrum
Assay		
Purity	HPLC [12]	[redacted]
Impurities		
Organic impurities:		
[redacted]	HPLC [12]	
[redacted]	HPLC [12]	
	HPLC [12]	
	HPLC [12]	
	HPLC [12]	
	HPLC [12]	
Unspecified organic impurity (each)	HPLC [12]	
Total of organic impurities	HPLC[12]	

S.2.4 Controls of Critical Steps and Intermediates

Adequate.

The [redacted] see Table 2.2.1 below). Since the temperature range is now [redacted] than previously proposed range, which the previous CMC reviewer concurred during the last review cycle, the change is acceptable.

2.2.1 Critical parameters

Parameter	Acceptable Operating Range
Dosage temperature of sodium hydroxide solution	[redacted]
Dosage time of sodium hydroxide solution	
Reaction temperature	

Real-time stability study results for the [redacted] have been added in order to support extension of the re-test period from [redacted] months. An amount of [redacted], obtained from a regular production, was stored at [redacted] The stability results are presented in Table 16 below. No trend of stability change is observed from [redacted] months and all data are within the [redacted] specification, previously accepted by the former CMC reviewer. This reviewer considers the newly proposed re-test period [redacted] months at a storage temperature of [redacted] °C) justified.

Table 16: HPLC results of stability study of (b) (4)

Time interval	(b) (4) (% m/m)	Total organic impurities (% a/a)	Assay on water, DMF and ethanol free substance (% m/m)
(b) (4)			

S.3 Characterization [name, manufacturer]

S.3.2 Impurities

Adequate.

The sponsor identified the second compound of the (b) (4) in peak RRT (b) (4) as (b) (4) The structure is presented below. The compound was not identified in the original NDA.

(b) (4)

Figure 15: Structural formula o (b) (4)

(b) (4)

Figure 17: Structural formula of (b) (4)

S.4 Control of Drug Substance [name, manufacturer]

S.4.1 Specification

Adequate.

The former CMC reviewer considered the drug substance specification adequate and recommended approval of the original NDA. The applicant made the following commitment during the last review cycle: Organon agrees to revisit the proposed impurity specifications following additional experience with the manufacture of the drug substance. Organon considered it important to have manufactured drug substance at full scale after having used at least 10 different production lots of the reagent (b) (4) Therefore, Organon proposed to revisit the impurity specifications once this data is available.

In the resubmission, the applicant has addressed the commitment using the data from the drug substance batches manufactured with ten different (b) (4) batches and the data from the completed stability studies.

The following acceptance criteria have been tightened. The new acceptance criteria are acceptable. See justification under 3.2.S.4.5.

Test	Original NDA	NDA resubmission
Org 25969	(b) (4)	(b) (4)
Total impurities		

As a result, the specification has been updated as follows to reflect the tightened impurity acceptance criteria.

1 SPECIFICATION

Test	Method principle	Acceptance criterion
Description		
Appearance	Visual	(b) (4)
Color	Visual	
Visible impurities	Visual	
Identification		
IR-spectrum	Ph.Eur., USP, JP [1]	Identical
Chromatogram (Org 25969)	HPLC [2]	Identical
Chromatogram (Org 48302)[1]	HPLC [2]	Identical
Sodium	ICP - AES [3]	Identical
Assay		
(b) (4)	HPLC [2]	(b) (4)
	HPLC [2]	
	HPLC [2]	
	ICP-AES [3]	
Impurities		
Organic impurities: Specified identified: (b) (4)	HPLC [2] HPLC [2] HPLC [2] HPLC [2] HPLC [2] HPLC [2] HPLC [2] HPLC [2] HPLC [2] HPLC [2]	
Specified unidentified: (b) (4)	HPLC [2] HPLC [2] HPLC [2] HPLC [2]	

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Table 42: Batch release data (b) (4)

(b) (4)

(b) (4)

(b) (4)

S.4.5 Justification of Specification

Adequate.

It should be noted that both CMC and Pharmacology/Toxicology accepted the impurities acceptance criteria in the original NDA during the last review cycle. In the resubmission, the applicant tightened the acceptance criteria for the impurities. Therefore, the changes ensure better quality and safety of the drug substance.

The applicant used the analytical data from batches AE to L00034435 to justify the tightening of the acceptance criteria as these batches were manufactured using the representative or identical commercial processes and equipment. The batches AE, AF, AG, and L00027721 were the primary stability batches manufactured at pilot scales and the batches AM, AN, and AQ were the stability batches manufactured at the production scale. The batch release data from the other production scale batches L00027960, L00027961, L00027962, L00029507, L00029508, L00029320, L00029510, L00029511, L00029512, L00029513, L00030939, L00031137,

L00031138, L00031139, L00034344, L00034434, and L00034435 were also used in the justification.

The following information justifies the proposed tightening of the acceptance criteria in the specification.

Assay of Org 48302:

The proposed acceptance criterion for Org 48302 content has been revised from (b) (4)% to (b) (4) m/m. The upper acceptance limit of (b) (4) is justified on the basis of the statistical evaluation of the batch data (mean plus 3 times standard deviation from batch AE onwards is (b) (4). The stability data show that the Org 48302 content is stable upon storage at the proposed storage condition. All representative batches AE – L00034435 comply with the acceptance criterion (see Figure 4).

Figure 4: Release values for Org 48302 content (bold line indicates the acceptance criterion)

Assay of Org 25969:

The proposed acceptance criterion for Org 25969 content has been revised from (b) (4) to (b) (4) m/m. The lower limit is obtained by the subtraction of the upper limit of the Org 48302 content (b) (4) m/m) from the lower limit of the sum of the contents of Org 25969 and Org 48302 (b) (4) m/m). The upper limit of (b) (4) (b) (4). The results of the 26 representative batches (AE – L00034435) showed Org 25969 assay values in the range of (b) (4) well within the range of the proposed acceptance limits (see Figure 5).

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All the additional stability data were within the acceptance criteria in the proposed specification and support the proposed retest period of (b) (4) months.

S.7.2 Postapproval Stability Protocol and Stability Commitment

Adequate.

The applicant states that "The stability studies with the 3 primary stability batches (AE, AF and AG), the 3 production scale batches (AM, AN and AQ) and the site specific stability batch (L00027721) of Org 25969 have been completed. The corresponding stability reports, which include stability data up to and including the proposed re-test period of (b) (4) months, have been included in the registration file. Therefore no post approval stability commitment for Org 25969 has to be made."

In accordance with the ICH Q1A, "Where the submission includes long term stability data on three production batches covering the proposed re-test period, a post approval commitment is considered unnecessary."

P DRUG PRODUCT [Name, Dosage form]

The previous CMC reviewer considered the drug product information in the original NDA adequate to support the NDA approval. In the resubmission, the applicant made some changes and updates to the drug product information. This review pertains to the changes and updates only.

P.1 Description and Composition of the Drug Product [name, dosage form]

Adequate.

The product is an injection solution, 100 mg/mL, filled in colorless (b) (4) (2 mL per vial) or (b) (5 mL per vial) vials of (b) (4) glass, type I, and closed with gray (b) (4) rubber closures (b) (4) of diameter 13 mm for the (b) (4) and 20 mm for the (b) (4) vials. The rubber closures are held in position on the glass vials by aluminium crimp-caps with a "flip-off" seal.

In the resubmission, the applicant removed the references to the (b) (4) This is acceptable as, for the US market, the excipients of the drug product do not have to be in compliance with (b) (4)

The compositions of the drug product are shown below. It should be noted that the strength is expressed as the total concentration (100 mg/mL) of the free acids of Org 25969 and Org 48302. This has been verified by the applicant in its response to a CMC information request (see 3.2.P. 3.2 Batch Formula).

Table 1: Complete composition Org 25969 solution for injection 100 mg/mL (2 mL per vial)

Component	Reference to quality standard	Function(s)	Quantity per vial (2.0 mL[1])	Quantity per mL
Org 25969 + Org 48302[2]	In-house standard	Drug substance	200 mg	100 mg
Sodium hydroxide[3]	Ph. Eur., NF	pH adjuster	q.s. to pH 7.5	q.s. to pH 7.5
Hydrochloric acid[3]	Ph. Eur., NF	pH adjuster	q.s. to pH 7.5	q.s. to pH 7.5
(b) (4)	Ph. Eur., USP	(b) (4)		(b) (4)
(b) (4)	Ph. Eur., NF			

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

(b) (4)

Table 2: Complete composition Org 25969 solution for injection 100 mg/mL (5 mL per vial)

Component	Reference to quality standard	Function(s)	Quantity per vial (5.0 mL[1])	Quantity per mL
Org 25969 + Org 48302[2]	In-house standard	Drug substance	500 mg	100 mg
Sodium hydroxide[3]	Ph. Eur., NF	pH adjuster	q.s. to pH 7.5	q.s. to pH 7.5
Hydrochloric acid[3]	Ph. Eur., NF	pH adjuster	q.s. to pH 7.5	q.s. to pH 7.5
(b) (4)	Ph. Eur., USP	(b) (4)		(b) (4)
(b) (4)	Ph. Eur., NF			

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

(b) (4)

P.3 Manufacture [name, dosage form]

P.3.1 Manufacturers

Evaluation pending.

The applicant has updated the Table 1 shown below.

Table 1: Names of manufacturers, including addresses and responsibilities

	Manufacturer	Manufacturing site	Responsibility
1	Organon (Ireland) Limited	Drynam Road, Swords, Co. Dublin, Ireland	Manufacturing Primary packaging Release testing Release of drug product Stability testing (excluding container closure integrity test)
2	N.V. Organon	Kloosterstraat 6, 5349 AB Oss, Netherlands	Release testing Stability testing
3	Merck Sharp & Dohme Corp.	4633 Merck Road Wilson, North Carolina NC 27893 USA	Labeling Secondary packaging Administrative release of drug product

The applicant removed Organon Development GmbH, Waltrop, Germany as the quality control site.

The labeling, secondary packaging and the administrative release of drug product will be conducted at Merck Sharp & Dohme in Wilson (USA).

The Office of Compliance has made an "Acceptable" recommendation for the Organon Ireland Ltd site (on 1/25/2013), but has not made a recommendation for the Merck site in EES.

P.3.2 Batch Formula

Adequate.

In this resubmission the applicant removed the references to the (b) (4) This is acceptable because for the US market the excipients of Org 25969 drug product do not have to be in compliance with (b) (4)

During the course of the review, the following information was requested to clarify whether the product strengths are expressed as the free acids or salts of the drug substance components and how the quantity of the drug substance is calculated for the batch manufcaturing.

FDA Comment #1: Your draft labeling states that (b) (4) The footnote 2 for Tables 1 and 2 in Module 3.2.P.1 and for Tables 1 and 2 in Module 3.2.P.3 states that (b) (4) Clarify whether the product strengths for all the clinical trial batches and commercial product are expressed as the free acids or the sodium salts of Org 25969 and Org 48302.

