CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022225Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 022225 SUPPL # HFD # 170

Trade Name: BRIDION

Generic Name: Sugammadex

Applicant Name: Organon USA Inc., a subsidiary of Merck & Co., Inc.

Approval Date, If Known: December, 15, 2015

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

c) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

d) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference

to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # YES ☐ ! NO ☐
! Explain:

Investigation #2 !
!
IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Diana Walker, PhD
Title: RPM for DAAAP
Date: December 15, 2015

Name of Office/Division Director signing form: Rigoberto Roca, M.D.
Title: Deputy Director, Office of Drug Evaluation II

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

DIANA L WALKER
12/15/2015

RIGOBERTO A ROCA
12/15/2015

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 22-225 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: October 31, 2007 PDUFA Goal Date: ___April 30, 2008___

HFD-170__ Trade and generic names/dosage form:_Bridion (suggamadex) Injection

Applicant: Organon Therapeutic Class: ___1P_

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- **X Yes. Please proceed to the next question.**
- **❑ No. PREA does not apply. Skip to signature block.**

**** SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.***

Indication(s) *previously approved* (please complete this section for supplements only):_____

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 1

Indication #1: 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
Is this an orphan indication?

- **❑ Yes. PREA does not apply. Skip to signature block.**
- **X No. Please proceed to the next question.**

Is there a full waiver for this indication (check one)?

- **☐ Yes: Please proceed to Section A.**
- **X No: Please check all that apply: ____Partial Waiver __x__Deferred ____Completed**

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- **❑ Products in this class for this indication have been studied/labeled for pediatric population**
- **☐ Disease/condition does not exist in children**
- **❑ Too few children with disease to study**
- **☐ There are safety concerns**
- **❑ Other:_____**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____
Reason(s) for partial waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:_____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg_____ mo._0_____ yr._0____ Tanner Stage_____
Max_____ kg_____ mo._____ yr.__17___ Tanner Stage_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- **X There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is this an orphan indication?

- ❑ **Yes. PREA does not apply. Skip to signature block.**
- ❑ **No. Please proceed to the next question.**

Is there a full waiver for this indication (check one)?

- ❑ **Yes: Please proceed to Section A.**
- ❑ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Other:_____**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below)::

Min _____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**
Max_____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**

Reason(s) for partial waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:_____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below)::

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

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

/s/

Parinda Jani
1/7/2008 04:31:18 PM

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 022225 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: BRIDION Established/Proper Name: Sugammadex Sodium Dosage Form: Injection		Applicant: Organon USA Inc., a subsidiary of Merck & Co., Inc. Agent for Applicant (if applicable):
RPM: Diana L. Walker		Division: DAAAP – HFD 170

NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is December 19, 2015	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None CR – April 22, 2015 CR – September 20, 2013 NA – July 31, 2008
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Reference ID: 3861132

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other require actions: CST SharePoint)

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments: The final cycle was standard, but on a 6-month (priority) timeline due to it being a Complete Response.

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☐ None ☒ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Actions and dates: AP – December 15, 2015 CR- April 22, 2015 CR – September 20, 2013 NA - July 31, 2008
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☐ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☐ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	Reviews July 22, 2015 December 19, 2014 July 25, 2014 July 16, 2013 April 15, 2013 Letters July 24, 2015 December 23, 2014 July 16, 2013 April 15, 2013 February 21. 2013 February 19, 2013 December 23, 2011
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☒ None DMEPA: ☐ None July 22, 2015 January 23, 2015 January 5, 2015 September 13, 2013 May 23, 2008 DMPP/PLT (DRISK): ☒ None OPDP: ☐ None November 18, 2015 March 17, 2015

	April 29, 2008 SEALD: ☒ None CSS: ☒ None Product Quality ☐ None Other: ☐ None Maternal Health: November 27, 2015 April 22, 2015
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	ADRA Review: July 30, 2008 Filing Review: July 11, 2008 ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC March 4, 2015 If PeRC review not necessary, explain: _____	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include previous action letters, as these are located elsewhere in package)*	Included
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	Included

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☐ N/A or no mtg June 11, 2015 June 5, 2015 (Preliminary Comments) March 4, 2015 November 21, 2013 November 19, 2013 (Preliminary Comments) June 14, 2012 July 23, 2009 December 1, 2008 November 24, 2008 (Preliminary Comments)
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg December 1, 2006
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg July 21, 2005
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	
❖ Advisory Committee Meetings	☐ No AC meeting
• Dates) of Meetings	November 6, 2015 March 11, 2008
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None December 15, 2015 April 22, 2015 September 20, 2013 July 31, 2008
Division Director Summary Review *(indicate date for each review)*	☐ None December 15, 2015 April 21, 2015 September 11, 2013 July 30, 2008
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None August 30, 2013 July 18, 2008
PMR/PMC Development Templates *(indicate total number)*	☐ None 4 templates: December 15, 2015
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Reviews *(indicate date for each review)*	☒ No separate review See CDTL reviews
• Clinical reviews *(indicate date for each review)*	April 3, 2015 August 23, 2013 June 27, 2008 June 24, 2008
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	Included in clinical reviews.
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☐ None November 23, 2015 April 28, 2015

	March 30, 2015 March 20, 2015 August 30, 2013 August 14, 2013 May 7, 2013 April 12, 2013 March 21, 2013 July 16, 2009 December 3, 2008 August 15, 2008 July 29, 2008 June 17, 2008 May 19, 2008 April 11, 2008 April 4, 2008 January 24, 2008
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	None. None. ☐ None November 29, 2015 March 27, 2015 March 6, 2008
❖ OSI Clinical Inspection Review Summaryies *(include copies of OSI letters to investigators)*	☐ None requested <u>Reviews:</u> November 18, 2015 March 25, 2015 August 27, 2013 March 28, 2008 <u>Letters:</u> December 10, 2015 October 16, 2015 September 14, 2015 August 6, 2015 June 1, 2015 April 20, 2015 February 5, 2015 January 12, 2015 November 19, 2014 October 7, 2014 September 5, 2014 July 2, 14, and 30, 2014 January 31, 2014 April 28, 2008 (2) March 28 and 31, 2008 February 20, 2008

Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Reviews *(indicate date for each review)*	☐ None August 30, 2013 August 22, 2013 March 13, 2008
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology reviews *(indicate date for each review)*	☐ None March 25, 2015 August 23, 2013 June 23, 2008
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review *(indicate date for each review)*	☐ No separate review April 21, 2015 July 18, 2008
• Supervisory Reviews *(indicate date for each review)*	☐ No separate review April 20, 2015 August 27, 2013 July 7, 2008 June 16, 2008
• Pharm/tox reviews, including referenced IND reviews *(indicate date for each review)*	☐ None March 25, 2015 August 23, 2013 July 17, 2008 June 20, 2008
❖ Reviews by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☐ None August 19, 2013 July 21, 2008 April 11, 2008
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• Tertiary review (*indicate date for each review*)	☐ None July 21, 2008
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	☐ None November 24, 2015 March 24, 2015 August 28, 2013 August 8, 2013 July 24, 2008 July 21, 2008 June 16, 2008 February 1, 2008 November 29, 2007
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☐ None Microbiology: March 24, 2015 May 15, 2013 March 3, 2008 Statistics: June 9, 2008
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	See CMC Product Quality reviews
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ Facilities inspections (*action must be taken prior to the re-evaluation date*) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable Re-evaluation date: ☐ Withhold recommendation ☐ Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☐ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☒ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

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/s/

DIANA L WALKER
12/15/2015

From:	Walker, Diana
To:	dori.glassner@merck.com
Subject:	NDA 22225 Clinical Snapshot Information Request 04Dec15
Date:	Friday, December 04, 2015 9:09:43 AM
Attachments:	BRIDION.xls

Dear Dori,

We are requesting your assistance in populating the attached tables (6 tabs in the attached spreadsheet) for your New Molecular Entity, BRIDION, currently under review in the Division.

As part of FDASIA 2012, information on demographic subgroups in clinical trials for newly-approved drugs and biologics will be made publicly available on www.fda.gov/drugtrialssnapshot.

The website will include information on study design, results of efficacy and safety studies, and whether there were any differences in efficacy and side effects within sex, race, and age subgroups. The website is not intended to replace or replicate the package insert (PI), which is intended for health care practitioners, and will contain the following:

- Information written in consumer-friendly language
- "MORE INFORMATION" sections that provide more technical, data-heavy information
- Information that focuses on subgroup data and analyses
- Links to the PI for the product and to the FDA reviews at Drugs@FDA

We are requesting you submit this information no later than **Friday, December 11, 2015**.

Thank you in advance for your cooperation. Please feel free to respond with any questions.

Regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
12/15/2015

Walker, Diana

From: Walker, Diana
Sent: Thursday, December 03, 2015 3:03 PM
To: dori.glassner@merck.com
Subject: NDA 22225 PMR Information Request 03Dec15

Dear Dori,

Please see below for four PMRs that the Divisions has determined are necessary for your product, NDA 22225, Sugammadex. Please submit your proposed milestone dates as soon as possible, but no later than Tuesday, December 8, 2015.

Note that, for PMR 3003-1, which is your PREA PMR, the milestone dates have already been populated per the dates you proposed in your NDA submission.

3003-1 A randomized, controlled trial evaluating the efficacy, safety, and pharmacokinetics of sugammadex when used to reverse neuromuscular blockade induced by either rocuronium or vecuronium must be conducted in pediatric patients ages birth to 17 years old.

Final Protocol Submission:	01/2017
Study/Trial Completion:	05/2021
Final Report Submission:	09/2021

For PMRs 3003-2 to 3003-4, please provide your proposed milestone dates.

Reference ID: 3855654

3003-2 In the clinical trials, some patients had either a delayed response or no response to sugammadex. These "non-responders," may be at risk for the following adverse consequences:

a) The administration of additional doses of sugammadex that could place them at higher risk for hypersensitivity reactions and/or anaphylaxis;
b) The need for continued ventilator support and sedation which carry their own potential for additional adverse consequences;
c) The risk of anoxia if they had received high doses of neuromuscular blocker because of expectations that sugammadex would be able to immediately reverse the neuromuscular blockade.

Thus, being able to identify potential non-responders would contribute to safer use of the drug.

Conduct a postmarketing study to analyze the demographic characteristics, concomitant medication use, and comorbid conditions in patients who did not respond to sugammadex reversal in the development program, in postmarket studies that have been conducted, or as described in cases of non-response/lack of efficacy reported as postmarketing adverse events. The goal of the study is to determine the characteristics and profile of patients who would be expected to be non-responders.

Final Protocol Submission: MM/YY
Study Completion: MM/YY
Final Report Submission: MM/YY

3003-3 Conduct a postmarketing clinical trial comparing sugammadex to placebo and/or drugs approved for the management of the reversal of the effects of neuromuscular blockade induced by rocuronium or vecuronium in a population of American Society of Anesthesiologists Class 3 and 4 patients. The goal of the study is characterization of the risks of bradycardia and other cardiac arrhythmias after sugammadex administration in this population that may have more severe outcomes related to cardiac arrhythmias experienced during reversal of neuromuscular blockade. Prespecify the case definition of bradycardia, tachycardia, and the other cardiac arrhythmias of interest.

Final Protocol Submission: MM/YY
Study Completion: MM/YY
Final Report Submission: MM/YY

3003-4 Conduct a postmarketing clinical trial comparing sugammadex to placebo and/or drugs approved for the management of the reversal of the effects of neuromuscular blockade induced by rocuronium or vecuronium in patients with morbid obesity. The goal of the study is generation of data to support dosing recommendations in morbidly obese patients, specifically whether to dose by actual vs. ideal body weight. Prespecify the case definition of morbid obesity that will establish who will be included in the trial.

Final Protocol Submission: MM/YY
Study Completion: MM/YY
Final Report Submission: MM/YY

Reference ID: 3855654

If you have any questions, feel free to contact me.