Applicant's Response #1: "It is confirmed that for all clinical trial batches and for all commercial product the content is expressed as the free acid and not as the sodium salt. In all these batches the strength of the sugammadex formulations is 100 mg/mL. This means that every mL solution contains 100 mg of sugammadex active entity (AE). In CTD section 3.2.P.1 and 3.2.P.3 it is mentioned how much sodium salt of sugammadex would technically need to be dissolved in order to obtain a formulation of 100 mg of sugammadex AE/mL (which would be 108.8 mg of the Org 25969 sodium salt (b) (4). Also in the proposed label for sugammadex (b) (4)

Evaluation: Adequate. The applicant confirmed that for all clinical trial batches and for all commercial product the content is expressed as the free acid and not as the sodium salt. The labeling statement is still not very clear. A comment will be sent when the team conducts labeling review.

FDA Comment #2: The executed batch record for the compounding batch 827868001 shows that a potency of (b) (4) for the drug substance was used in calculating the amount of the drug substance to be used. Clarify how the potency of the drug substance is determined. Revise the Batch Formula Tables 1 and 2 in Module 3.2.P.3 to show the determination of potency of the

drug substance and the use of potency in determining the amount of drug substance for each batch.

Applicant's Response #2: "The potency of sugammadex (i.e. Org 25969 + Org 48302) drug substance (DS) is mentioned on the Certificates of Analyses (CoAs) that go with the DS batches to be shipped to the drug product (DP) manufacturer. The potency is added to the CofAs of sugammadex DS so that the DP manufacturer can use this information for the calculation of the amount of sugammadex DS needed to prepare the formulation of 100 mg of sugammadex active entity (AE) per mL. The potency of sugammadex DS, which is mentioned as "content for processing" on the CofA is calculated with formula 1:

Formula 1

(b) (4)

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The applicant has revised the footnote 2 in the batch formula as follows:

Table 1. Batch formula for a (b) (4) batch Org 25969 Solution for Injection 100 mg/mL (2 mL per vial)

Component	Reference to quality standard	Quantity per vial	Quantity per batch
		(b) (4)	(b) (4)
Org 25969 + Org 48302	In-house standard		
Sodium hydroxide and/or Hydrochloric acid[3]	Ph. Eur., NF	q.s. to pH 7.5	q.s. to pH 7.5
(b) (4)	Ph. Eur., USP	(b) (4)	
	Ph. Eur., NF		

(b) (4)

Table 2. Batch formula for a (b) (4) batch of Org 25969 Solution for injection 100 mg/mL (5 mL per vial)

Component	Reference to quality standard	Quantity per vial	Quantity per batch
		(b) (4)	
Org 25969 + Org 48302	In-house standard		
Sodium hydroxide and/or Hydrochloric acid[3]	Ph. Eur., NF	q.s. to pH 7.5	q.s. to pH 7.5
(b) (4)	Ph. Eur., USP	(b) (4)	
	Ph. Eur., NF		

(b) (4)

P.3.3 Description of Manufacturing Process and Process Controls

Adequate.

Two minor changes have been made to the manufacturing process:

(b) (4)

The Microbiology review, dated 5/10/13, considers this change acceptable.

P.3.5 Process Validation and/or Evaluation

Adequate.

The following changes have been included to the sterilization process validation:

1. (b) (4)
2. The container closure integrity test has been re-validated.
3. The text in section 5 on (b) (4) has been removed and replaced with the text (b) (4)
4. The Floor plan in section 14.1 has been updated.

The Microbiology review, dated 5/10/13 determined that these changes/updates are not critical.

P.4 Control of Excipients [name, dosage form]

Adequate.

References to (b) (4) ave been removed as the excipients do not need to comply with (b) (4) or the product marketed in the US.

P.5 Control of Drug Product [name, dosage form]

P.5.1 Specification(s)

Adequate.

The following limits for the impurities have been tightened. This is to fulfill the applicant's commitment to "revisit the specifications for degradants in the drug product following additional experience with the commercial manufacturing process."

The new acceptance criteria are acceptable. See justification under 3.2.P.5.6.

Test	Acceptance criterion	
	Original NDA	NDA resubmission
		(b) (4)

The revised drug product specification is reproduced below.

Test	Method principle	Acceptance criterion	
		Shelf life[1]	Release
Description			
Appearance	Visual	Aqueous liquid	
Color	Ph. Eur. (+VIS) [1]	(b) (4)	
Identification			
Active ingredient identical with standard	HPLC[2]		
Active ingredient identical with reference spectrum (UV-DAD)	HPLC[2]		
Assay			
(b) (4)	HPLC[2]		
	HPLC[2]		
	HPLC[2]		
Impurities			
Degradation products[3] Specified identified: (b) (4) Specified unidentified: (b) (4) Unspecified (others): Each individual Total degradation products	HPLC[2]		

Test	Method principle	Acceptance criterion	
		Shelf life[1]	Release
Pharmaceutical technical tests			
Extractable volume	Ph. Eur., USP [3]	(b) (4)	
pH	Ph. Eur., USP [4]	7.0 to 8.0	
Osmolality	Ph. Eur., USP [5]	300 to 500 mOsm/kg	
Clarity	Ph. Eur. [6]	Clear	
Visible particles	Ph. Eur. [7]	Practically free from particles	
Particulate matter (b) (4)	Ph. Eur., USP [8]	(b) (4) particles per vial particles per vial	
Microbial tests			
Bacterial endotoxins	Ph. Eur., USP [9]	(b) (4) endotoxin units per mL	
Sterility	Ph. Eur., USP [10]	Sterile	
Container closure integrity	Closure integrity [11]	(b) (4) per vial	Not tested

1 Unless specified otherwise shelf life specifications are the same as release specifications

2 Expressed as active entity, 100 mg/mL of the active entity corresponds to 108.8 mg/mL of the Org 25969 (=sodium salt) (b) (4)

3 Specifications are based on a maximum clinical dose of 16 mg/kg

2 References

P.5.4 Batch Analyses

Adequate.

The batch data for the following batches have been added:

- Two new clinical batches of (b) (4) (5 mL vials), 529679001 and 718420001 . These batches were manufactured after the last review cycle.
- First commercial batch of (b) (4) (2 mL vials) , 760606, manufactured at the commercial site Swords. The applicant states that no commercial (b) (4) batches have been manufactured at Swords yet.
- Three (b) (4) filling revalidation batches (849870. 856777, and 867454) .

The information for all batches manufactured so far is summarized under 2.3.P.5.4 and reproduced below.

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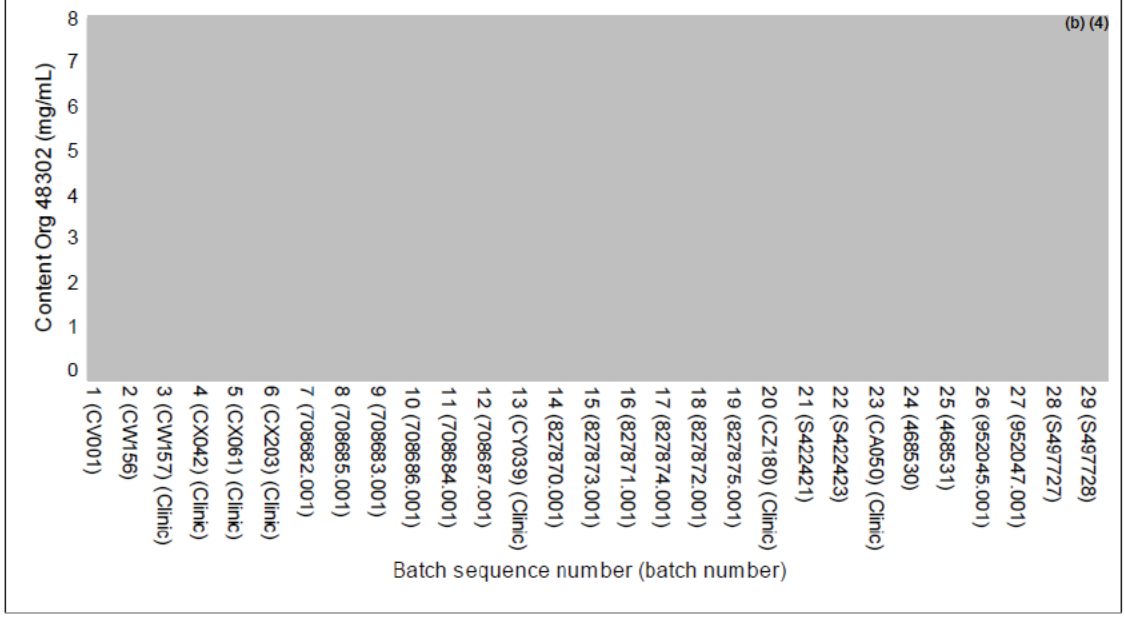
In Table 24 (reproduced from NDA 2.3.P.5.4) under the section 3.2.P.5.4, an overview of all clinical, stability and production scale batches of Org 25969 drug product manufactured at N.V. Organon, Oss, the Netherlands and manufactured at Organon (Ireland), Swords, Ireland, is provided. The applicant states that "From batch 7 onwards the batches are considered representative for the commercial batches, as they have been manufactured in a production facility, with a manufacturing process and manufacturing equipment that are representative for those that will be used for the commercial batches. These batches have therefore been used to establish the acceptance criteria for Org 25969 drug product. Batch 13 (i.e. clinical batch CY039) has not been manufactured in a production facility, but at a smaller facility dedicated for the manufacture of clinical batches."

Justification for assay of Org 25969 + Org 48302:
The proposed assay acceptance criteria are tighter than the (b) (4) % range usually used for the USP products. The batch release and stability data supports the tighter acceptance criteria.

Justification for assay of Org 48302:
The batch release and stability data summarized in the Figure 9 below support the proposed acceptance criterion of NMT (b) (4) Note the three phase 3 clinical batches all had the assay values for Org 48302 between (b) (4)



No data point means that the Org 48302 content was not determined in that batch or that it was determined at a (b) (4) concentration. Bold lines (——) indicate release and shelf life limit.

Figure 9: Content of assay of Org 48302 at release (O) and after 36 months (batches 7-12 and 14–19) of storage (X) at 30 °C/75% RH.

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(b) (4)

[redacted]

P.8.2 Postapproval Stability Protocol and Stability Commitment

Adequate.

The stability studies with the primary stability batches and the production scale batches of the drug product manufactured at Organon (Ireland) Limited, Swords, Ireland have been completed as they have reached the products shelf life of 36 months. Therefore, no post-approval stability study is necessary in accordance with the ICH Q1A.