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
12/03/2015

From:	Walker, Diana
To:	"Glassner, D. (Dori)"
Subject:	NDA 22225 Labeling Comments 25Nov15
Date:	Wednesday, November 25, 2015 4:59:56 PM
Attachments:	sugammadex draft-labeling-text-uspi 25Nov15- to Merck.doc
Importance:	High

Dear Dori,

Pleased find attached the draft Package Insert label with FDA comments and edits. Please note that these are our preliminary comments, as Dr. Rosebraugh has not yet reviewed the label, and so there may be other minor adjustments nearer to the final label. Please review this label, and please do the following:

1. Accept those changes with which you agree.
2. Address any questions or comments from the reviewers.
3. Make any edits to language with which you do not agree. Please edit in track changes so that we can see your revisions.
4. Include comments or annotations on your revisions.
5. Please review for any typos, formatting errors, etc. that we may have missed.

Please return your comments to us as soon as possible via email (an official submission is not required at this time, as we will negotiate the labeling via email). Please send us your revisions by Wednesday, December 2, if possible, or by noon on Thursday, December 3. Again, please send me the draft label by email only.

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Email: Diana.Walker@fda.hhs.gov

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

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/s/

DIANA L WALKER
11/27/2015

From: Walker, Diana
To: dori.glassner@merck.com
Subject: NDA 22225 Clinical Information Request 07Aug15
Date: Friday, August 07, 2015 9:31:04 AM

Dear Dori,

I have received the following information request from our review team. Please respond as soon as possible with a response to your NDA 22225.

Your submission dated June 19, 2015, to NDA 022225 is currently under review.

Provide the total number of suspected hypersensitivity events (n=137 non-adjudicated events captured per the protocol for evaluation by the adjudication committee) over the total number of exposures by treatment group and interval. Provide the data for the total number of suspected hypersensitivity events as it appears for confirmed events in Table 11, on page 26, in the statistical report for the MK8616 P101sensitivity analysis.

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
08/20/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 022225

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Organon USA Inc., a subsidiary of Merck & Co., Inc.
126 East Lincoln Avenue
P.O. Box 2000, RY34-B188
Rahway, NJ 07065-0900

Attention: Dori L. Glassner
Director, Global Regulatory Affairs

Dear Ms. Glassner:

Please refer to your Class 2 resubmission for your New Drug Application (NDA) dated and received June 19, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sugammadex Sodium Injection, 200 mg/ 2mL and 500 mg/ 5mL.

We also refer to your correspondence, dated and received June 19, 2015, requesting review of your proposed proprietary name, Bridion.

We have completed our review of the proposed proprietary name, Bridion and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your June 19, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Lisa Skarupa, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2219. For any other information regarding this application, contact Diana L. Walker, Regulatory Project Manager in the Office of New Drugs, at (301) 796-4029.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES
07/24/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 022225

ACKNOWLEDGE –
CLASS 2 RESUBMISSION

Organon USA Inc., a subsidiary of Merck & Co., Inc.
126 East Lincoln Avenue
P.O. Box 2000, RY34-B188
Rahway, NJ 07065-0900

Attention: Dori L. Glassner
Director, Global Regulatory Affairs

Dear Ms. Glassner:

We acknowledge receipt on your June 19, 2015, resubmission to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sugammadex Sodium Injection, 100 mg/mL.

We consider this a complete, class 2 response to our April 22, 2015, action letter. Therefore, the user fee goal date is December 19, 2015.

If you have any questions, call me at (301) 796-4029.

Sincerely,

{See appended electronic signature page}

Diana L. Walker, Ph.D.
Sr. Regulatory Project Manager
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

DIANA L WALKER
07/02/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 022225

MEETING MINUTES

Organon USA Inc., a subsidiary of Merck & Co., Inc.
126 E. Lincoln Avenue, P.O. Box 2000
RY34-B188
Rahway, NJ 07065-0900

Attention: Dori L. Glassner
Director, Global Regulatory Affairs

Dear Ms. Glassner:

Please refer to your New Drug Application (NDA) dated October 30, 2007, received October 31, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sugammadex Sodium Injection, 100 mg/mL.

We also refer to your October 22, 2014, submission, which constituted a complete response to our September 20, 2013, action letter, and to the Complete Response Letter dated April 22, 2015.

We further refer to your request received May 14, 2015, for an End-of-Review meeting to discuss the April 22, 2015, Complete Response letter and containing your meeting questions.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-4029.

Sincerely,

{See appended electronic signature page}

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type A
Meeting Category: End of Review

Meeting Date and Time: June 11, 2015, 12:00 p.m. (Eastern)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1419
Silver Spring, Maryland 20903

Application Number: NDA 022225
Product Name: Sugammadex Sodium Injection, 100 mg/mL
Indication: Routine reversal of moderate or deep NMB by rocuronium or vecuronium
Sponsor/Applicant Name: Organon USA, Inc., a subsidiary of Merck & Co., Inc.

Meeting Chair: Rigoberto Roca, MD, Deputy Director, DAAAP
Meeting Recorder: Diana Walker, PhD, Sr. Regulatory Project Manager, DAAAP

Merck/Organon Representatives	Title
Christopher Assaid, PhD	Senior Principal Scientist, Biostatistics
Mark Forman, MD	Clinical Pharmacology
Dori Glassner	Director, Regulatory Affairs
Tamra Goodrow, PhD	Executive Director, Regulatory
W. Joseph Herring, MD, PhD	Executive Director, Clinical Research
Jerald Schindler, PhD	Associate Vice President, Biostatistics
David Michelson, MD	Vice President, Clinical Research
K. Chris Min, MD, PhD	Senior Principal Scientist, Clinical Pharmacology
Cynthia Silber, MD	Senior Principal Scientist, Drug Safety
Jayne Ware	Director, Regulatory Affairs
Sandra Milligan, MD	Senior Vice President, Regulatory Affairs
Bryan Kropp	Executive Director, Clinical Data Management
FDA	**Title**
Sharon Hertz, MD	Division Director, DAAAP
Rigoberto Roca, MD	Deputy Director, DAAAP
Arthur Simone, MD, PhD	Medical Officer, DAAAP
Freda Cooner, PhD	Biostatistics Team Leader, Division of Biometrics II (DBII)
Janice Pohlman, MD, MPH	Team Lead, GCPAB, DCCE, OSI
Kassa Ayalew, MD, MPH	Branch Chief, GCP Assessment Branch, DCCE, OSI
Martin Pollock	Safety Evaluator, Division of Pharmacovigilance, OSE
Diana Walker, PhD	Sr. Regulatory Project Manager, DAAAP

1.0 BACKGROUND

NDA 022225 received a Complete Response letter on September 20, 2013. The October 22, 2014, resubmission received a Complete Response letter dated April 22, 2015. The Applicant requested an End-of-Review meeting to discuss the deficiency in the April 22, 2015, letter and to obtain agreement on the Applicant's plan to address the deficiency, specifically, the proposed sensitivity analysis and supporting documents. The Applicant received responses to their meeting questions via email on June 5, 2015. The Applicant provided a handout for the meeting, which is appended to these meeting minutes.

2.0 DISCUSSION

The Sponsor's original questions are incorporated below in *italics* followed by the FDA preliminary responses in **bold** font. Discussions that took place during the meeting are captured following the question to which it pertains in normal text.

Sensitivity Analyses

Merck proposes to provide the requested sensitivity analyses as described in Section 6 of the background document.

Question 1. *Does the Agency agree that Merck's proposals, as described in Section 6, will address the requests for sensitivity analyses described in points 1), 1a) and 1b) of the Complete Response Letter dated April 22, 2015?*

Agency Response:
Your proposed approach to provide cumulative summaries is acceptable. Additionally, although all subjects were enrolled prior to March 11, 2014, adverse event data was collected both before and after March 11, 2014. Therefore, as previously required:

> ***Perform a sensitivity analysis comparing the study findings prior to and after the unblinding and also when blinding was re-established. Include an evaluation of the incidence rate and types of adverse events for the following time intervals:***
>
> - ***Time Interval 1: Prior to March 11, 2014 (data given to company statistician possible unblinding)***
> - ***Time Interval 2: Between March 11, 2014 and April 8, 2014 (unblinded period)***
> - ***Time Interval 3: After April 8, 2014 (blinding possibly re-established)***

In addition to the cumulative summaries that you propose to provide, provide case-by-case documentation for all changes that were made to adverse event and hypersensitivity case

reports from March 11, 2014, until database lock, including changes made in the course of data management/screening/cleaning.

Your meeting background document describes two separate Per Protocol groups (i.e., PP1 and PP2) for whom cumulative summaries will be provided. PP1 excludes all subjects with major protocol deviations. Major protocol violations were not clearly defined in the protocol or the Clinical Study Report. Provide your definition of major protocol deviations used for Study P101. Provide a list of all protocol deviations that occurred during Study P101, divided into major and minor classifications, as determined by you, for review prior to your resubmission.

Discussion

The Applicant stated that they plan to provide both cumulative and interval-based summaries. The Applicant stated that very few adverse event terms changed between the intervals, but proposed that they will provide a full listing between the two intervals. The Agency agreed that the proposal was acceptable.

Regarding the documentation of case-by-case changes between intervals to hypersensitivity reports, the Applicant proposed to provide: 1) if the encoded term changed between intervals, 2) an audit trail list, 3) AE encoded term and causality, and 4) the hypersensitivity yes/no field. The Agency agreed that this proposal appears to be acceptable, but once the information is submitted further information may be requested if necessary.

The Applicant reviewed the appended handout regarding the definition of protocol deviations, separation of roles, and categories of deviations.

The Agency asked the Applicant to clarify the definition of major versus minor deviations as it relates to the sensitivity analysis. The Applicant stated that, as this was a safety study, no subjects were ever intended to be excluded for any analyses, including all the sensitivity analyses requested by the Agency. However, subjects with major protocol deviations may be removed for additional sensitivity analyses.

As outlined in slide 5 of the handout, the Applicant stated that there were minor protocol deviations regarding dosing that occurred at study site 002. The Agency asked about the timing of the protocol deviations. The Applicant responded as follows:

Observation1a: Vital sign measurement of one group February 3
Dosing of a different group February 24
Observation 1b: Dosing of a subject February 3, who subsequently withdrew from the study.
Collection of AE information from the subject March 17
Observation 1c/1d/1e: predose activities/dosing of the same 3 subjects February 12/13

The Agency asked for further information on the timing and reason for study withdrawal for the subject in Observation 1b. The Applicant stated that no reason for withdrawal was provided by the subject, but that the withdrawal occurred approximately one month after dosing.

The Agency asked whether, based on observations at the recent site inspections, subjects were excluded from the analysis. The Applicant stated that no subjects were excluded from the analysis, but they were flagged. One observation was the duration of the bolus administration of the study drug. Although several major protocol deviations were cited for the duration of bolus administration being too long, this was a pre-defined, pre-specified protocol deviation, and thus, these subjects were not excluded from the analysis.

The Applicant stated they will provide a list of all protocol deviations that occurred during Study P101, divided into major and minor classifications for review prior to the resubmission and asked whether the Agency will provide feedback. The Agency stated that, unless there are any concerns raised during review of the list, no feedback will be provided.

Source Documents

Merck proposes to provide the following source documents, as described in Section 6, to support the inclusion of the remaining subjects incorporated in the reanalyses:

1. *Dosing records (with the initials of who administered study drug for each subject in each period)*
2. *AE records (with the initials of all those who participated in AE collection/assessment)*
3. *Targeted Hypersensitivity Assessments (THAs) with initials/signature of staff who performed the assessment*

In addition, the Roles and Responsibility logs for each site will be provided as this document includes the signatures and initials of each staff member involved in the study.

Question 2. Does the Agency agree with Merck's proposed list of source documents?

Agency Response:
Yes, we agree with the proposed list; however, send this information for all of the subjects in the study and identify the subset of subjects included in the analysis. Refer to the comments in Question 1 for additional listings requested.

Discussion
The Applicant asked for clarification of "Refer to the comments in Question 1 for additional listings requested." The Agency stated that this statement was to reinforce that all of the information and documents requested in the response to Question 1 are also requested. The Applicant agreed to provide the requested source documents.