The applicant states that "Subsequent to the first year of commercial production one batch of Org 25969 Solution for injection 100 mg/mL in each container/closure type will be selected on an annual basis and tested at the long term condition to provide additional assurance of the shelf life. Stability samples will be packaged using the same primary packaging as the marketed product. The stability test parameters and analytical test procedures will be followed as per current registered specification. Samples will be tested according to the schedule in Table 1, at a minimum. Additional time points may be added as appropriate."

Table 1: Stability study storage conditions and testing intervals

Storage conditions	Time interval (months)[1,2]			
	Initial	12	24	36
25°C/60% RH	ABCD	AD	AD	ACD

[1] The codes A, B, C and D are explained in Table 2

[2] (b) (4) [redacted]

Table 2 : Test parameters, analytical test methods and number of replicates

Test parameters		Method principle
Test	**Code[1]**	
Description		
Appearance	A	Visual
Color	A	Ph. Eur. (+VIS)
Identification		
Active ingredient identical with standards	B	HPLC
Active ingredient identical with reference spectrum (UV-DAD)	B	HPLC
Assay		
(b) (4)	A	HPLC
	A	HPLC
	A	HPLC
Impurities		
Degradation products Specified identified (b) (4) Specified unidentified (b) (4) Unspecified (others): Each individual Total degradation products	A	HPLC
Pharmaceutical technical tests		
Extractable volume	C	Ph. Eur./USP
pH	A	Ph. Eur./USP
Osmolality	C	Ph. Eur./USP
Clarity	A	Ph. Eur.
Visible particles	A	Ph. Eur.

Test parameters		Method principle
Test	**Code[1]**	
Particulate Matter	A	Ph. Eur./USP
Microbial Tests		
Bacterial endotoxins	C	Ph. Eur./USP
Sterility	C	Ph. Eur./USP
Container closure integrity	D	Closure integrity

[1] See Table 1

In summary, the applicant agrees to the following commitments:

i. To place at least one commercial batch of each container/closure type into the routine stability program annually. The stability study of this batch will be conducted in accordance with the stability study design presented in Table 1.

ii. The annual stability data will be reviewed for conformance to established acceptance criteria. Any production batch that does not meet the approved acceptance criteria will be promptly investigated and the proper action will be taken.

The annual stability studies, although not required by the ICH Q1A(R2), help ensure consistent product quality during production. The post-approval stability commitments are acceptable.

P.8.3 Stability Data

Adequate.

The notable changes of the drug product on stability were the assay and degradation products. A summary of the assay and degradation products data for the primary stability batches produced at both Oss, the Netherlands and Swords, Ireland is presented in the tables below (reproduced from QOS 2.3.P.8.1). The data support the shelf-life conclusion in P.8.1 above.

Figure 18: Total (Org 25969 + Org 48302) assay results at different conditions (primary stability batches Oss)

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(b) (4)

[redacted]

R REGIONAL INFORMATION

(b) (4)

(b) (4)

[redacted]

The proposed reporting category is Changes Being Effected - 30 Days (CBE-30).

(b) (4)

1

(b) (4)

2

(b) (4)

The agency held a teleconference with the applicant on 4/24/2013 to communicate about the deficiencies.

The applicant submitted a formal request dated 5/8/2013 to the NDA to (b) (4)

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

Inadequate.

The applicant is recommended to make the following revisions (highlighted in yellow) to the Prescribing Information. It should be noted that the Pharmacology/Toxicology team is evaluating whether the drug should be labeled as a (b) (4) proposed in the "Description" section of the Prescribing Information.

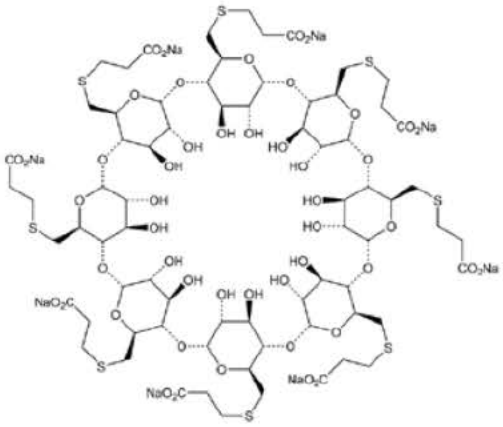
(b) (4)

3 DOSAGE FORMS AND STRENGTHS

(b) (4)

11 DESCRIPTION

[TRADENAME] sugammadex [redacted] (b) (4) [redacted] a modified gamma cyclodextrin [redacted] (b) (4) chemically designated as *6^A,6^B,6^C,6^D,6^E,6^F,6^G,6^H-Octakis-S-(2-carboxyethyl)-6^A,6^B,6^C,6^D,6^E,6^F,6^G,6^H-octathio-γ-cyclodextrin sodium salt (1:8)* with a molecular weight of 2178.01. The structural formula is:



[TRADENAME] is supplied as a sterile, non-pyrogenic aqueous solution that is clear, colorless to slightly yellow for intravenous injection only. Each mL contains 100 mg sugammadex [redacted] (b) (4) [redacted], equivalent to 108.8 mg/mL sugammadex sodium. The aqueous solution is adjusted to a pH of between 7 and 8 with hydrochloric acid, [redacted] (b) (4) and/or sodium hydroxide, [redacted] (b) (4) The osmolality of the product is between 300 and 500 mOsmol/kg.

[TRADENAME] may contain [redacted] (b) (4), up to 7 mg/mL of the mono OH-derivative of sugammadex *[see Clinical Pharmacology (12.2)]*. [redacted] (b) (4) [redacted] is 6^A, 6^B, 6^C, 6^D, 6^E, 6^F, 6^G-heptakis-S-(2-carboxyethyl)-6^A, 6^B, 6^C, 6^D, 6^E, 6^F, 6^G-heptathio-γ-cyclodextrin [redacted] (b) (4) sodium salt with a molecular weight of 2067.9. The structural formula [redacted] (b) (4) is:

(b) (4)

[redacted]

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

[TRADENAME] is available in the following presentations:

- [TRADENAME] 2-mL single-dose vials containing 200 mg sugammadex (b) (4) (100 mg/mL)
  Box of 10 NDC (b) (4)
- [TRADENAME] 5-mL single-dose vials containing 500 mg sugammadex (b) (4) (100 mg/mL)
  Box of 10 NDC (b) (4)

The packaging of this produc (b) (4) is not made of natural rubber (latex).

Storage

Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) (see USP Controlled Room Temperature). Protect from light. When not protected from light, the vial should be used within 5 days.

The applicant is also recommended to make the following revisions to the carton/container labels.

1. Label the product name and strength based on the active moiety. The product name and strength should be [TRADENAME] (sugammadex) Injection, 100 mg/mL instead of [TRADENAME] (sugammadex (b) (4) Injection, 100 mg/mL.

2. When possible, the information about the salt is included on the side panel. For example, The Each mL contains 100 mg sugammadex, equivalent to 108.8 mg sugammadex sodium.

B. Environmental Assessment Or Claim Of Categorical Exclusion

Acceptable according to the previous CMC review (#2).

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/s/

YONG HU
08/07/2013

PRASAD PERI
08/08/2013
I concur

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: July 24, 2008

FROM: Alan C. Schroeder, Ph.D.

SUBJECT: Second Addendum to Chemistry Review #2 of NDA 22-225 for [redacted] (b) (4) (sugammadex sodium) Injection
Original NDA received October 30, 2007
Applicant: Organon USA

TO: NDA 22-225 file

This is a final follow up to Chemistry Review #2 (CR2) for the purposes of indicating resolution of non-CMC consult issues that were open when CR2 was completed.

Compliance has provided (on July 24, 2008) an overall acceptable recommendation for the facilities used in manufacture and control of the drug product and drug substance under this NDA.

CMC Recommendation for NDA 22-225: Approval

cc:	Orig. NDA#22-225 ONDQA/Division File ONDQA/ACSchroeder/7-24-08 ONDQA/AAl-Hakim ONDQA/PM	File: N22225_second_addendum_memo.doc

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/s/

Alan Schroeder
7/24/2008 02:29:15 PM
CHEMIST

Ali Al-Hakim
7/24/2008 03:05:37 PM
CHEMIST

Ezvera®
(sugammadex sodium)
Injection

NDA 22-225

Division Director Review
Chemistry, Manufacturing, and Controls

Applicant: Organon USA Inc.
56 Livingston Avenue
Roseland, NJ 07068

Indication: reversal of shallow or profound neuromuscular blockade which is induced by the rocuronium and vecuronium, and for immediate reversal of neuromuscular blockade at 3 minutes after administration of rocuronium.

Presentation: [(b) (4)] Injection is supplied as a single strength, sterile, [(b) (4)] 100 mg/mL solution of sugammadex sodium filled in single-use, 2 mL or 5 mL vial, sealed with a grey [(b) (4)] rubber stopper and a aluminum flip-top overseal cap. Box of 10.

EER Status:		**Pending**	
Consults:	Biometrics	Acceptable	9-JUN-2008
	Microbiology	Approval	3-MAR-2008
	PharmTox	Approval	20-JUN-2008
	PharmTox – Impurity	Approval	17-JUL-2008
	EA – Categorical exclusion granted under 21 CFR §25.31(b)		
	Methods Validation –	Validation will not be requested.	

Original Submission: 30-OCT-2007

Post-Approval Agreements:

The applicant agreed to revisit the impurity specifications for the drug substance once the applicant has manufactured drug substance at full scale using at least 10 different production lots of the [(b) (4)].

The applicant agreed to revisit the specifications for degradants in the drug product following additional experience with the commercial manufacturing process.

Background:

This application was chosen by the Division of Anesthesia, Analgesia, and Rheumatology Products to serve as the pilot for the *Good Review Management Principles and Practices (GRMPs) for PDUFA Products (April 2005).*

Drug Substance:

The drug substance (sugammadex sodium) is a modified γ-cyclodextrin that forms one-to-one inclusion complexes with rocuronium and vecuronium. It is a semi-synthetic, new molecular entity (NME) with an empirical formula of $C_{72}H_{104}O_{48}S_8Na_8$ and a molecular weight of 2178.01. Known chemically as $6^A,6^B,6^C,6^D,6^E,6^F,6^G,6^H$-octakis-S-(2-carboxyethyl)-$6^A,6^B,6^C,6^D,6^E,6^F,6^G,6^H$ - octathio-γ-cyclodextrin octasodium salt, it is a (b) (4)

(b) (4)

The drug substance contains 40 chiral centers, (b) (4)

The manufacture of drug substance is a (b) (4)

The structure of sugammadex sodium was elucidated using (b) (4)

The proposed release specification for sugammadex sodium (b) (4)

Adequate stability data were provided to support the proposed (b) (4) month retest date for the bulk drug substance, stored at controlled room temperature, (b) (4) inside (b) (4)

Conclusion: Drug substance is acceptable.

Drug Product:

The drug product is supplied as a single strength, sterile, (b) (4) solution of sugammadex sodium (100 mg/mL) filled in a single-use, 2 mL or 5 mL vial, sealed with a grey (b) (4) rubber stopper and a aluminum flip-top overseal cap.

- Each 2 mL vial of (b) (4) contains 200 mg (100 mg/mL) of sugammadex sodium, (b) (4) and sodium hydroxide USP and hydrochloric acid USP adjusted to pH 7.5.
- Each 5 mL vial of (b) (4) contains 500 mg (100 mg/mL) of sugammadex sodium, (b) (4) and sodium hydroxide USP and hydrochloric acid USP adjusted to pH 7.5.

The drug product is (b) (4)

The proposed release specification of the drug product includes: appearance by visual inspection, identification by RP-HPLC, identification by UV, assay by RP-HPLC, impurities and degradation products by RP-HPLC, extractable volume, pH, osmolality, clarity, visible particles, particulate matter, bacterial endotoxins, and sterility. The applicant referred to information for the sugammadex sodium reference standard when testing the drug product. All test methods are compendial or have been appropriately validated for their intended purpose.

Adequate stability data were provided to support the proposed expiration dating of 36 months for the drug product in 2 mL and 5 mL vials, 200 mg and 500 mg dose/vial, stored at 25°C (77°F), excursions permitted to 15°C to 30°C (59°F to 86°F), and protected from light. When not protected from light, the vial should be used within 5 days

Conclusion: Drug product is acceptable.

Additional Items:

- All associated Drug Master Files (DMFs) are acceptable or the pertinent information has been adequately provided in the application.

- The applicant agreed to continue the stability studies on the primary stability batches through 36 months to firmly establish the proposed shelf life.

- The applicant agreed to continue the long-term stability studies of the first three commercial production lots of drug product for each strength and package configuration following the approved stability protocol.

- The applicant agreed to place at least one commercial production lot of the drug product per year on stability for each strength and package configuration following the approved stability protocol.

- The applicant agreed to submit the results of the ongoing stability studies periodically in the NDA Annual Report per 21 CFR Part 314.81(b)(2)(iv).

- The applicant agreed to withdraw from the market any lots found to fall outside the approved specification for the drug product, unless evidence is available that the deviation is a single occurrence that does not affect the safety and efficacy of the drug product, and the continuing distribution of the batch has been agreed to by the FDA.

- The analytical methods used in the testing procedures (release, stability, and in-process) are well known and widely used by the pharmaceutical industry and revalidation by Agency laboratories will not be requested.

Overall Conclusion:

From a CMC perspective, the application is recommended for **Approval ,** pending a satisfactory recommendation from the Office of Compliance.

Blair A. Fraser, Ph.D.
Director
DPA I/ONDQA

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/s/

Blair Fraser
7/21/2008 03:16:03 PM
CHEMIST

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: July 21, 2008

FROM: Alan C. Schroeder, Ph.D.

SUBJECT: Addendum to Chemistry Review #2 of NDA 22-225 for (b) (4) (sugammadex sodium) Injection
Original NDA received October 30, 2007
Applicant: Organon USA

TO: NDA 22-225 file

This is a follow up to Chemistry Review #2 (CR2) for the purposes of indicating resolution of non-CMC consult issues that were open when CR2 was completed.

The following comments pertain to the CMC request for a microbiology consult review of the (b) (4) This issue is now resolved. No written microbiology review of DMF (b) (4) was performed because of an acceptable review of DMF (b) (4) (microbiology review #1 dated March 21, 2005 by Brenda Pillari, Ph.D.). Following is the rationale for this decision as explained by microbiologist Vinayak Pawar, Ph.D. in an e-mail sent on July 7, 2008:

"At the time of my review of DMF (b) (4) I found no change in the (b) (4) I did see an amendment dated December 18, 2007, in which the most recent endotoxin reduction information was for (b) (4) . This (b) (4) is not used in the manufacture of Bridion product by Organon. With no new information there was no need for a DMF review."

Dr. Vinayak later clarified that the process has not changed since originally reviewed in 2005. The only change was that (b) (4) had recently tightened the acceptance criteria.

The following comments pertain to the CMC informal consult request for pharmacology/toxicology evaluation of impurities and degradation products in the drug substance and drug product. The pharmacologist's secondary review, including safety evaluation of levels of impurities and degradants present, was completed by Dr. Adam Wasserman on June 16, 2008. The primary pharmacology/toxicology review was completed by Dr. Zengjun Xu on June 20, 2008. Approval of the NDA from a pharm/tox

perspective for the adult population was recommended. An addendum to this review was completed by Dr. Zengjun Xu on July 17, 2008 to evaluate the safety of reported levels of [redacted] a degradant formed during [redacted] of the drug product. His recommendation was that no action is necessary, and "the specifications for [redacted] are acceptable." This recommendation must pertain to the levels of [redacted] reported, as there are no specifications to control [redacted] because of the following observation. The applicant has noted that [redacted] even under stressed conditions for the drug product, never [redacted]

The only open issue from a CMC perspective is (at the present time) the lack of a Compliance recommendation pertaining to the manufacturing and control facilities for this NDA.

Recommendation: All CMC issues have been satisfactorily addressed. This application may be approved when Compliance provides an overall acceptable recommendation for the facilities used in manufacture and control of the drug product and drug substance.

cc:	Orig. NDA#22-225 ONDQA/Division File ONDQA/ACSchroeder/7-21-08 ONDQA/AAI-Hakim ONDQA/PM	F/T by: ACSchroeder/ File: N22225_addendum_memo.doc

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/s/

Alan Schroeder
7/21/2008 02:15:57 PM
CHEMIST

Ali Al-Hakim
7/21/2008 02:30:40 PM
CHEMIST

NDA 22-225

(b) (4) (sugammadex sodium) Injection

Organon USA Inc.

Chemistry Review #2

Alan C. Schroeder, Ph.D.
ONDQA/Division I/Branch II

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-225

2. REVIEW #2:

3. REVIEW DATE: June 12, 2008

4. REVIEWER: Alan C. Schroeder, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original NDA	October 30, 2007
Amendment (mfg. site contact information)	November 19, 2007

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (BC)	January 22, 2008
Amendment (BC)	February 1, 2008
Amendment (BC)	March 10, 2008
Amendment (BC)	March 25, 2008
Amendment (BC)	May 21, 2008
Amendment (BC)	June 4, 2008

7. NAME & ADDRESS OF APPLICANT:

Name:	Organon USA Inc.
Address:	56 Livingston Ave. Roseland, NJ
Representative:	Sabina Rouf, Ph.D. Manager, Regulatory Affairs (contact for CMC issues)

Chemistry Review Data Sheet

Telephone: (973) 325-5303

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: (b) (4) Injection
b) Non-Proprietary Name (USAN): sugammedex sodium injection
c) Code Name/#Org 25969:
d) Chem. Type/Submission Priority:

- Chem. Type: 1 (NME)
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: selective relaxant binding agent for routine reversal of shallow or profound neuromuscular blockade induced by rocuronium or vecuronium and for immediate reversal of neuromuscular blockade at 3 minutes after administration of rocuronium.

11. DOSAGE FORM: Injection, solution

12. STRENGTH/POTENCY: 100 mg/mL (expressed as the free acid)

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___x__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

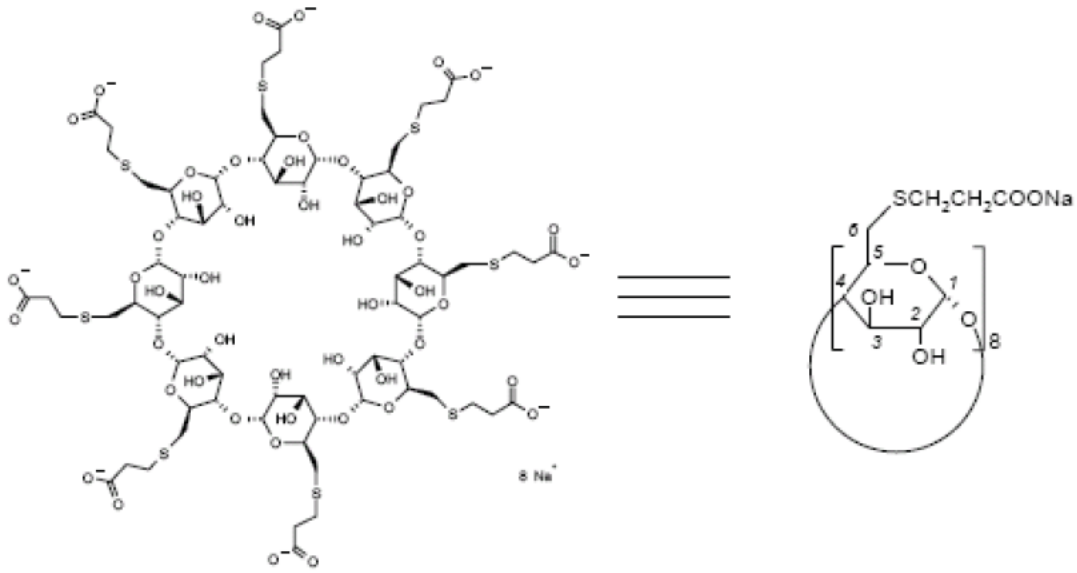


Figure 1: Structural formula of Org 25969

1. CA: $6^A,6^B,6^C,6^D,6^E,6^F,6^G,6^H$ –octakis- *S*-(2-carboxyethyl) - $6^A,6^B,6^C,6^D,6^E,6^F,6^G,6^H$ – octathio-γ-cyclodextrin octasodium salt
2. IUPAC: octakis(6-S-(2-carboxyethyl)-6-thio)cyclomaltooctaose octasodium salt
Molecular formula: $C_{72}H_{104}O_{48}S_8Na_8$
Molecular Weight: 2178.01 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	4	N/A		(b) (4) meet USP requirements, per information in NDA. No review of DMF is necessary.
	III			3	Adequate	05-Oct-2007 by Jane L. Chang, Ph.D.	LOA dated 3/29/07 provided by

Chemistry Review Data Sheet

		Services					applicant on 1/10/2008
(b) (4)	III	(b) (4)		7	Under review by micro. as part of the microbiology consult request		

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	68,029	Org 25969 injection

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	See end of this review for discussion (prior to the attachments).	06/09/2008	Ms. Roswitha Kelly
EES	pending	[requested 11/15/2007]	
Pharm/Tox	pending	[informal consult requested 12/12/2007]	
Biopharm	N.A.		
Methods Validation		not yet submitted	
EA	Adequate – request for categorical exclusion	Evaluated in this review.	
Microbiology	Approval recommended from microbiological quality standpoint. (but an additional review is underway, e.g., for	3/3/2008 (signature date)	Vinayak Pawar, Ph.D.

	microbiological evaluation of the process in DMF (b) (4))		

The Chemistry Review for NDA 22-225

The Executive Summary:

I. Recommendations

A. Recommendation and Conclusion on Approvability

APPROVABLE pending satisfactory EER, microbiology consult review of the [redacted] (b) (4) and pharmacology review of impurities and degradation products. CMC concerns have been satisfactorily addressed.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

The applicant has made the following agreements during the course of the review of this NDA:

The standard stability agreements (see the last attachment to this review).