Additional Comments:

1. **During the inspection, a communication (dated April 9, 2014) was noted from Site #3 (Dr. Gartner, (b) (4) Lincoln, NE) to (b) (4) IRB indicating that you**

made a request for the site to include a telephone follow-up call at least seven days following dosing to subjects who had experienced a potential hypersensitivity event.

a. **Clarify what prompted this change.**

b. **Clarify whether any other changes were made, at this site or the others, during the course of the study to follow-up potential hypersensitivity events.**

2. **Provide the MRL-IT Standard Operating Procedure (SOP) version regarding the Computing Platform Integration (CPI) system that was active prior to initiation of Study P101 in January 2014 and any revised versions after that date.**

Discussion
The Applicant agreed to provide the requested information.

3.0 ATTACHMENTS AND HANDOUTS

Handout titled "Merck's approach for assessment of major vs minor protocol deviations". Appended to these meeting minutes.

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/s/

DIANA L WALKER
06/23/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 022225

MEETING PRELIMINARY COMMENTS

Organon USA Inc., a subsidiary of Merck & Co., Inc.
126 E. Lincoln Avenue, P.O. Box 2000
RY34-B188
Rahway, NJ 07065-0900

Attention: Dori L. Glassner
Director, Global Regulatory Affairs

Dear Ms. Glassner:

Please refer to your New Drug Application (NDA) dated October 30, 2007, received October 31, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sugammadex Injection, 100 mg/mL.

We also refer to your October 22, 2014, submission, which constituted a complete response to our September 20, 2013, action letter, and to the Complete Response Letter dated April 22, 2015.

We further refer to your correspondence dated and received May 14, 2015, requesting an End-of-Review meeting to discuss the April 22, 2015, Complete Response letter. This submission also contained your meeting questions and meeting package.

Our preliminary responses to your meeting questions are enclosed.

You should provide to me a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me at (301) 796-4029.

Sincerely,

{See appended electronic signature page}

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

PRELIMINARY MEETING COMMENTS

Meeting Type: Type A
Meeting Category: End of Review

Meeting Date and Time: June 11, 2015, 12:00 p.m. (Eastern)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1419
Silver Spring, Maryland 20903

Application Number: NDA 022225
Product Name: Sugammadex Sodium Injection, 100 mg/mL
Indication: Routine reversal of moderate or deep NMB by rocuronium or vecuronium
Sponsor/Applicant Name: Organon USA, Inc., a subsidiary of Merck & Co., Inc.

Meeting Chair: Rigoberto Roca, MD, Deputy Director, DAAAP
Meeting Recorder: Diana Walker, PhD, Sr. Regulatory Project Manager, DAAAP

Merck/Organon Representatives	Title
Christopher Assaid, PhD	Senior Principal Scientist, Biostatistics
Mark Forman, MD	Clinical Pharmacology
Dori Glassner	Director, Regulatory Affairs
Tamra Goodrow, PhD	Executive Director, Regulatory
W. Joseph Herring, MD, PhD	Executive Director, Clinical Research
Jerald Schindler, PhD	Associate Vice President, Biostatistics
David Michelson, MD	Vice President, Clinical Research
K. Chris Min, MD, PhD	Senior Principal Scientist, Clinical Pharmacology
Cynthia Silber, MD	Senior Principal Scientist, Drug Safety
Jayne Ware	Director, Regulatory Affairs
FDA	**Title**
Sharon Hertz, MD	Division Director, DAAAP
Rigoberto Roca, MD	Deputy Director, DAAAP
Arthur Simone, MD, PhD	Medical Officer, DAAAP
Freda Cooner, PhD	Biostatistics Team Leader, Division of Biometrics II (DBII)
Janice Pohlman, MD, MPH	Team Lead, GCPAB, DCCE, OSI
Kassa Ayalew, MD, MPH	Branch Chief, GCP Assessment Branch, DCCE, OSI
Banu Karimi-Shah, MD	Clinical Team Leader, DPARP
Erika Torjusen, MD	Medical Officer, DPARP
Diana Walker, PhD	Sr. Regulatory Project Manager, DAAAP

Reference ID: 3775509

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for June 11, 2015, between Organon USA, Inc., a subsidiary of Merck & Co., Inc., and the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP). We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face-to-face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

1.0 BACKGROUND

NDA 022225 received a Complete Response letter on September 20, 2013. The October 22, 2014, resubmission received a Complete Response letter dated April 22, 2015. The Applicant requested an End-of-Review meeting to discuss the deficiency in the April 22, 2015, letter and to obtain agreement on the Applicant's plan to address the deficiency, specifically, the proposed sensitivity analysis and supporting documents.

The questions from the background package are shown below in *italic* font. The Division responses are shown in **bold** font.

2.0 DISCUSSION

Sensitivity Analyses

Merck proposes to provide the requested sensitivity analyses as described in Section 6 of the background document.

Question 1. *Does the Agency agree that Merck's proposals, as described in Section 6, will address the requests for sensitivity analyses described in points 1), 1a) and 1b) of the Complete Response Letter dated April 22, 2015?*

Reference ID: 3775509

Agency Response:
Your proposed approach to provide cumulative summaries is acceptable. Additionally, although all subjects were enrolled prior to March 11, 2014, adverse event data was collected both before and after March 11, 2014. Therefore, as previously required:

> ***Perform a sensitivity analysis comparing the study findings prior to and after the unblinding and also when blinding was re-established. Include an evaluation of the incidence rate and types of adverse events for the following time intervals:***
>
> - ***Time Interval 1: Prior to March 11, 2014 (data given to company statistician possible unblinding)***
> - ***Time Interval 2: Between March 11, 2014 and April 8, 2014 (unblinded period)***
> - ***Time Interval 3: After April 8, 2014 (blinding possibly re-established)***

In addition to the cumulative summaries that you propose to provide, provide case-by-case documentation for all changes that were made to adverse event and hypersensitivity case reports from March 11, 2014, until database lock, including changes made in the course of data management/screening/cleaning.

Your meeting background document describes two separate Per Protocol groups (i.e., PP1 and PP2) for whom cumulative summaries will be provided. PP1 excludes all subjects with major protocol deviations. Major protocol violations were not clearly defined in the protocol or the Clinical Study Report. Provide your definition of major protocol deviations used for Study P101. Provide a list of all protocol deviations that occurred during Study P101, divided into major and minor classifications, as determined by you, for review prior to your resubmission.

Source Documents

Merck proposes to provide the following source documents, as described in Section 6, to support the inclusion of the remaining subjects incorporated in the reanalyses:

1. *Dosing records (with the initials of who administered study drug for each subject in each period)*
2. *AE records (with the initials of all those who participated in AE collection/assessment)*
3. *Targeted Hypersensitivity Assessments (THAs) with initials/signature of staff who performed the assessment*

In addition, the Roles and Responsibility logs for each site will be provided as this document includes the signatures and initials of each staff member involved in the study.

Reference ID: 3775509

Question 2. Does the Agency agree with Merck's proposed list of source documents?

Agency Response:
Yes, we agree with the proposed list; however, send this information for all of the subjects in the study and identify the subset of subjects included in the analysis. Refer to the comments in Question 1 for additional listings requested.

Additional Comments:

1. **During the inspection, a communication (dated April 9, 2014) was noted from Site #3 (Dr. Gartner, (b) (4) Lincoln, NE) to (b) (4) IRB indicating that you made a request for the site to include a telephone follow-up call at least seven days following dosing to subjects who had experienced a potential hypersensitivity event.**

    a. **Clarify what prompted this change.**

    b. **Clarify whether any other changes were made, at this site or the others, during the course of the study to follow-up potential hypersensitivity events.**

2. **Provide the MRL-IT Standard Operating Procedure (SOP) version regarding the Computing Platform Integration (CPI) system that was active prior to initiation of Study P101 in January 2014 and any revised versions after that date.**

Reference ID: 3775509

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/s/

PARINDA JANI
06/05/2015
For Diana Walker

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 022225

MEETING REQUEST GRANTED

Organon USA Inc., a subsidiary of Merck & Co., Inc.
126 E. Lincoln Avenue, P.O. Box 2000
RY34-B188
Rahway, NJ 07065-0900

Attention: Dori L. Glassner
Director, Global Regulatory Affairs

Dear Ms. Glassner:

Please refer to your New Drug Application (NDA) dated October 30, 2007, received October 31, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sugammadex Sodium Injection, 100 mg/mL.

We also refer to your October 22, 2014, submission, which constituted a complete response to our September 20, 2013, action letter, and to the Complete Response Letter dated April 22, 2015.

We further refer to your correspondence dated and received May 14, 2015, requesting an End-of-Review meeting to discuss the April 22, 2015, Complete Response letter.

This submission also contained your meeting questions and constituted your meeting package. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting.

The meeting is scheduled as follows:

Date: June 11, 2015
Time: 12:00 p.m. (Eastern)
Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1419
Silver Spring, Maryland 20903

Invited CDER Participants:

Sharon Hertz, M.D.	Division Director, DAAAP
Rigoberto Roca, M.D.	Deputy Director, DAAAP
Arthur Simone, M.D., Ph.D.	Medical Officer, DAAAP
Freda Cooner, Ph.D.	Team Leader, Biometrics, Office of Biostatistics

Erika Torjusen, M.D.	Medical Officer, DPARP
Banu Karimi-Shah, M.D.	Clinical Team Leader, DPARP
Kassa Ayalew, MD, MPH	Branch Chief, GCP Assessment Branch, DCCE, OSI
Janice Pohlman, MD, MPH	Team Lead, GCPAB, DCCE, OSI
Diana Walker, Ph.D.	Sr. Regulatory Project Manager, DAAAP

Other FDA Attendees to be determined.

Please e-mail me any updates to your attendees at Diana.Walker@fda.hhs.gov, at least one week prior to the meeting. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least 10 days prior to the meeting. A foreign visitor is any non-U.S. citizen who does not have Permanent Resident Status or a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

A few days before the meeting, you may receive an email with a barcode generated by FDA's Lobbyguard system. If you receive this email, bring it with you to expedite your group's admission to the building. Ensure that the barcode is printed at 100% resolution to avoid potential barcode reading errors.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with either of the following numbers to request an escort to the conference room: Diana Walker, x64029; the Division secretary, x61602.

If you have any questions, call me at (301) 796-4029.

Sincerely,

{See appended electronic signature page}

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Foreign Visitor Data Request Form

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH **(MM/DD/YYYY)**	
PLACE OF BIRTH **(city and country)**	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	June 11, 2015, 12:00 p.m. (Eastern)
MEETING ENDING DATE AND TIME	June 11, 2015, 1:00 p.m. (Eastern)
PURPOSE OF MEETING	Industry Meeting
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	WO Bldg. 22, Room 1419
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	No
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	Diana Walker, PhD Sr. Regulatory Health Project Manager WO Bldg 22, Room 3240 301-796-4029
ESCORT INFORMATION (If different from Hosting Official)	N/A

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

/s/

DIANA L WALKER
05/15/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 022225
IND 068029

ACKNOWLEDGE ADDRESS CHANGE

Organon USA Inc., a subsidiary of Merck & Co., Inc.
126 E. Lincoln Avenue, P.O. Box 2000
RY34-B188
Rahway, NJ 07065-0900

Attention: Dori L. Glassner
Director, Global Regulatory Affairs

Dear Ms. Glassner:

We acknowledge receipt on February 24, 2015, and April 9, 2015, of your correspondence to your NDA and IND respectively notifying the Food and Drug Administration (FDA) that the corporate address has been changed from

One Merck Drive P.O. Box 100
Whitehouse Station, NJ 08889

to

2000 Galloping Hill Road
Kenilworth, New Jersey 07033

for the following new drug application (NDA) and investigational new drug application (IND):

NDA 022225 for Sugammadex injection, 100 mg/mL.
IND 068029 for Sugammadex injection, 100 mg/mL.

We have revised our records to reflect this change.

Please cite the appropriate application number listed above at the top of the first page of all submissions to these applications. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia, and Addiction Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call me at (301) 796-4029.