An agreement to revisit the impurity specifications for the drug substance once the applicant has manufactured drug substance at full scale using at least 10 different production lots of the [redacted] (b) (4)

An agreement to revisit the specifications for degradants in the drug product following additional experience with the commercial manufacturing process.

Note that the applicant has fulfilled and satisfied the prior agreement to complete development of an assay method for Intermediate [redacted] (b) (4) in the manufacture of the drug substance, and then to validate the method and collect data to propose acceptance criteria.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance (Org 25969), an octasodium salt, is a modified γ-cyclodextrin and its mode of action is based on the formation of 1:1 inclusion complexes with rocuronium or vecuronium. The drug substance contains [redacted] (b) (4) Org 48302, which is said to have an activity and pharmacological profile comparable to that of Org 25969, and therefore it is treated as an active entity. Org 48302 is typically present at [redacted] (b) (4) in the representative drug substance batches. The drug product is formulated as a solution for injection and therefore, solid state properties of the drug substance such as polymorphism and particle size distribution are not critical for the drug product. The drug substance is highly soluble in water; it is highly hygroscopic and its hygroscopicity is managed by controlling manufacturing and storage conditions. The drug substance [redacted] (b) (4) have been extensively investigated, characterized/identified and controlled.

Batches AE to L00027692 of drug substance are said to be representative of the commercial manufacturing process. Actually, based upon the Addendum 1 in the section on manufacturing process development, batches from Z to L00027962 are generally more representative of the commercial process, with few exceptions. Multiple batches from A through AE and AE through L00027692 were used for pre-clinical studies; clinical studies used batches Q, V and AE.

The drug product is a sterile parenteral solution for intravenous administration. It is prepared by (b) (4) adjusting the pH to 7.5 with sodium hydroxide or hydrochloric acid, (b) (4) into 2 mL and 5 mL vials, and (b) (4) The target concentration of the active ingredients is 100 mg/mL (expressed as the free acid). The container closure system is as follows: type I glass vials with a latex-free, (b) (4) rubber closure and an aluminum flip off cap. The drug product is intended for reversal of neuromuscular block by rocuronium or vecuronium, through the formation of complexes between the cyclodextrin drug and the neuromuscular blocking agents. All 100 mg/mL clinical preparations are considered representative for the market formulation. Batches identified as pivotal clinical batches are indicated to be manufactured by a process and at a scale comparable to the primary stability batches. Critical process steps for the manufacture of the drug product include the following: (b) (4) . Key drug product parameters related to performance are as follows: pH, osmolality, particulate matter and color. Key drug product parameters related to manufacturability are as follows: (b) (4)

In stability studies, the only trending parameters are as follows: (b) (4) products.

The drug product is sensitive to light (b) (4)) and the applicant proposes that the (b) (4) container be exposed to light no longer than for 5 days. It is indicated that (b) (4) . Photostability data support the 5 day maximum limit on exposure to normal indoor lighting, (b) (4)

B. Description of How the Drug Product is Intended to be Used

The proposed indications are routine reversal of shallow or profound neuromuscular blockade induced by rocuronium or vecuronium, and immediate reversal of neuromuscular blockade at 3 minutes after administration of rocuronium. The recommended doses are 2 mg/kg or 4 mg/kg for routine reversal, and 16 mg/kg for immediate reversal. The injection is to be given as a single dose. The drug product concentration is 100 mg/mL, to be marketed in 2 mL and in 5 mL vials.

A shelf life of 36 months at 25°C is acceptable for the drug product based primarily on the 24 months of stability data of the supporting batches and 18 months data of the primary stability batches manufactured at Oss and the statistical evaluation of the results (from the QOS, section 2.3.P, pg. 89).

The storage statement in the "How Supplied" section of the draft labeling is the following. " Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) (see USP Controlled Room Temperature). (b) (4) protect from light. When not protected from light, the vial should be used within 5 days)."

C. Basis for Approvability or Not-Approval Recommendation

Outstanding comments from chemistry review #1 were satisfactorily addressed in amendments subsequent to the original NDA.

Stability data indicate that the drug product does have some (b) (4) The drug product does have some sensitivity to light as indicated above. Other drug product attributes do not appear to have trends over time. Stability data and proposed expiry period (36 months) are acceptable. This review discusses the conclusions of the biometrics reviewer, pertaining to the stability data and the expiration dating period.

Sterility assurance during drug product manufacturing, and microbiological controls are evaluated separately in a microbiology consult review. (b) (4) are being separately reviewed by the microbiology reviewer.

Levels of impurities and degradation products permitted by the specifications are being separately evaluated in a pharmacology/toxicology consult review.

Our Office of Compliance has not yet made a final determination of the cGMP status of the manufacturing and testing facilities for this NDA.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Alan C. Schroeder, Ph.D./6-12-2008
Ali Al-Hakim, Ph.D./Date
ProjectManagerName/Date

C. CC Block

updated drug product specifications:

1 SPECIFICATION SHEET

Test	Method principle	Acceptance criterion	
		Shelf life[1]	Release
Description			
Appearance	Visual	Aqueous liquid	
Color	Ph. Eur. (+VIS) [1]	(b) (4)	
Identification			
Active ingredient identical with standard	HPLC[2]		
Active ingredient identical with reference spectrum (UV-DAD)	HPLC[2]		
Assay			
(b) (4)	HPLC[2]		
	HPLC[2]		
	HPLC[2]		
Impurities			
Degradation products[3] Specified identified: (b) (4) Specified unidentified: (b) (4) Unspecified (others): Each individual Total degradation products	HPLC[2]		

Updated drug product specifications, continued:

Test	Method principle	Acceptance criterion	
		Shelf life[1]	Release
Pharmaceutical technical tests			
Extractable volume	Ph. Eur., USP, JP [3]	For 2.0 mL: individual volume ≥ 2.0 mL per vial For 5.0 mL: individual volume ≥ 5.0 mL per vial	
pH	Ph. Eur., USP, JP [4]	7.0 to 8.0	
Osmolality	Ph. Eur., USP, JP [5]	300 to 500 mOsm/kg	
Clarity	Ph. Eur. [6]	Clear	
Visible particles	Ph. Eur., JP [7]	Practically free from particles	
Particulate matter (b) (4)	Ph. Eur., USP, JP [8]	(b) (4) particles per vial particles per vial	
Microbial tests			
Bacterial endotoxins	Ph. Eur., USP, JP [9]	(b) (4) endotoxin units per mL	
Sterility	Ph. Eur., USP, JP [10]	Sterile	
Container closure integrity	Closure integrity [11]	(b) (4) per vial	Not tested

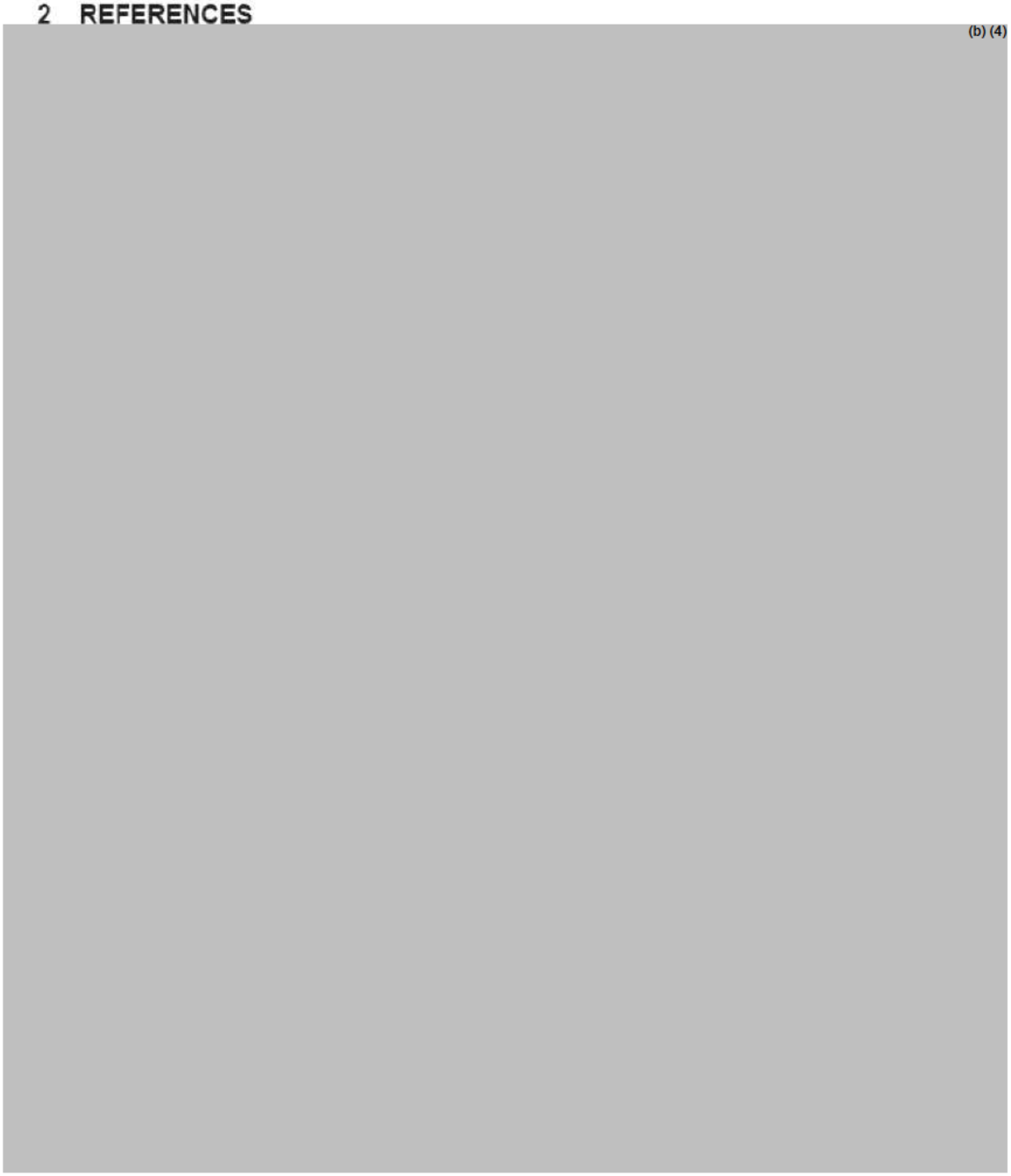
1 Unless specified otherwise shelf life specifications are the same as release specifications

2 Expressed as active entity, 100 mg/mL of the active entity corresponds to 108.8 mg/mL of the Org 25969 (=sodium salt) (b) (4)

3 Specifications are based on a maximum clinical dose of 16 mg/kg

2 REFERENCES

(b) (4)



Specification(s)

Updated stability study design for first three stability batches (Table 4, below) and for the annual stability batches (Tables 5 & 6, below).

Table 4 : Stability study design of Org 25969 Solution for injection 100 mg/mL

Storage conditions	Time interval (months)							
	Initial	3	6	9	12	18	24	36
5°C/amb. RH	ABCD	A	A	A	A	AD	A	ABCD
25°C/60% RH		A	A	A	A	AD	A	ABCD
30°C/75% RH		A	A	A	A	AD	A	ABCD
40°C/75% RH		A	ACD	–	–	–	–	–

The abbreviations ABCD are explained in Table 3

All samples will be inverted for storage, as the inverted position is considered worst case.

All samples will be stored in the dark.

Annual stability batches prior to submission to the FDA (annual report) of full stability data from the first three production scale batches:

Table 5: Stability study design of annual batches of Org 25969 Solution for injection 100 mg/mL

Storage conditions	Time interval (months)								
	Initial	3	6	9	12	18	24	AE	36
25°C/60%RH	ABCD	A	A	A	AD	A	AD	ACD	ACD

ABCD are explained in Table 3

(b) (4)

(b) (4)

Annual stability batches subsequent to submission to the FDA (annual report) of full stability data from the first three production scale batches:

Table 6: Stability study design of annual batches of Org 25969 Solution for injection 100 mg/mL

Storage conditions	Time interval (months)					
	Initial	6	12	24	AE	36
25°C/60%RH	ABCD	A	AD	AD	ACD	ACD

ABCD are explained in Table 3

(b) (4)

(b) (4)

Codes for tests in above stability protocol tables:

A = description (appearance, color), assay tests, impurities and degradation products, pH, clarity, particles, particulate matter,

B= identification tests

C=extractable volume, osmolality, bacterial endotoxins, sterility

D=container closure integrity

3.5 STABILITY COMMITMENT

Organon agrees to the following commitments:

i. To continue the long-term stability study of the primary stability batches through 36 months.

ii. To continue the long-term stability study of the three production scale batches through 36 months and accelerated stability study up to 6 months.

iii. To place at least one commercial batch of each presentation into the routine stability program annually thereafter. Stability study of this batch will be conducted in accordance with the stability study design presented in Table 5.

iv. To submit the results of the ongoing stability studies periodically in the NDA Annual Report per 21 CFR Part 314.81(b) (2) (iv).

v. To withdraw from the market any lots found to fall outside the approved specification for the drug product, unless evidence is available that the deviation is a single occurrence that does not affect the safety and efficacy of the drug product, and the continuing distribution of the batch has been agreed to by the FDA.

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/s/

Alan Schroeder
6/16/2008 11:11:20 AM
CHEMIST

Ali Al-Hakim
6/16/2008 01:24:45 PM
CHEMIST

NDA 22-225

Bridion (sugammadex sodium) Injection

Organon USA Inc.

Alan C. Schroeder, Ph.D.
ONDQA/Division I/Branch II

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-225

2. REVIEW #1:

3. REVIEW DATE: January 30, 2008

4. REVIEWER: Alan C. Schroeder, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
none	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original NDA	October 30, 2007
Amendment (mfg. site contact information)	November 19, 2007

7. NAME & ADDRESS OF APPLICANT:

Name:	Organon USA Inc.
Address:	56 Livingston Ave. Roseland, NJ
Representative:	Sabina Rouf, Ph.D. Manager, Regulatory Affairs (contact for CMC issues)
Telephone:	(973) 325-5303

8. DRUG PRODUCT NAME/CODE/TYPE:

Chemistry Review Data Sheet

a) Proprietary Name: Bridion Injection
b) Non-Proprietary Name (USAN): sugammedex sodium injection
c) Code Name/#Org 25969:
d) Chem. Type/Submission Priority:

- Chem. Type: 1 (NME)
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: selective relaxant binding agent for routine reversal of shallow or profound neuromuscular blockade induced by rocuronium or vecuronium and for immediate reversal of neuromuscular blockade at 3 minutes after administration of rocuronium.

11. DOSAGE FORM: Injection, solution

12. STRENGTH/POTENCY: 100 mg/mL (expressed as the free acid)

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___x__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

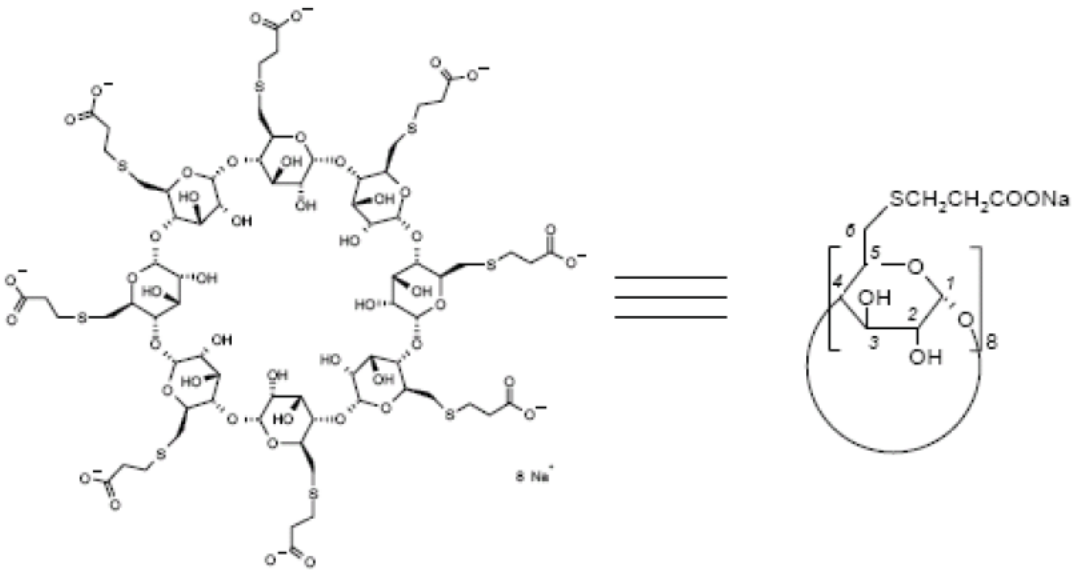

Figure 1: Structural formula of Org 25969

1. CA: $6^A,6^B,6^C,6^D,6^E,6^F,6^G,6^H$ –octakis- *S*-(2-carboxyethyl) - $6^A,6^B,6^C,6^D,6^E,6^F,6^G,6^H$ – octathio-γ-cyclodextrin octasodium salt
2. IUPAC: octakis(6-S-(2-carboxyethyl)-6-thio)cyclomaltooctaose octasodium salt
Molecular formula: $C_{72}H_{104}O_{48}S_8Na_8$
Molecular Weight: 2178.01 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		4	N/A		(b) (4) meet USP requirements, per information in NDA. No review of DMF is necessary.
	II			3	Adequate	05-Oct-2007 by Jane L. Chang, Ph.D.	LOA dated 3/29/07 provided by applicant on 1/10/2008

Chemistry Review Data Sheet

(b) (4)	III	(b) (4)				Under review as part of the microbiology consult request

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	68,029	Org 25969 injection

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	pending	[consult requested 1/17/08 for evaluation of expiry and site specific stability data]	
EES	pending	[requested 11/15/2007]	
Pharm/Tox	pending	[informal consult requested 12/12/2007]	
Biopharm	N.A.		
DMETS	pending	[consult requested by DAARP 11/8/2007]	
Methods Validation	pending	not yet submitted	
OPDRA			

Chemistry Review Data Sheet

EA	Adequate – request for categorical exclusion	Evaluated in this review.	
Microbiology	pending	[consult request from DAARP project manager dated 11/13/2007]	

Radiopharmaceutical	N.A.		

The Chemistry Review for NDA ##-###

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The drug product is approvable, pending resolution of requested consult reviews and pending adequate responses to comments provided to the applicant. It is intended that there will be a second CMC review within this review cycle.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

It is requested that the applicant provide an agreement to re-evaluate the drug substance and drug product specifications after they have more experience with the manufacturing process.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance (Org 25969), an octasodium salt, is a modified γ-cyclodextrin and its mode of action is based on the formation of 1:1 inclusion complexes with rocuronium or vecuronium. The drug substance contains (b) (4) Org 48302, which is said to have an activity and pharmacological profile comparable to that of Org 25969, and therefore it is treated as an active entity. Org 48302 is typically present at (b) (4) in the representative drug substance batches. The drug product is formulated as a solution for injection and therefore, solid state properties of the drug substance such as polymorphism and particle size distribution are not critical for the drug product. The drug substance is highly soluble in water; it is highly hygroscopic and its hygroscopicity is managed by controlling manufacturing and storage conditions. The drug substance (b) (4) have been extensively investigated, characterized/identified and controlled.

Batches AE to L00027692 of drug substance are said to be representative of the commercial manufacturing process. Actually, based upon the Addendum 1 in the section on manufacturing process development, batches from Z to L00027962 are generally more representative of the commercial process, with few exceptions. Multiple batches from A through AE and AE through L00027692 were used for pre-clinical studies; clinical studies used batches Q, V and AE.

The drug product is a sterile parenteral solution for intravenous administration. It is prepared by (b) (4), adjusting the pH to 7.5 with sodium hydroxide or hydrochloric acid, (b) (4) into 2 mL and 5 mL vials, and (b) (4) The target concentration of the active ingredients is 100 mg/mL

(free acid). The container closure system is as follows: type I glass vials with a latex-free, (b) (4) rubber closure and an aluminum flip off cap. The drug product is intended for reversal of neuromuscular block by rocuronium or vecuronium, through the formation of complexes between the cyclodextrin drug and the neuromuscular blocking agents. All 100 mg/mL clinical preparations are considered representative for the market formulation. Batches identified as pivotal clinical batches are indicated to be manufactured by a process and at a scale comparable to the primary stability batches. Critical process steps for the manufacture of the drug product include the following: (b) (4) Key drug product parameters related to performance are as follows: pH, osmolality, particulate matter and color. Key drug product parameters related to manufacturability are as follows: (b) (4)

In stability studies, the only trending parameters are as follows: (b) (4) products.

The drug product is sensitive to light (b) (4) and the applicant proposes that the (b) (4) container be exposed to light no longer than for 5 days. It is indicated (b) (4)

B. Description of How the Drug Product is Intended to be Used

The proposed indications are routine reversal of shallow or profound neuromuscular blockade induced by rocuronium or vecuronium, and immediate reversal of neuromuscular blockade at 3 minutes after administration of rocuronium. The recommended doses are 2 mg/kg or 4 mg/kg for routine reversal, and 16 mg/kg for immediate reversal. The injection is to be given as a single dose. The drug product concentration is 100 mg/mL, to be marketed in 2 mL and in 5 mL vials.