Sincerely,

{See appended electronic signature page}

Diana L. Walker, Ph.D.
Sr. Regulatory Project Manager
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

DIANA L WALKER
05/07/2015

From:	Walker, Diana
To:	Glassner, D. (Dori)
Cc:	Goodrow, Tamra L
Subject:	RE: NDA 22-225: Proposal for next resubmission
Date:	Wednesday, May 06, 2015 8:21:51 AM
Attachments:	Plan for next resubmission.pdf

Dear Dori,

Please see the text below for the Division response to your proposed plan for resubmission (attached as a PDF):

On March 31, 2015, you provided you Plan for Resubmission via e-mail to the Division. We have reviewed the plan and have the following comments:

1. Your plans to include only the Post-Marketing Data (Module 5.3.6); Literature Reports (Module 5.4), and appropriate Module 1 documents, while excluding the Clinical Overview (Module 2.5), is acceptable provided no new clinical trials are completed prior to the time of resubmission.
2. Submitting the Safety Update Report (SUR) document in the same format as was used in the 2014 resubmission, including integrated data from the global clinical database displayed in pooled datasets as well as postmarketing data with specific relevant discussion of safety findings updated from 2014 submission, is acceptable provided an updated, searchable, integrated, postmarketing dataset is also included.
3. Provided there are no new clinical trials completed by the time of resubmission, there is no need to update the integrated clinical safety dataset and analyses that were submitted with the 2014 resubmission or during the review cycle for that resubmission.
4. It is acceptable to describe completed investigator-initiated studies in the post-marketing section of the SUR along with an updated clinical literature review and English translations of all literature (full texts) related to sugammadex.
5. The new cut-off date for the spontaneous post-marketing reports that will be included in the resubmission should be no more than 3 months before the date of the resubmission and should provide the data and discussion of cumulative from market launch to that date. Your plan to update the previously conducted analyses for hypersensitivity and cardiac post-marketing data is acceptable as is your proposal to not adjudicate reports of anaphylaxis, but instead count all reports of anaphylaxis in your totals.
6. Your plan to again adjudicate serious reports of hypersensitivity to identify any reports of anaphylaxis which may be represented by these reports, but not coded specifically as anaphylaxis is acceptable as is the plan to submit the postmarketing data consistent with the methods you used for the 2014 resubmission, i.e., including the following:
    - One PSUR
    - Cumulative adverse event summary tabulations
    - Line listings for the events of anaphylaxis, serious hypersensitivity, arrhythmia, hemorrhage, and bronchospasm
    - CIOMS forms for the events of anaphylaxis, hypersensitivity, arrhythmia, hemorrhage and bronchospasm
    - A line listing of all post-marketing SAEs
    - CIOMS forms and narratives of all post-marketing SAE

- Post-marketing datasets and definition document
- A line listing of post-marketing case numbers with hyperlinks to the CIOMS forms
- A line listing of cases derived from publications with hyperlinks to the literature report
- English translations of foreign literature reports

Any advance notice of your timeline for resubmission would be appreciated for planning purposes.

Warm regards,

Diana

From: Glassner, D. (Dori) [mailto:dori.glassner@merck.com]
Sent: Tuesday, March 31, 2015 2:27 PM
To: Walker, Diana
Cc: Goodrow, Tamra L
Subject: NDA 22-225: Proposal for next resubmission

Diana,
As discussed last week, we are anxious to resubmit as soon as possible following receipt of the CR letter in April. Therefore, as discussed, I am providing the proposal for our next resubmission. This proposal assumes a request for a Safety Update. During our conversation, you indicated that it may be possible to have this reviewed by the Medical Reviewer in about two weeks.
Do you want me to follow-up with an official submission?
As always, any questions please let me know.

Regards,
Dori
****

Dori L. Glassner
Regulatory Affairs
T: +1 732 594 2735
F: +1 732 594 1030
dori.glassner@merck.com
Merck and Co., Inc.
126 East Lincoln Avenue
PO Box 2000
Mailstop RY34-B188
Rahway, NJ 07065

Office location RY34-B1124
****

Notice: This e-mail message, together with any attachments, contains information of Merck & Co., Inc. (2000 Galloping Hill Road, Kenilworth, New Jersey, USA 07033), and/or its affiliates Direct contact information for affiliates is available at http://www.merck.com/contact/contacts.html) that may be confidential,

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PLAN FOR RESUBMISSION

This sugammadex resubmission will consist of Safety Update Report (SUR) (Module 5.3.5.3.3); Post-Marketing Data (Module 5.3.6); Literature Reports (Module 5.4), and appropriate Module 1 documents.

A Clinical Overview (Module 2.5) will not be provided since there are no new Merck-initiated clinical studies and all of the updated post-marketing information will be presented in the SUR.

Detailed below are the proposals for the updated presentation of clinical and post-marketing data.

SAFETY UPDATE

The SUR document will be the same format submitted in the 2014 resubmission including integrated data from the global clinical database displayed in pooled datasets as well as post-marketing data with specific relevant discussion of safety findings updated from presentations similar to the 2014 submission, as noted below. The SUR will also include updates as appropriate based on FDA comments received during the review of the 2014 resubmission.

Clinical Data

At the time of the 2015 NDA resubmission there will be no new completed Merck-initiated clinical studies or Merck-initiated clinical studies enrolling subjects. Therefore, there will be no updates to the integrated clinical safety dataset and analyses that were submitted with the 22 October 2014 NDA resubmission or during the review of that resubmission.

There are currently ongoing investigator-initiated studies (IIS); and three IIS studies have completed since the 2014 resubmission. Similar to the 2014 resubmission, these studies will be described in the post-marketing section of the SUR.

An updated clinical literature review and short English abstracts for literature related to sugammadex will be included.

Post-marketing Data

Consistent with the request of the Agency for the 2014 resubmission, Merck is proposing to provide the data and discussion of cumulative spontaneous post-marketing reports from market launch (2008) to a new cut-off date of 01 February 2015. It should be noted that due to the dynamic nature of the post-marketing database, cases included in the previous resubmission may have changed due to receipt of follow-up information.

Previously conducted analyses for hypersensitivity and cardiac post-marketing data will also be updated. Merck proposes not to adjudicate reports of anaphylaxis, but will count all reports of anaphylaxis in our totals, in keeping with the approach taken by the FDA in its background document for the Advisory Committee Meeting (provided to Merck on February 26, 2015). However, Merck will again adjudicate serious reports of hypersensitivity to identify any reports of anaphylaxis which may be represented by these reports, but not coded specifically as anaphylaxis.

In addition, consistent with the 2014 resubmission, the following updated information will be provided in this resubmission:

- one PSUR;
- cumulative adverse event summary tabulations;
- line listings for the events of anaphylaxis, serious hypersensitivity, arrhythmia, hemorrhage and bronchospasm;
- CIOMS forms for the events of anaphylaxis, hypersensitivity, arrhythmia, hemorrhage and bronchospasm events;
- a line listing of all post-marketing SAEs;
- CIOMS forms and narratives of all post-marketing SAE;
- post-marketing datasets and definition document;
- a line listing of post-marketing case numbers with hyperlinks to the CIOMS forms;
- a line listing of cases derived from publications with hyperlinks to the literature report; and
- English translations of foreign literature reports.

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

/s/

DIANA L WALKER
05/06/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 022225

MEETING MINUTES

Organon USA Inc., a subsidiary of Merck & Co., Inc.
126 East Lincoln Avenue
P.O. Box 2000, RY34-B188
Rahway, NJ 07065-0900

Attention: Dori L. Glassner
Director, Global Regulatory Affairs

Dear Ms. Glassner:

Please refer to your New Drug Application (NDA) dated October 30, 2007, received October 31, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sugammadex Sodium Injection, 100 mg/mL.

We also refer to the meeting between representatives of your firm and the FDA on March 4, 2015. The purpose of the meeting was to discuss the inspection observations for Study P101, conducted to support the October 14, 2014, resubmission.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-4029.

Sincerely,

{See appended electronic signature page}

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: FDA Requested Meeting
Meeting Category: Discussion of inspection findings

Meeting Date and Time: March 4, 2015 at 1:30 p.m. (Eastern)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1315
Silver Spring, Maryland 20903

Application Number: NDA 022225
Product Name: Sugammadex Injection, 100 mg/mL
Indication: Reversal of moderate or deep NMB by rocuronium or vecuronium
Sponsor/Applicant Name: Organon USA, Inc., a subsidiary of Merck & Co., Inc.

Meeting Chair: Rigoberto Roca, MD, Deputy Division Director, DAAAP
Meeting Recorder: Diana Walker, PhD, Sr. Regulatory Project Manager, DAAAP

Merck/Organon Representatives	Title
Tamra Goodrow	Executive Director, Regulatory Affairs
Sandra Milligan	Senior Vice President, Regulatory Affairs
Chris Min	Director, Clinical Research
Chan Beals	Chan Beals, Vice President, Clinical Research
Chris Assaid	Senior Principal Scientist, Biostatistics
Ray Bain	Vice President, Biostatistics
Ted Frank	Vice President, Compliance
Andy Lee	Senior Vice President, Clinical Research
Debbie Henderson	Executive Director, Regulatory Affairs
Jayne Ware	Director Regulatory Affairs
Phil Ronca	Associate Vice President, Clinical Operations
Sandy Tremps	Executive Director, IT Account Management
David Gutstein (Via telephone)	Executive Director, Clinical Research
Dori Glassner (Via telephone)	Director, Regulatory Affairs
David Michelson (Via telephone)	Vice President, Clinical Research
Joe Herring (Via telephone)	Executive Director, Clinical Research
FDA	**Title**
John Jenkins, MD	Director, Office of New Drugs
Curtis J. Rosebraugh, MD, MPH	Director, Office of Drug Evaluation II (ODE II)
Mary Parks, MD	Deputy Director, ODE II
Rigoberto Roca, MD	Deputy Director, DAAAP
Arthur Simone, MD, PhD	Medical Officer, DAAAP
Judith Racoosin, MD	Deputy Director for Safety, DAAAP
Sally Seymour, MD	Deputy Director for Safety, DPARP
Banu Karimi-Shah, MD	Clinical Team Leader, DPARP
Erika Torjusen, MD	Medical Officer, DPARP

Lisa LaVange, PhD	Director, Office of Biostatistics
Ni Aye Khin, MD	Director, Division of Clinical Compliance Evaluation (DCCE), OSI
Kassa Ayalew, MD, MPH (Via telephone)	Branch Chief, GCP Assessment Branch, DCCE, OSI
Janice Pohlman, MD, MPH	Team Lead, GCPAB, DCCE, OSI
Cynthia Kleppinger, MD	Medical Officer, GCPAB, DCCE, OSI
CDR Jonee Mearns, MSN, RN (Via telephone)	Investigator, Office of Regulatory Affairs
Judith Racoosin, MD	Deputy Director for Safety, DAAAP
Sara Stradley (Via telephone)	ADRA, ODE II
Diem-Kieu Ngo, CDR, USPHS (Via telephone)	Team Lead, Office of Executive Programs/Division of Advisory Committee and Consultant Management (OEP/DACCM)
Stephanie Begansky, PharmD LCDR, USPHS (Via telephone)	Designated Federal Officer, OEP/DACCM
Parinda Jani	Chief, Project Management Staff, DAAAP
Diana Walker, PhD	Sr. Regulatory Project Manager, DAAAP

1.0 BACKGROUND

NDA 022225 received a Not Approvable action letter on July 31, 2008, and a complete response to this letter was submitted on December 19, 2012. This submission ultimately received a Complete Response Letter (CRL) dated September 20, 2013. The Applicant submitted a response to this CRL on October 14, 2014. Routine Sponsor and clinical site inspections of Study P101 were requested by DAAAP. During these inspections, specific observations were made that are concerning to the Agency. The purpose of this meeting is to discuss the Office of Scientific Investigations inspection observations, primarily Observation #1 concerning the unblinding of the statisticians, which is of concern to the Agency.

2.0 DISCUSSION

The Applicant gave a brief introduction, indicating their concern over the unblinding of the statisticians that occurred during the study. The Applicant acknowledged that certain operational errors were made, but stated that they believe that the integrity of the study data was not compromised and that the study site staff and adjudicators were never unblinded. The Applicant presented PDF slides 1 through 10 regarding Observation 1a, describing the root cause of the inadvertent unblinding, and slides 11 through 14 discussing the topic of audit trails. These PDF slides are attached to these meeting minutes.

The Agency asked the Sponsor to clarify why, in this case, the dosing information was mapped to two variables, EXDOSE and EXIVDOSE, and why this data handling process had changed from the process used with the hypersensitivity study data submitted in 2012.