A shelf life of 36 months at (b) (4) is proposed for the drug product based primarily on the 24 months of stability data of the supporting batches and 18 months data of the primary stability batches manufactured at Oss and the statistical evaluation of the results (from the QOS, section 2.3.P, pg. 89).

C. Basis for Approvability or Not-Approval Recommendation

This review pertains only to the original NDA and the November 19, 2007 amendment. Outstanding comments include the following, for example: a request for additional stability summary data, a request to further demonstrate the assurance of the quality and purity of the starting material (b) (4) used in the manufacture of the drug substance, and a request for additional information pertaining to the assurance of the quality of intermediates in the drug substance manufacturing process. The issue of the starting material includes the possibility of multiple sources, the qualification process, and the specifications and the robustness of the analytical method. Information was requested pertaining to other drug substance impurities which may have been observed. A recommendation was made for additional drug substance specifications. Limits are needed, with supporting data, (b) (4). A number of clarifications have been or will be requested. Modification of the post-approval drug product stability protocol will be requested.

Preliminary review of stability data indicates that the drug product does have some (b) (4) (b) (4) . The drug product does have some sensitivity to light as indicated above. Other drug product attributes do not appear to have trends over time. Outstanding consult reviews will be involved in evaluation of the expiration dating period and multiple manufacturing sites, and of the maximum levels of impurities/degradation products permitted. Review of requested additional CMC stability data will also be relevant to this issue.

Stability data and proposed expiry period (36 months) are being assessed in a Biometrics consult review, and additional summary stability data have been requested from the applicant.

Sterility assurance during drug product manufacturing, and microbiological controls are being evaluated in a Microbiology consult review.

Levels of impurities and degradation products permitted by the specifications are being evaluated in a pharmacology/toxicology consult review.

CMC IR comments were sent to the applicant in the filing letter dated December 27, 2007. Additional IR comments are included at the end of this review. In addition, the applicant was requested to provide certain additional stability summary data. Review of these items are pending their receipt.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Alan C. Schroeder, Ph.D./Date: January 30, 2008
Ali Al-Hakim, Ph.D./Date
ProjectManagerName/Date

C. CC Block

Chemistry Assessment

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data

S DRUG SUBSTANCE [sugammadex sodium]

S.1 General Information

S.1.1 Nomenclature

Modified Recommended International Non-proprietary Name (rINNM)	sugammadex sodium
Recommended International Non-proprietary Name (rINN)	sugammadex (for active entity)
Other non-proprietary name(s)	
– US Adopted Name (USAN)	sugammadex sodium
– (b) (4)	
Systematic chemical name(s)	
– CA Index Name	6A, 6B, 6C, 6D, 6E, 6F, 6G, 6H –octakis-S-(2-carboxyethyl) -6A, 6B, 6C, 6D, 6E, 6F, 6G, 6H octathio-γ-cyclodextrin octasodium salt
– IUPAC Name	octakis(6-S-(2-carboxyethyl)-6-thio)cyclomaltooctaose octasodium salt
CAS Registry Number	343306-79-6
Company or Laboratory code	Org 25969
Other Name	(b) (4)

S.1.2 Structure

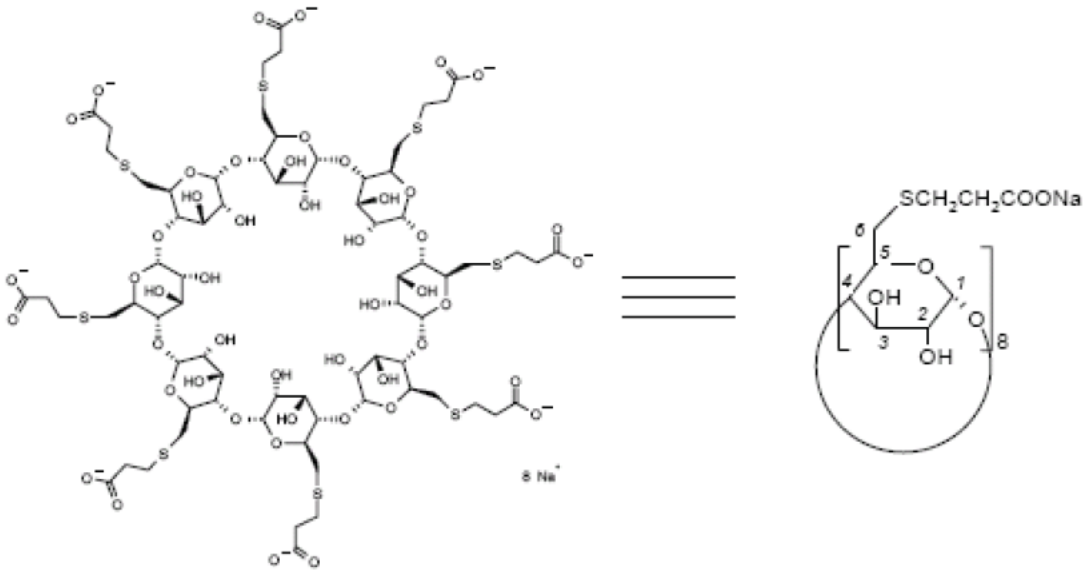

Figure 1: Structural formula of Org 25969

S 1.3 General Properties

General properties are listed, including solubility, melting point, hygroscopicity, partition coefficient, pH and pKa in solution, specific optical rotation, and UV spectrum.

(b) (4)

Table 2: pKa values of Org 25969

Form	pK_a
(b) (4)	

The applicant states that since the drug product is a solution, particle size distribution is not relevant and has not been determined. (b) (4) is said to vary from batch to batch and the drug substance contains (b) (4) The applicant claims that the (b) (4) has not been shown to affect chemical stability, solubility and the processability of the drug substance.

Evaluation: Inadequate. The applicant should provide a brief summary of data to support their claim (b) (4)

Comment: Provide a brief summary of data to demonstrate that the (b) (4) of the drug substance do not affect chemical stability, solubility and processability of the drug substance. [included in the filing letter]

S.2 Manufacture [sugammadex sodium]

S.2.1 Manufacturers

Manufacturer	Manufacturing site	Responsibility
N.V. Organon Registration number (CFN): 9610343	Kloosterstraat 6, 5349 AB Oss, The Netherlands	API manufacture Release testing Stability testing
N.V. Organon Registration number (CFN): 9614567	Veersemeer 4, 5347 JN Oss, The Netherlands	API manufacture
Organon Development GmbH Registration number (CFN): FEI 3003046251	Im Wirrigen 25, 45731 Waltrop, Germany	Stability testing (for assay and organic impurity testing only)

Evaluation: See cover pages for status of the facilities involved with this NDA, which will be evaluated by Compliance.

S.2.2 Description of Manufacturing Process and Process Controls

The starting material proposed is [redacted] (b) (4) The manufacturing process is summarized in the flow chart on the next page.

[redacted]

APPEARS THIS WAY ON ORIGINAL

P DRUG PRODUCT

P.1 Description and Composition of the Drug Product

The drug product is a "clear colorless to slightly yellow aqueous solution for injection filled in (b) (4) (2 ml per vial) or (b) (4) (5 ml per vial) vials." It is filled in 2 mL and 5 mL vials at an active ingredient concentration of 100 mg/mL.

Table 1:
Complete composition Org 25969 solution for injection 100 mg/mL (2 mL per vial)

Component	Reference to quality standard	Function(s)	Quantity per vial (2.0 mL[1])	Quantity per mL
Org 25969 + Org 48302[2]	In-house standard	Drug substance	200 mg	100 mg
Sodium hydroxide[3]	Ph. Eur., NF, JP	pH adjuster	q.s. to pH 7.5	q.s. to pH 7.5
Hydrochloric acid[3]	Ph. Eur., NF, JP	pH adjuster	q.s. to pH 7.5	q.s. to pH 7.5
(b) (4)	Ph. Eur., USP, JP	(b) (4)	(b) (4)	
	Ph. Eur., NF		-	-

(b) (4)

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

(b) (4)

Table 2: Complete composition Org 25969 solution for injection 100 mg/mL (5 mL per vial)

Component	Reference to quality standard	Function(s)	Quantity per vial (5.0 mL[1])	Quantity per mL
Org 25969 + Org 48302[2]	In-house standard	Drug substance	500 mg	100 mg
Sodium hydroxide[3]	Ph. Eur., NF, JP	pH adjuster	q.s. to pH 7.5	q.s. to pH 7.5
Hydrochloric acid[3]	Ph. Eur., NF, JP	pH adjuster	q.s. to pH 7.5	q.s. to pH 7.5
(b) (4) (b) (4)	Ph. Eur., USP, JP	(b) (4)	(b) (4)	
	Ph. Eur., NF		-	-

[2] Declared amount of 100 mg/mL drug substance corresponds with 108.8 mg/mL Org 25969 (sodium salt)

(b) (4)

(b) (4)

C

Org 25969 Solution for injection 100 mg/mL, is filled in colorless, (b) (4) 2 mL per vial) or (b) (4) (5 mL per vial) vials of (b) (4) glass, type I, and closed with gray (b) (4) rubber closures (b) (4) of diameter 13 mm for the (b) (4) and 20 mm for the (b) (4) vials. The rubber closures are held in position on the glass vials by aluminium crimp-caps with a "flip-off" seal.

Evaluation: Adequate. The excipients are listed as conforming to NF. See later in this review for container closure evaluation.

P.2 Pharmaceutical Development

P.2.1 Components of the Drug Product

P.2.1.1 Drug Substance

See earlier in this review for a discussion of drug substance properties (in the drug substance section). Early stability studies demonstrated that the drug substance is compatible with the excipients. Key physical properties of the drug substance are considered to be the following: (b) (4)

P.2.1.2 Excipients

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/s/

Alan Schroeder
2/1/2008 02:39:42 PM
CHEMIST

Ali Al-Hakim
2/1/2008 03:36:47 PM
CHEMIST

Initial Quality Assessment
Division of Pre-Marketing Assessment I, Branch II
Office of New Drug Quality Assessment
Division of Anesthesia, Analgesia and Rheumatology Products

OND Division:	Anesthesia, Analgesia and Rheumatology
NDA:	22-225
Applicant:	Organon
Stamp date:	October 30, 2007
PDUFA Date:	April 30, 2008
Trademark:	Bridion®
Established Name:	Suggammadex Sodium (USAN)
Dosage Form:	Intravenous Injection (100 mg/ml)
Route of Administration:	Parenteral (IV)
Indication:	Reversal of neuromascular block
Pharmaceutical Assessment Lead:	Danae D. Christodoulou, Ph.D.

	YES	NO
ONDQA Fileability:	√	___
Comments for 74-Day Letter:	√	___

Summary, Critical Issues and Comments

A. Summary

The application is filed as a 505(b)(1), priority NDA with 6-month review clock, for the New Molecular Entity suggammadex sodium.

Org 25969 (sugammadex sodium) is a novel compound, developed for the reversal of neuromuscular block which is induced by the neuromuscular blockers rocuronium and vecuronium. Org 25969 is a New Molecular Entity (NME), according to the definitions in the FDA Drug Classification MAPP 7500-3. Structurally, Org 25969 is a modified γ-cyclodextrin which forms 1:1 inclusion complexes with rocuronium or vecuronium. Sequestering of the free neuromascular agent results to rapid reversal of the neuromascular blockade.

Bridion® (suggammadex sodium) Injection, is a sterile solution for intravenous injection; its strength is 100 mg/ml packaged in single dose vials. The recommended clinical doses are 2 and 4 mg/kg for routine and 16 mg/kg for immediate reversal of rocuronium.

B. Review, Comments and Recommendations

Drug Substance

Molecular Structure, Chemical Name, Molecular Formula and Molecular Weight

Org 25969

1. CA: $6^A,6^B,6^C,6^D,6^E,6^F,6^G,6^H$ –octakis- *S*-(2-carboxyethyl) - $6^A,6^B,6^C,6^D,6^E,6^F,6^G,6^H$ – octathio-γ-cyclodextrin octasodium salt

2. IUPAC: octakis(6-S-(2-carboxyethyl)-6-thio)cyclomaltooctaose octasodium salt

Molecular formula: $C_{72}H_{104}O_{48}S_8Na_8$

Molecular Weight: 2178.01 g/mol

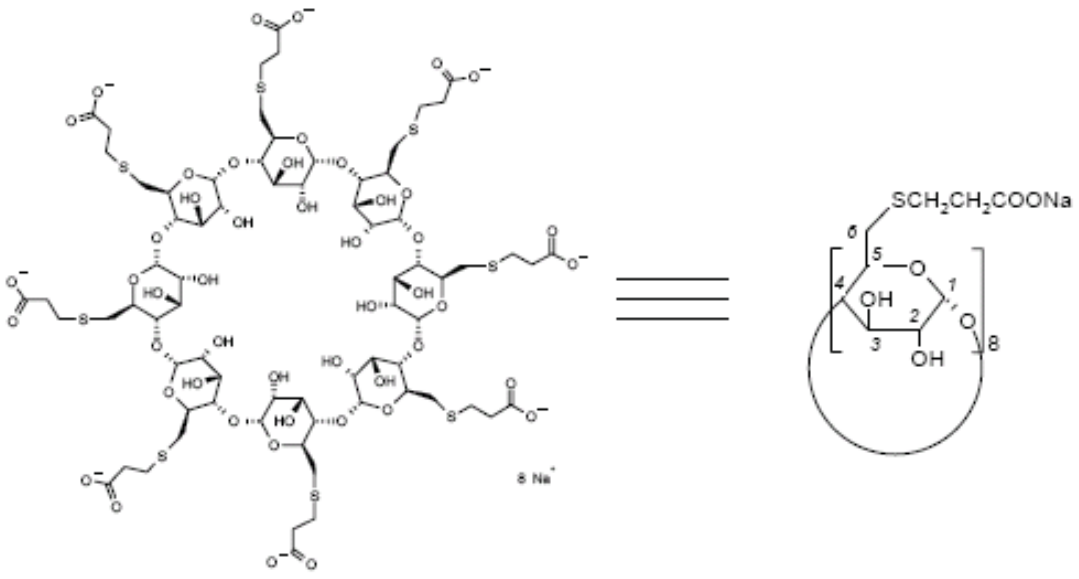


Figure 1: Structural formula of Org 25969

(b) (4)

Molecular formula: (b) (4)
Molecular Weight: 2067.90 g/mol

(b) (4)

Figure 2: Structural formula of Org 48302

The drug substance consists of the (b) (4)

(b) (4)

The drug substance is manufactured by two different sites of N. V. Organon, in the Netherlands. Alternate stability testing is performed by a third Organon site, in Germany.

(b) (4)

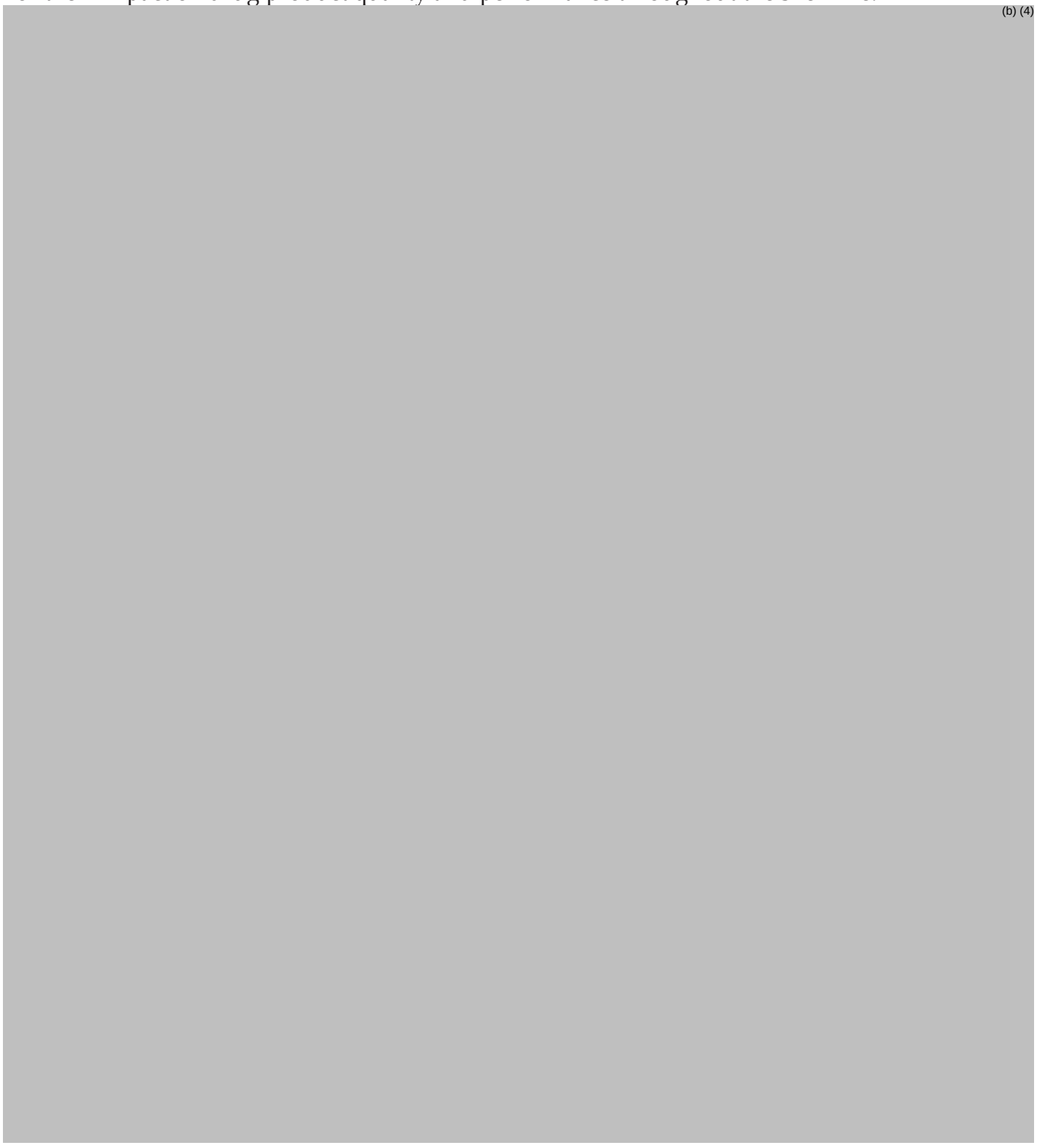
Flow chart of synthesis of Org 25969 (suggammadex sodium)

14 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

C. Critical issues for review and recommendation

During assessment of the CMC information provided in this NDA, the primary reviewer should consider addressing issues identified above and other related ones, summarized here, for their impact on drug product quality and performance throughout the shelf-life:

(b) (4)



(b) (4)

D. **Comments for 74-day Letter**:

- Provide a name contact and telephone number at the foreign manufacturing sites. This information is required by the Office of Compliance in order to schedule foreign inspections.
- Provide a Letter of authorization for DMF (b) (4) and identify the referenced item and DMF holder.

E. **Recommendation for fileability**: The NDA is fileable based on sufficient number of primary stability, production scale and clinical batches, and 24 month long term stability data for the drug substance and product. The NDA is suitable for evaluation and assessment based on FDA and ICH guidelines for submitting CMC information for New Drug Applications.

Recommendation for Team Review: The NDA is not recommended for team review. Even though the drug substance is an NME, the (b) (4)

Consults:

Since Bridion® is an injectable product, microbiology consult is required and was initiated.

Specifications for impurities including structural alerts should be evaluated in consultation with the Toxicology reviewer.

The primary reviewer, in conjunction with the project manager, should initiate the following consults/requests as soon as possible (see fileability template below).

Danae D Christodoulou, Ph.D. 11/16/2007
Pharmaceutical Assessment Lead Date

Ali Al-Hakim, Ph.D. 11/20/2007
Branch II Chief Date

Fileability Template

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	√		
2	Is the section indexed and paginated adequately?	√		
3	On its face, is the section legible?	√		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	√		Contact names and telephone numbers not provided for the foreign sites
5	Is a statement provided that all facilities are ready for GMP inspection?	√		
6	Has an environmental assessment report or categorical exclusion been provided?	√		Categorical exclusion requested
7	Does the section contain controls for the drug substance?	√		
8	Does the section contain controls for the drug product?	√		
9	Has stability data and analysis been provided to support the requested expiration date?	√		Stability data have been provided with statistical analysis
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	N/A		**Supporting IND:** 68,029
11	Have draft container labels been provided?	√		
12	Has the draft package insert been provided?	√		
13	Has a section been provided on pharmaceutical development/ investigational formulations section?	√		
14	Is there a Methods Validation package?	√		
15	Is a separate microbiological section included?	√		Injectable
16	Have all consults been identified and initiated?	√ √ N/A √ √ √		Pharm/Tox Statistics OCP/CDRH/CBER LNC DMETS/ODS Microbiology

Have all DMF References been identified? Yes ( ) No (√)

DMF Number	Holder	Description	LoA Included	Status
(b) (4) Type III		(b) (4)	Yes	pending
ype III			No	pending
Type III			Yes	pending

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/s/

Danae Christodoulou
11/29/2007 10:56:18 AM
CHEMIST
Initial Quality Assessment

Ali Al-Hakim
11/29/2007 02:44:49 PM
CHEMIST