Discussion of Observation 1

The Applicant stated that the additional EXIVDOSE variable was added to distinguish an IV dose from an oral dose. As this additional variable was recently added it was inadvertently left off of the default list for blinding, and was left unhidden. Normally the blinded numeric fields in the Clinical Data Repository (CDR) would be hidden as 99999 and the blinded text fields would be left blank. In the case of EXIVDOSE, actual numbers were displayed (0, 25,100). The Applicant further clarified that, as the previous study submitted in 2012 had been analyzed using the former Sponsor, Schering-Plough's analysis platform, these trial data were collected and processed using the Merck data analysis platform, and thus the data were handled differently.

The Agency asked the Applicant to clarify why the statisticians were looking at the data when the trial was still ongoing, and whether there is any existing documentation, aside from attestations, as to who accessed the datasets.

The Applicant stated that, as the critical variables are normally suppressed, there are two reasons that the data are accessed during an ongoing trial: medical monitoring and file specification development. In the case of the CDR, there is a full audit trail, but in the case of the platform in question, the Computing Platform Integration (CPI) system, security clearance is required, but there is no automated audit system in the directory. However, datasets are read-only, and data fields cannot be changed and datasets cannot be deleted from the directory. The statistician who discovered the potential for unblinding was engaged in the process of developing specifications for preparing future datasets. During this process, the statistician saw three groups of numbers in the EXIVDOSE field and suspected those data might enable the treatment assignments to be identified. She attested that she did not link the fields to any subject IDs, which would have exposed treatment assignments for those subjects, and that she closed the dataset and reported it to her manager, who in turn reported the potential for unblinding to compliance the same day. A subsequent internal audit identified four of the 11 staff who had access to the unblinded datasets had actually accessed the datasets and two had downloaded them onto their computers.

The Agency asked whether the statisticians who access the database while a study is ongoing are familiar with the clinical protocol, and whether they communicate with the clinical sites or clinical study personnel.

The Applicant stated that, as they are developing specifications for the development of future datasets, the statisticians are familiar with the protocol. The Applicant also acknowledged that the statistician who discovered the unblinding could have contacted the clinical lead; however, the medical monitor stated that she did not communicate with him.

The Agency stated that, while it is recognized that the Applicant is in compliance with the current data handling regulations, it would be beneficial if additional audit processes were put into place so that attestations are not the only means of assessing an event such as this. The Applicant agreed and stated that they have initiated adding an additional audit trail system.

The Agency noted particular concern with the current potential data integrity situation with this second repeat-dose hypersensitivity study, given the data integrity problems that were found with

the first repeat-dose hypersensitivity study in the previous review cycle. The Applicant affirmed that the attestations are the only information available that can be relied on, in the absence of any automated system that identified who accessed certain fields when in the CPI database. The Agency asked the Applicant to clarify why they did not inform the Agency of this event in real-time, when actions such as the initiation of an immediate inspection or advice on actions such as retaining the downloaded datasets could have been conveyed. The Applicant acknowledged that, while they did follow their internal processes, they did not report the event in real-time, which in hindsight would have been a good idea.

Discussion of Observation 2

The Applicant provided a background document, attached to these minutes, discussing the protocol deviation that occurred at one of the inspected sites. This protocol deviation concerned study personnel who performed both dosing and AE assessment duties in patients, although in this situation subjects were not assessed by the same individual who had given them the medication dose.

The Applicant explained that at one site it was asked if the individuals administering the study drug (doser) and assessing the reactions to it (assessor) could reverse roles on different patients. Another site had the same request a month prior and that site was told by the medical monitor that the doser could not be engaged with any other additional activity with the study, including assessing adverse events. However, the study monitor agreed to allow the second site to have the doser assess adverse events. When this decision was brought to the attention of the supervisor of the medical monitor, the site was informed that role reversal was not acceptable, and that the role of doser or assessor should be exclusive. The two study personnel who had already switched roles were dismissed from the study. Additionally, six subjects were identified as protocol deviations and reported as such in the Clinical Study Report, although none of the subjects were dosed and assessed by the same person. The Applicant stated that a sensitivity analysis excluding the six subjects had not been done, but offered to do so.

Post Meeting Note
We note your plan to add an additional audit trail. However, an audit trail usually just identifies changes to data fields with time/date stamps and does not necessarily create flags for every instance that a dataset was read. Beyond the additional audit trail, provide a plan to make access to the system more transparent.

3.0 ACTION ITEMS

1. The Agency will assess the information provided by the Applicant and discussed during the meeting and will determine whether the integrity of the data for study P101 can be relied upon to support both the NDA approval and the Agency's presentation of the application to the Advisory Committee. As the Advisory Committee meeting is scheduled for March 18, 2015, the Agency will discuss this issue internally and decide whether the meeting should go forward as planned or should be postponed.

2. The Agency will inform the Applicant as to whether a sensitivity analysis of the study should be provided.

4.0 ATTACHMENTS AND HANDOUTS

The following documents were provided by Merck for the March 4, 2015, meeting:

(a) Background document for the March 4, 2015 meeting regarding sugammadex Inspection Observations

(b) Overview of Observation 1a, CPI & Audit Trail (MK8616-101)

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/s/

DIANA L WALKER
04/08/2015

PeRC Meeting Minutes
March 4, 2015

PeRC Members Attending:
Lynne Yao
Rosemary Addy
Jane Inglese
Hari Cheryl Sachs
Wiley Chambers
Tom Smith
Karen Davis-Bruno
Peter Starke (did not review Non Responsive and Bridion)
Andrew Mulberg
Gregory Reaman
Daiva Shetty (only reviewed Non Responsive
Shrikant Pagay
Andrew Mosholder
Freda Cooner
Gilbert Burckart for Lily Mulugeta
Nisha Jain (Non Responsive
Barbara Buch Non Responsive
Robert Nelson
Maura O'Leary (only reviewed Non Responsive Bridion, Non Responsive
Dianne Murphy
Sonal Vaid Non Responsive

Agenda

Non Responsive			
NDA	22225	Bridion (sugammadex) Deferral/Plan	Reversal of moderate or deep neuromuscular blockade induced by rocuronium or vecuronium
Non Responsive			

Non Responsive

Bridion (sugammadex) Deferral/Plan

- NDA 22225 seeks marketing approval for Bridion (sugammadex) for reversal of moderate or deep neuromuscular blockade induced by rocuronium or vecuronium.
- The application triggers PREA as directed to a new active ingredient.
- The application has a PDUFA goal date of April 22, 2015.
- The Division clarified that an iPSP was not submitted as part of this application because it was a fourth cycle review (three previous complete responses). This product will be discussed at an upcoming advisory committee meeting. The efficacy of the product has been established but there continue to be serious safety concerns (e.g., immunogenicity, anaphylaxis, and hypersensitivity reactions) that may prevent approval and will be discussed at the AC meeting. The Division note, however, that these safety concerns would not necessarily need to be studied post-approval. Therefore, if the product is approved pediatric studies could be initiated without delay due to safety concerns.
- *PeRC Recommendations:*

- The PeRC agreed with a deferral for all pediatric patients because adult studies have been completed and the product is ready for approval.
- The PeRC recommended that after the AC meeting, if the Division moves towards an approval, the timeline for pediatric studies should be advanced significantly. The protocol should be submitted in 2015, and the study completion and final study report submission dates should be advanced accordingly.

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/s/

JANE E INGLESE
03/15/2015

From:	Walker, Diana
To:	Goodrow, Tamra L (tamra_goodrow@merck.com); dori.glassner@merck.com
Subject:	NDA 22225 Clinical Information Request 04Mar2015
Date:	Wednesday, March 04, 2015 9:30:04 AM
Importance:	High

Dear Dori and Tamra,

I have received a clinical information request. Please provide the following as soon as possible:

In your AE dataset, in the safety population (i.e., ASTY=1) there are 3,731 rows for which there is subject information but no information regarding an adverse event.

Clarify whether there were adverse events for these subjects receiving these treatments. If so, provide the missing information; if not, provide an explanation as to why these rows are included in the dataset.

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
03/04/2015

From: Walker, Diana
To: dori.glassner@merck.com; Goodrow, Tamra L (tamra_goodrow@merck.com)
Subject: NDA 22225 Clinical Information Request #2 02Mar2015
Date: Monday, March 02, 2015 5:14:28 PM
Importance: High

Dear Dori and Tamra,

I have received a second clinical information request today. Please provide the following as soon as possible:

In P07981, two subjects were reported to have adverse events related to muscle weakness, 000020 and 000023. Provide a description of how these adverse events manifested themselves and the treatments, if any, that were taken to treat these events.

Also in P07981, the protocol describes other clinical exploratory endpoints in section 9.5.2.1.5 on p. 59 of the final study report. Specifically, it refers to

- **Number of respiratory therapist bedside visits for management of respiratory events and the time of each visit.**

- **Number of airway interventions and type of airway intervention (e.g., increase in O2, jaw thrust, placement of an oral/nasal airway, Laryngeal Mask Airway (LMA), intubation).**

On p. 98 of the document, under section 11.6, it states:

Bedside visits by the PACU nurse, physician or respiratory therapist to assess/manage the respiratory status which were reported for two subjects in each

treatment group are presented in [14.2.10.9]. An airway intervention was reported for one subject treated with sugammadex (increase in O2) and two subjects from the usual care group (increase in O2, Continuous Positive Airway Pressure (CPAP)).

Confirm whether these were the only airway interventions made in the study and provide any additional information available about them, e.g., why were the interventions considered necessary, why was CPAP used (was increased O_2 tried but did not resolve the issue).

Warm regards,

Diana

From: Walker, Diana
Sent: Monday, March 02, 2015 1:37 PM
To: dori.glassner@merck.com; Goodrow, Tamra L (tamra_goodrow@merck.com)
Subject: NDA 22225 Clinical Information Request 02Mar2015

Dear Dori and Tamra,

I have received a clinical information request. Please provide the following as soon as

possible:

For Study P07981, provide a list of the subjects who received doses of sugammadex and neostigmine exceeding the protocol-prescribed doses (you report 14 for sugammadex and 2 for neostigmine), along with the actual dose administered and the reason provided by the investigator for exceeding the prescribed dose.

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
03/03/2015

From: Walker, Diana
To: dori.glassner@merck.com; Goodrow, Tamra L (tamra_goodrow@merck.com)
Subject: NDA 22225: 3nd Follow-up to Response to FDA request for Information 24Feb15
Date: Friday, February 27, 2015 10:15:32 AM
Importance: High

Dear Dori and Tamra,

I received an additional set of follow-up questions concerning the datasets. Please note that #6 is very similar to the information request sent on February 24, but is more extensive. You can combine the response to those two requests. Please submit the information as soon as possible by email, followed by a submission to your NDA – you can combine all of the 3 sets of responses into one NDA submission. If at all possible, please send me the responses via email by Monday, March 2.

Submit or indicate where in the latest submission the following (#1 – 4) can be found:

1. **Total number of subjects who had an AE over the entire clinical development program broken down by treatment and dose.**
2. **Total number of subjects who had an SAE over the entire clinical development program broken down by treatment and dose.**
3. **Total AE counts for the entire clinical development program broken down by treatment and dose.**
4. **Total SAE counts for the entire clinical development program broken down by treatment and dose.**

5. **Provide a description of the steps that were taken to modify the 10/22/14 version of the DOSING dataset to develop the version submitted to FDA on 2/20/15.**
6. **In our counts of unique subjects in the remaining safety datasets, using both JMP and SAS, the Division has come up with the following values:**
   - **3,965 in the AE dataset**
   - **286 in the ECG dataset**
   - **117 in the ADJHYPS dataset**
   - **5,276 in the MEDANEST dataset (exceeds the 4,466 in the Merck count)**
   - **3,552 in the NEUROMUS dataset**
   - **4,941 in the RECOVDAT dataset (exceeds the 4,466 in the Merck count)**
   - **1,573 in the TEMPERAT dataset**
   - **6,634 in the VITALSIG dataset (exceeds the 4,466 in the Merck count)**
   - **6,723 in the MEDICATI dataset (exceeds the 4,466 in the Merck count)**
   - **6,734 in the GENMEDIC dataset (exceeds the 4,466 in the Merck count)**
   - **6,735 in the EOT dataset (exceeds the 4,466 in the Merck count)**
   - **61 in the SAFLAB_V dataset**

   Confirm which of these counts match your analyses and determine whether the steps taken to partially rectify the differences between FDA and Merck for the DOSING counts should be taken with these datasets as well.

Regards,

Diana

From: Walker, Diana
Sent: Thursday, February 26, 2015 9:16 AM
To: dori.glassner@merck.com; Goodrow, Tamra L (tamra_goodrow@merck.com)
Subject: NDA 22225: 2nd Follow-up to Response to FDA request for Information 24Feb15

Dear Dori and Tamra,

I received a second follow-up concerning the datasets. Sorry for the delay.

Please confirm whether the number of unique subjects (USUBJID) were:

286 in the ECG dataset
117 in the ADJHYPS dataset
5,276 in the MEDANEST dataset (exceeds the 4,466 in the Merck count)
3,552 in the NEUROMUS dataset
4,941 in the RECOVDAT dataset (exceeds the 4,466 in the Merck count)
1,573 in the TEMPERAT dataset
6,634 in the VITALSIG dataset (exceeds the 4,466 in the Merck count)
6,723 in the MEDICATI dataset (exceeds the 4,466 in the Merck count)
6,734 in the GENMEDIC dataset (exceeds the 4,466 in the Merck count)

In addition, the following datasets also have 6,735 unique subjects by our counts:
EOT
SAFLAB

Regards,

Diana

From: Walker, Diana
Sent: Wednesday, February 25, 2015 6:33 PM
To: dori.glassner@merck.com; Goodrow, Tamra L (tamra_goodrow@merck.com)
Subject: NDA 22225: Follow-up to Response to FDA request for Information 24Feb15
Importance: High

Dear Dori and Tamra,

As a follow-up to our teleconference this afternoon, here is a list of the main items our review team is requesting. Please send me this information via email as soon as possible, followed by a submission to your NDA. We would appreciate the email submission by Thursday if possible or if not by Friday at noon. Please contact me if you want to discuss the timeline.

1. **Modify the TRTACT column in the DOSING, and all of the other files in your ISS that contain the TRTACT column, to differentiate the placebo treatments that were administered intravenously from those that were administered as skintests. Use of the terms "pbo" and "skintest pbo" is preferred. Submit the revised dataset(s) to the NDA.**

2. **In the Define.pdf file, provide the labels for TRTSEQA and TRTSEQP, which currently are labeled "over)" and provide comments for those variables that currently have digits that are not defined, e.g., in DOSING, NMBCMPND.**

3. **Provide the location of the ISS table with the exposure summaries. Provide SAS programs in .txt format that generate the ISS table and that define all of the variables including "subset01". Modify the define.pdf file to include these definitions in the comment column.**

4. **There are 6,735 unique subjects listed in the DEMOG dataset (substantially more than the 4,466 stated as being in the development program). Please determine whether the original problem affecting the DOSING dataset has also affected this one, and if so, revise the dataset send it back as soon as possible. The AE data set similarly has more unique subjects in it than the stated 4,466.**

Regards,

Diana

From: Goodrow, Tamra L [mailto:tamra_goodrow@merck.com]
Sent: Friday, February 20, 2015 3:39 PM
To: Walker, Diana
Cc: Glassner, D. (Dori)
Subject: NDA 22225: Response to FDA request for information

Dear Diana,
Dori is out of the office this afternoon so I am forwarding our response to your request of February 18, 2015. The content of the attachments to this e-mail are as follows:

- The "efficacy-information-amendment-20Feb2015.pdf" file contains Merck's response to the FDA's request

- The "dosing.xpt" file is the revised DOSING dataset

- The "define.pdf" file is the Data Definitions document that was written to assist the reviewer in understanding the organization of the DOSING dataset

Please note that we will submit these documents, in the appropriate CTD format through the electronic gateway on Monday, February 23.

Please give me a call at 215 305-6677 if you have any questions or if I can be of further assistance.

Thank you.
With regards,
Tamra

Tamra Goodrow, PhD
Global Regulatory Affairs
Merck Research Laboratories,
Upper Gwynedd, PA

Phone: (267) 305-6677
e-mail: tamra_goodrow@merck.com

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From: Walker, Diana
To: dori.glassner@merck.com; Goodrow, Tamra L (tamra_goodrow@merck.com)
Subject: NDA 22225: 2nd Follow-up to Response to FDA request for Information 24Feb15
Date: Thursday, February 26, 2015 9:16:02 AM

Dear Dori and Tamra,

I received a second follow-up concerning the datasets. Sorry for the delay.

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Importance: High

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Thank you.
With regards,
Tamra

Tamra Goodrow, PhD
Global Regulatory Affairs
Merck Research Laboratories,
Upper Gwynedd, PA

Phone: (267) 305-6677
e-mail: tamra_goodrow@merck.com

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From: Walker, Diana
To: dori.glassner@merck.com; Goodrow, Tamra L (tamra_goodrow@merck.com)
Subject: NDA 22225: Follow-up to Response to FDA request for Information 24Feb15
Date: Wednesday, February 25, 2015 6:33:28 PM
Importance: High

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4. **There are 6,735 unique subjects listed in the DEMOG dataset (substantially more than the 4,466 stated as being in the development program). Please determine whether the original problem affecting the DOSING dataset has also affected this one, and if so, revise the dataset send it back as soon as possible. The AE data set similarly has more unique subjects in it than the stated 4,466.**

Regards,

Diana

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Sent: Friday, February 20, 2015 3:39 PM
To: Walker, Diana
Cc: Glassner, D. (Dori)
Subject: NDA 22225: Response to FDA request for information

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- The “efficacy-information-amendment-20Feb2015.pdf” file contains Merck’s response to the FDA’s request

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Please give me a call at 215 305-6677 if you have any questions or if I can be of further assistance.

Thank you.
With regards,
Tamra

Tamra Goodrow, PhD
Global Regulatory Affairs
Merck Research Laboratories,
Upper Gwynedd, PA

Phone: (267) 305-6677
e-mail: tamra_goodrow@merck.com

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From:	Walker, Diana
To:	dori.glassner@merck.com
Subject:	NDA 22225 Clinical Information Request 18Feb2015
Date:	Wednesday, February 18, 2015 5:36:30 PM
Importance:	High

Dear Dori,

We have the following information request. Please respond via email as soon as possible, or by Friday, February 20, 2015. If you have any questions about this timeline, please contact me.

In the ISS (p. 51 of the current submission), you list 5,999 total exposures to IV sugammadex in 4,466 unique subjects. However, the dosing data set provided (DOSING) has only 3,238 unique subjects exposed to IV sugammadex and under 5,000 total exposures. Clarify the discrepancy and indicate how the correct values can be obtained from the ISS datasets.

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
02/27/2015

Walker, Diana

From: Walker, Diana
Sent: Wednesday, January 21, 2015 3:12 PM
To: dori.glassner@merck.com
Subject: NDA 22225 Clinical Information Request 21Jan15

Importance: High

Dear Dori,

I have received the following information request from our review team. Please respond to me as soon as possible, or no later than Monday, January 26, 2015, via email. Please follow this email with an official submission to your NDA 22225.

Please respond to the following:

Your submission dated October 21, 2014, is currently under review. We have the following request(s) for information:

In our review of the clinical adverse event line listings (Module 5.3.5.4, pages 7-89), we have identified a number of subjects whose adverse events would meet the agreed-upon definition of potential hypersensitivity as listed in the Signs and Symptoms of Hypersensitivity (Module 5.3.5.4, Section 12.6) and identified by the Targeted Hypersensitivity assessment. However, these subjects were not included in your evaluation of potential hypersensitivity cases. We have provided a listing of these subjects in Table 1 below. **Provide clarification as to why these subjects/AEs were not included in the list of subjects with potential hypersensitivity.**

Table 1. Clinical Adverse Events Not Included as Potential Hypersensitivity Cases

Subject	Adverse Event MedDRA Preferred Term (PT) [Adverse Event, Verbatim Term]
Placebo	
2078	Rhinorrhea [Runny Nose]
3034	Wheezing [Wheezing]
3056	Diarrhea [Loose Stools x12], Vomiting [Vomiting]
5079	Presyncope [Vasovagal Response]
6041	Dermatitis Contact [Contact Dermatitis Second ECG Lead]
Sugammadex 4mg/kg	
1014	Nausea [Nausea]
1019	Nasal Congestion [Nasal Congestion]
2007	Nausea [Nausea]
2027	Nausea [Nausea]
2053	Abdominal Discomfort [Stomach Upset], Abdominal Pain [Abdominal Cramps]
2057	Cough [Dry Cough]
3023	Pruritus [Pruritus to Bottom Right Foot]
3030	Nasal Congestion [Nasal Congestion], Nausea [Nausea]
3032	Rash [Red Patches Mid Chest at Nipple Line]
3036	Presyncope [Vasovagal Reaction to Blood Draw], Vomiting [Vomiting]
3048	Rash Macular [Red Patches Surrounding Mole Removal Area]

Reference ID: 3690401

Subject	Adverse Event MedDRA Preferred Term (PT) [Adverse Event, Verbatim Term]
3045	Hot flush [Hot Flash], Rash Pustular (Pustules Right Side of Face, Right Side of Nose]
4043	Dizziness [Dizziness due to sleep wake transition]
5002	Presyncope [Vasovagal Response]
5060	Presyncope [Intermittent Vasovagal response]
5067	Presyncope [Presyncope]
6040	Dermatitis Contact [Contact Dermatitis Secondary to ECG Leads]
6042	Nasal Congestion [Nasal Congestion]
Sugammadex 16mg/kg	
1017	Syncope [Syncope]
1025	Dysphonia [Hoarseness of Voice], Rash Vesicular [Vesicular Eruption]
2001	Dizziness [Dizziness]
2031	Abdominal Pain Upper [Stomach Cramps], Diarrhea [Loose Stools]
2062	Cough [Dry Cough Intermittent]
3035	Vomiting [Vomiting]
3054	Diarrhea [Loose Stools x5], Vomiting [Vomiting x10]
4044	Sneezing [Sneezing]
4053	Dizziness [Dizziness]
4056	Nausea [Nausea due to meal]
5004	Presyncope [Vasovagal Response]
5056	Presyncope [Vasovagal Response]
6016	Vomiting [Vomiting]
(Compiled by medical reviewer, Listing of Subjects With Clinical Adverse Events on pages 7-89, Module 5.3.5.4)	

Please feel free to contact me if you need clarification on this request.

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Email: Diana.Walker@fda.hhs.gov

Reference ID: 3690401

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/s/

DIANA L WALKER
01/21/2015

From: Walker, Diana
To: dori.glassner@merck.com
Subject: NDA 22225 DMEPA Information Request 05jan15
Date: Monday, January 05, 2015 9:28:42 AM

Dear Dori,

I have received a request from our DMEPA review team, who is reviewing your carton and container labeling. There is no need to submit to me via email, just submit to your NDA at your earliest convenience. Please respond to the following request:

Add the proprietary name, Bridion, to the container labels and carton labeling, and resubmit them for review.

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
01/06/2015

From: Walker, Diana
To: dori.glassner@merck.com
Subject: NDA 22225 DMEPA Information Request 05jan15
Date: Monday, January 05, 2015 9:28:42 AM

Dear Dori,

I have received a request from our DMEPA review team, who is reviewing your carton and container labeling. There is no need to submit to me via email, just submit to your NDA at your earliest convenience. Please respond to the following request:

Add the proprietary name, Bridion, to the container labels and carton labeling, and resubmit them for review.

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
01/05/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 022225

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Organon USA Inc.
P.O. Box 2000, RY34-B188
Rahway, NJ 07065-0900

ATTENTION: Dori L. Glassner
Director, Global Regulatory Affairs

Dear Ms. Glassner:

Please refer to your Class 2 resubmission for your New Drug Application (NDA), dated and received October 22, 2014, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Sugammadex Sodium Injection, 200 mg/2 mL and 500 mg/5 mL.

We also refer to your correspondence, dated and received October 23, 2014, requesting reconsideration of your proposed proprietary name, Bridion.

We have completed our review of the proposed proprietary name, Bridion and have concluded that it is acceptable.

If any of the proposed product characteristics as stated in your October 23, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Lisa Skarupa, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2219. For any other information regarding this application, contact Diane Walker, Regulatory Project Manager in the Office of New Drugs, at (301) 796-4029.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Deputy Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

KELLIE A TAYLOR
12/23/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 022225

ACKNOWLEDGE –
CLASS 2 RESUBMISSION

Organon USA Inc., a subsidiary of Merck & Co., Inc.
126 East Lincoln Avenue
P.O. Box 2000, RY34-B188
Rahway, NJ 07065-0900

Attention: Dori L. Glassner
Director, Global Regulatory Affairs

Dear Ms. Glassner:

We acknowledge receipt on your October 22, 2014, resubmission to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sugammadex Sodium Injection, 100 mg/mL.

We consider this a complete, class 2 response to our September 20, 2013, action letter. Therefore, the user fee goal date is April 22, 2015.

If you have any questions, call me at (301) 796-4029.

Sincerely,

{See appended electronic signature page}

Diana L. Walker, Ph.D.
Sr. Regulatory Project Manager
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

DIANA L WALKER
10/30/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 022225

MEETING MINUTES

Organon USA, Inc.
P.O. Box 2000, RY33-204
Rahway, NJ 07065

Attention: Dori L. Glassner
Director, Global Regulatory Affairs, Merck & Co., Inc.

Dear Ms. Glassner:

Please refer to your New Drug Application (NDA) dated October 30, 2007, received October 31, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sugammadex Sodium Injection, 100 mg/mL.

We also refer to the End-of-Review meeting between representatives of your firm and the FDA on November 21, 2013. The purpose of the meeting was to discuss the September 20, 2013, Complete Response letter.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-4029.

Sincerely,

{See appended electronic signature page}

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type A
Meeting Category: End of Review

Meeting Date and Time: November 21, 2013, 1:30 p.m. (Eastern)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1415
Silver Spring, Maryland 20903

Application Number: NDA 022225
Product Name: Sugammadex Sodium Injection, 100 mg/mL
Indication: Routine reversal of moderate or deep NMB by rocuronium or vecuronium, and immediate reversal of NMB at 3 minutes after administration of rocuronium
Sponsor/Applicant Name: Organon USA, Inc., a subsidiary of Merck & Co., Inc.

Meeting Chair: Christopher Breder, MD, PhD, Clinical Team Leader, DAAAP
Meeting Recorder: Diana Walker, PhD, Sr. Regulatory Project Manager, DAAAP

Merck/Organon Representatives	Title
Chan Beals, MD	VP, Clinical Pharmacology
Alison Chalker, PhD	Executive Director, Project Leadership
Hein Fennema, PhD	Director, Biostatistics
Dori Glassner	Director, Regulatory Affairs
Tamra Goodrow, PhD	Executive Director, Regulatory
David Gutstein, MD	Executive Director, Clinical Pharmacology
Ekopimo Ibia	Director, Regulatory Affairs
David Michelson, MD	VP, Clinical Research
Chris Min, MD	Principal Scientist, Clinical Pharmacology
Cynthia Silber, MD	Senior Principal Scientist, Drug Safety
Armin Szegedi, MD, PhD	Executive Director, Clinical Research
FDA	**Title**
Curtis J. Rosebraugh, MD, MPH	Director, ODE II
Bob A. Rappaport, MD	Division Director, DAAAP
Rigoberto Roca, MD	Deputy Director, DAAAP
Christopher Breder, MD, PhD	Clinical Team Leader, DAAAP
Arthur Simone, MD, PhD	Medical Officer, DAAAP
Janice Derr, PhD	Biostatistics Team Leader, Division of Biometrics II (DBII)
Yan Zhou, PhD	Biostatistics Reviewer, DBII
Amelia Luckett, MD	Medical Officer, DAAAP
Banu Karimi-Shah, MD	Clinical Team Leader, DPARP
Erika Torjusen, MD, MHS	Medical Officer, DPARP
Susan Limb, MD	Medical Officer, DPARP
Diana Walker, PhD	Sr. Regulatory Project Manager, DAAAP

1.0 BACKGROUND

NDA 022225 received a Not Approvable action letter on July 31, 2008, and submitted a complete response on December 19, 2012. This submission received a Complete Response Letter (CRL) dated September 20, 2013. The Sponsor requested an End-of-Review meeting to discuss CRL on October 25, 2013.

The purpose of this meeting is to obtain input and agreement on the Sponsor's plan to address the deficiency in the CRL received on September 20, 2013, specifically, the key elements of the proposed trial, a proposed cut-off date, and plans to present the new clinical and post-marketing data in the Safety Update.

2.0 DISCUSSION

The Sponsor's original questions are incorporated below in *italics* followed by the FDA preliminary responses in **bold** font. The discussion points sent by the Sponsor follow the Agency responses, again in *italics*. Discussions that took place during the meeting are captured following the question to which it pertains in normal text.

Hypersensitivity Study

Merck has evaluated the two options that were outlined in the Complete Response Letter and has decided to conduct a trial similar to study P06042 to confirm the results from this study and to address the deficiency.

The design of the proposed study is similar to P06042 with regard to the objectives, the administration of three doses of sugammadex each separated by approximately 5 weeks, and the number of subjects administered sugammadex 4 mg/kg. As in P06042, subjects with symptoms and/or signs of hypersensitivity will be referred to an independent blinded external Clinical Adjudication Committee. The key differences for the new proposed study from P06042 including a rationale for these changes are provided in Section 6 of the background package and the protocol concept sheet for the study is provided in Appendix 1 of the background package.

Question 1. *Does the Agency concur that the study as described in Appendix 1 of the background package will address the deficiency? Specifically, does the Agency agree with each of the key elements of the proposed study design for the new hypersensitivity trial?*

Agency Response:
We do not agree. (b) (4) **, in addition to the 4 mg/kg and placebo groups. Due to the serious data integrity concerns,** (b) (4)

(b) (4)
.

In addition, the protocol should ensure that administration (i.e., the method and duration of infusion) of the drug is standardized and consistent with the intended labeled use of the product.

Discussion

(b) (4)

The Agency (b) (4) stated that use of the 16 mg/kg dose may not be as rare as predicted by the Sponsor and, in fact, may be widely used in clinical practice. Examples of situations in which the high dose could be used include reversing paralysis at the end of surgeries; after a quick procedure where the patient should not be under anesthesia for an extended period, such as the setting of a fracture; and secondary to cultural pressure in the U.S. in comparison to Europe to move patients out of the operating room more quickly. Therefore, it is essential to collect safety data in order for the risks to be accurately characterized and included in the product labeling.

(b) (4)
. The Agency stated that the 16 mg/kg dose would still need to be evaluated because the use of the 16 mg/kg dose has been widely publicized through the previous Advisory Committee meeting, the medical literature, and is already approved and used in Europe. Because the 16 mg/kg dose has been promoted as a rescue medication, the likelihood of use by physicians in the situations described in the previous paragraph is very high. In order for physicians to make an informed risk-benefit decision, even in these emergency settings, the magnitude of the risk must be accurately characterized.

The Sponsor asked whether, (b) (4) they could provide a reassessment of the 16 mg/kg dose data from the previous study combined with other clinical data. The Agency agreed that this approach is a possibility, as outlined in option #1 in the Complete Response Letter. However, prior to any Agency agreement regarding the adequacy of this approach, the Sponsor should submit a detailed proposal to the Agency for review and comment.

The Agency told the Sponsor that the mode by which the drug is administered, either via pushing or infusing, as well as the total time it takes to administer, may play a role in the rate of

anaphylaxis and should be standardized in the protocol to best approximate the intended labeled use of the product, as there were some inconsistencies noted in the study P06042. The Sponsor agreed that the rate of administration may play a role in the rate of anaphylaxis, and for that reason the proposed study will clearly define the time of infusion to be 10 seconds, with deviation in the range of 7 – 15 seconds.

The Agency agreed that the Sponsor's attempts to standardize the procedures in the protocol and to mimic as closely as possible the manner in which the drug will be labeled for use are appropriate. The Agency also agreed that the design changes, other than the exclusion of the 16 mg/kg dosing arm in the proposed protocol compared to the original study, are acceptable.

Safety Update Report
Merck understands that the resubmission will need to include a Safety Update with new safety data as specified in the Complete Response Letter.

Clinical Studies: At the time of the NDA resubmission there will be limited new clinical data and when compared to the already extensive clinical database it is not anticipated that the safety data from these trials would alter the data and conclusions in the Safety Update submission in December 2012. Given this, there are no plans to update the integrated clinical safety dataset and analysis that were submitted with the NDA resubmission on December 20, 2012. The safety data from any new clinical studies would be summarized and provided to the Agency in the resubmission. For a clinical study that is ongoing at the time of the resubmission, we propose including interim safety data for only SAEs. All new clinical study reports will also be provided.

Question 2. Does the Agency agree that the safety data from any new clinical studies can be provided separately in the Safety Update and not integrated with the previous safety dataset?

Agency Response:
The integrated clinical safety data set and its analyses will need to be updated and included in the Complete Response. Data from all clinical studies completed at the time of the submission will need to be incorporated into the database and the analyses. A summary of the new safety data should be provided as proposed. Interim safety data from any ongoing studies may be submitted, but should not be incorporated into the safety database.

Discussion
The Sponsor stated that they understood the Agency response and agreed to submit the requested materials. The Agency stated that the Sponsor must ensure that the safety datasets contain the appropriate variables and preferred terms at the time of submission.

Post-marketing data: The cut-off date used for the post-marketing data included in the NDA resubmission in December 2012 was June 15, 2012. Subsequent to the December

2012 resubmission, we provided the PSUR with a reporting period of February 1, 2012 to January 31, 2013 and at the request of the FDA provided CIOMS forms for all postmarketing events from market launch to May 31, 2013. For the Safety Update in this new resubmission, Merck is proposing a cut-off date of approximately 6 months prior to the resubmission. The post-marketing data presented would be an interval update from the cut-off date in the previous resubmission (June 15, 2012) to the new cut-off date (6 months prior to the new resubmission). Additionally, we will provide CIOMS forms from June 1, 2013 to the new cut-off date. Previously conducted analysis for hypersensitivity post-marketing data would also be updated which will include the adjudication of any new cases of hypersensitivity.

Question 3. Does the Agency agree with Merck's proposed cut-off date and plans to present the new post-marketing data in the Safety Update?

Agency Response:
The 6-month cut-off date is acceptable, as is the submission of the new CIOMS forms as proposed. However, all post-marketing reports, from product launch to the cut-off date, must be incorporated into a searchable database that includes the following column headers:

1. **Case number**
2. **Country**
3. **Publication (if applicable)**
4. **Age**
5. **Gender**
6. **Product**
7. **Route**
8. **Dose**
9. **Date of treatment**
10. **Event onset date or time to onset**
11. **Event**
    a. **Verbatim term**
    b. **SOC**
    c. **Preferred term**
12. **SAE (y/n)**
13. **Severity**
14. **Patient outcome**
15. **As reported causality**
16. **Concomitant medications**

In addition, the case number needs to be linked to the narrative.

Your plan to update the previously conducted analysis for post-marketing hypersensitivity data along with the inclusion of the adjudication of any new cases of hypersensitivity is acceptable.

<u>Discussion</u>

The Sponsor stated that they understood the Agency response and agreed to submit a searchable database. The Sponsor asked for clarification on the column header "Publication" and whether the entry in this column should contain the publication citation. The Agency agreed, but stated that the citations also need to be hyperlinked to the actual publications in the submission.

3.0 ACTION ITEMS

3.1 The Agency agreed to review and comment on a detailed proposal to reassess the 16 mg/kg data from the previous study, if the Sponsor chooses to take this approach.

3.2 The Sponsor agreed to submit the clinical safety datasets configured as requested by the Agency.

3.3 The Sponsor agreed to submit a searchable database of the postmarketing safety reports, configured as requested by the Agency. The Sponsor also agreed to provide all referenced publications.

4.0 ATTACHMENTS AND HANDOUTS

None

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/s/

DIANA L WALKER
12/19/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 022225

MEETING PRELIMINARY COMMENTS

Organon USA, Inc.
P.O. Box 2000, RY33-204
Rahway, NJ 07065

Attention: Dori L. Glassner
Director, Global Regulatory Affairs, Merck & Co., Inc.

Dear Ms. Glassner:

Please refer to your New Drug Application (NDA) dated October 30, 2007, received October 31, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sugammadex Sodium Injection, 100 mg/mL.

We further refer to your correspondence dated and received October 25, 2013, requesting an End-of-Review meeting to discuss the September 20, 2013, Complete Response letter. This submission also contained your meeting questions and meeting package.

Our preliminary responses to your meeting questions are enclosed.

You should provide to me a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me at (301) 796-4029.

Sincerely,

{See appended electronic signature page}

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

PRELIMINARY MEETING COMMENTS

Meeting Type: Type A
Meeting Category: End of Review

Meeting Date and Time: November 21, 2013, 1:30 p.m. (Eastern)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1415
Silver Spring, Maryland 20903

Application Number: NDA 022225
Product Name: Sugammadex Sodium Injection, 100 mg/mL
Indication: Routine reversal of moderate or deep NMB by rocuronium or vecuronium, and immediate reversal of NMB at 3 minutes after administration of rocuronium
Sponsor/Applicant Name: Organon USA, Inc., a subsidiary of Merck & Co., Inc.

Meeting Chair: Christopher Breder, MD, PhD, Clinical Team Leader, DAAAP
Meeting Recorder: Diana Walker, PhD, Sr. Regulatory Project Manager, DAAAP

Merck/Organon Representatives	Title
Chan Beals, MD	VP, Clinical Pharmacology
Alison Chalker, PhD	Executive Director, Project Leadership
Hein Fennema, PhD	Director, Biostatistics
Dori Glassner	Director, Regulatory Affairs
Tamra Goodrow, PhD	Executive Director, Regulatory
David Gutstein, MD	Executive Director, Clinical Pharmacology
Ekopimo Ibia	Director, Regulatory Affairs
David Michelson, MD	VP, Clinical Research
Chris Min, MD	Principal Scientist, Clinical Pharmacology
Cynthia Silber, MD	Senior Principal Scientist, Drug Safety
Armin Szegedi, MD, PhD	Executive Director, Clinical Research
FDA	**Title**
Bob A. Rappaport, MD	Division Director, DAAAP
Rigoberto Roca, MD	Deputy Director, DAAAP
Christopher Breder, MD, PhD	Clinical Team Leader, DAAAP
Arthur Simone, MD, PhD	Medical Officer, DAAAP
Janice Derr, PhD	Biostatistics Team Leader, Division of Biometrics II (DBII)
Yan Zhou, PhD	Biostatistics Reviewer, DBII
Badrul Chowdhury, MD	Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Banu Karimi-Shah, MD	Clinical Team Leader, DPARP
Erika Torjusen, MD	Medical Officer, DPARP
Susan Limb, MD	Medical Officer, DPARP
Diana Walker, PhD	Sr. Regulatory Project Manager, DAAAP

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for November 21, 2013, between Organon USA, Inc., a subsidiary of Merck & Co., Inc., and the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP). We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

1.0 BACKGROUND

NDA 022225 received a Not Approvable action letter on July 31, 2008, and submitted a complete response on December 19, 2012. This submission received a Complete Response Letter (CRL) dated September 20, 2013. The Sponsor requested an End-of-Review meeting to discuss CRL on October 25, 2013.

The purpose of this meeting is to obtain input and agreement on the Sponsor's plan to address the deficiency in the CRL received on September 20, 2013, specifically, the key elements of the proposed trial, a proposed cut-off date, and plans to present the new clinical and post-marketing data in the Safety Update.

The questions from the background package are shown below in *italic* font. The Division responses are shown in **bold** font.

2.0 DISCUSSION

Hypersensitivity Study
Merck has evaluated the two options that were outlined in the Complete Response Letter and has decided to conduct a trial similar to study P06042 to confirm the results from this study and to address the deficiency.

The design of the proposed study is similar to P06042 with regard to the objectives, the administration of three doses of sugammadex each separated by approximately 5 weeks, and the number of subjects administered sugammadex 4 mg/kg. As in P06042, subjects with symptoms and/or signs of hypersensitivity will be referred to an independent blinded external Clinical Adjudication Committee. The key differences for the new proposed study from P06042 including a rationale for these changes are provided in Section 6 of the background package and the protocol concept sheet for the study is provided in Appendix 1 of the background package.

Question 1. *Does the Agency concur that the study as described in Appendix 1 of the background package will address the deficiency? Specifically, does the Agency agree with each of the key elements of the proposed study design for the new hypersensitivity trial?*

Agency Response:
We do not agree. (b) (4) **), in addition to the 4 mg/kg and placebo groups. Due to the serious data integrity concerns,** (b) (4)

In addition, the protocol should ensure that administration (i.e., the method and duration of infusion) of the drug is standardized and consistent with the intended labeled use of the product.

Safety Update Report
Merck understands that the resubmission will need to include a Safety Update with new safety data as specified in the Complete Response Letter.

Clinical Studies: At the time of the NDA resubmission there will be limited new clinical data and when compared to the already extensive clinical database it is not anticipated that the safety data from these trials would alter the data and conclusions in the Safety Update submission in December 2012. Given this, there are no plans to update the integrated clinical safety dataset and analysis that were submitted with the NDA resubmission on December 20, 2012. The safety data from any new clinical studies would be summarized and provided to the Agency in the resubmission. For a clinical study that is ongoing at the time of the resubmission, we propose including interim safety data for only SAEs. All new clinical study reports will also be provided.

Question 2. *Does the Agency agree that the safety data from any new clinical studies can be provided separately in the Safety Update and not integrated with the previous safety dataset?*

Agency Response:
The integrated clinical safety data set and its analyses will need to be updated and included in the Complete Response. Data from all clinical studies completed at the time of the

submission will need to be incorporated into the database and the analyses. A summary of the new safety data should be provided as proposed. Interim safety data from any ongoing studies may be submitted, but should not be incorporated into the safety database.

Post-marketing data: The cut-off date used for the post-marketing data included in the NDA resubmission in December 2012 was June 15, 2012. Subsequent to the December 2012 resubmission, we provided the PSUR with a reporting period of February 1, 2012 to January 31, 2013 and at the request of the FDA provided CIOMS forms for all postmarketing events from market launch to May 31, 2013. For the Safety Update in this new resubmission, Merck is proposing a cut-off date of approximately 6 months prior to the resubmission. The post-marketing data presented would be an interval update from the cut-off date in the previous resubmission (June 15, 2012) to the new cut-off date (6 months prior to the new resubmission). Additionally, we will provide CIOMS forms from June 1, 2013 to the new cut-off date. Previously conducted analysis for hypersensitivity post-marketing data would also be updated which will include the adjudication of any new cases of hypersensitivity.

Question 3. Does the Agency agree with Merck's proposed cut-off date and plans to present the new post-marketing data in the Safety Update?

Agency Response:
The 6-month cut-off date is acceptable, as is the submission of the new CIOMS forms as proposed. However, all post-marketing reports, from product launch to the cut-off date, must be incorporated into a searchable database that includes the following column headers:

1. **Case number**
2. **Country**
3. **Publication (if applicable)**
4. **Age**
5. **Gender**
6. **Product**
7. **Route**
8. **Dose**
9. **Date of treatment**
10. **Event onset date or time to onset**
11. **Event**
    a. **Verbatim term**
    b. **SOC**
    c. **Preferred term**
12. **SAE (y/n)**
13. **Severity**
14. **Patient outcome**
15. **As reported causality**
16. **Concomitant medications**

In addition, the case number needs to be linked to the narrative.

Your plan to update the previously conducted analysis for post-marketing hypersensitivity data along with the inclusion of the adjudication of any new cases of hypersensitivity is acceptable.

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/s/

DIANA L WALKER
11/19/2013

From:	Walker, Diana
To:	Glassner, D. (Dori)
Subject:	NDA 22225 Pediatric Plan Comments 12Nov13
Date:	Tuesday, November 12, 2013 1:22:39 PM
Importance:	High

Dear Dori,

As we discussed via telephone, we had not sent comments previously on your pediatric plan because the application was given a Complete Response. In light of your plans to submit a PPSR, we are providing preliminary comments on the plan submitted to your NDA in February 2013 to provide you with feedback on your plan. However, please note that these are preliminary comments, and that we will review in detail the PPSR that you plan to submit. As with all PPSRs, your plan will be reviewed by both the Division and the Pediatric Review Committee (PeRC).

We have the following comments regarding your proposed pediatric plan submitted to your NDA on February 13, 2013:

(b) (4)

1.

2.

3.

4.

5. [redacted] (b) (4)

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

From: Glassner, D. (Dori)
Sent: Monday, October 28, 2013 11:33 AM
To: 'Walker, Diana'
Subject: RE: Pediatric Plan

Diana,
I know that we never received any comments on the pediatric plan that we provided in Feb 2013. I was wondering if we can still expect to receive any comments now that we got the complete response letter. I didn't think the peds plan review was directly tied to the review of the previous resubmission, but I wanted to get your feedback on what our options might be in obtaining these comments and also for submitting a PPSR in light of the complete response letter.

Regards,
Dori
****

Dori L. Glassner
Regulatory Affairs
T: +1 732 594 2735
F: +1 732 594 1030
dori.glassner@merck.com
Merck and Co., Inc.
126 East Lincoln Avenue
PO Box 2000
Mailstop RY33-204
Rahway, NJ 07065

Office location RY32-217
****

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/s/

DIANA L WALKER
11/12/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 022225

MEETING REQUEST GRANTED

Organon USA, Inc.
P.O. Box 2000, RY33-204
Rahway, NJ 07065

Attention: Dori L. Glassner
Director, Worldwide Regulatory Affairs

Dear Ms. Glassner:

Please refer to your New Drug Application (NDA) dated October 30, 2007, received October 31, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sugammadex Sodium Injection, 100 mg/mL.

We also refer to your December 19, 2012, submission, which constituted a complete response to our July 31, 2008, action letter, and to the Complete Response Letter dated September 20, 2013.

We further refer to your correspondence dated and received October 25, 2013, requesting an End-of-Review meeting to discuss the September 20, 2013, Complete Response letter.

This submission also contained your meeting questions and constituted your meeting package. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting.

The meeting is scheduled as follows:

Date: November 21, 2013
Time: 1:30 p.m. (Eastern)
Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1415
Silver Spring, Maryland 20903

Invited CDER Participants:

Bob A. Rappaport, M.D.	Division Director, DAAAP
Rigoberto Roca, M.D.	Deputy Director, DAAAP
Christopher Breder, M.D., Ph.D.	Clinical Team Leader, DAAAP
Arthur Simone, M.D., Ph.D.	Medical Officer, DAAAP
Erika Torjusen, M.D.	Medical Officer, DPARP
Banu Karimi-Shah, M.D.	Clinical Team Leader, DPARP

Diana Walker, Ph.D. Sr. Regulatory Project Manager, DAAAP

Other FDA Attendees to be determined.

Please e-mail me any updates to your attendees at Diana.Walker@fda.hhs.gov, at least one week prior to the meeting. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least 10 days prior to the meeting. A foreign visitor is any non-U.S. citizen who does not have Permanent Resident Status or a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

A few days before the meeting, you may receive an email with a barcode generated by FDA's Lobbyguard system. If you receive this email, bring it with you to expedite your group's admission to the building. Ensure that the barcode is printed at 100% resolution to avoid potential barcode reading errors.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with either of the following numbers to request an escort to the conference room: Diana Walker, x64029; the Division secretary, x61602.

If you have any questions, call me at (301) 796-4029.

Sincerely,

{See appended electronic signature page}

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Foreign Visitor Data Request Form

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH **(MM/DD/YYYY)**	
PLACE OF BIRTH **(city and country)**	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	November 21, 2013, 1:30 p.m. (Eastern)
MEETING ENDING DATE AND TIME	November 21, 2013, 2:30 p.m. (Eastern)
PURPOSE OF MEETING	Industry Meeting
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	WO Bldg. 22, Room 1415
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	No
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	Diana Walker, PhD Sr. Regulatory Health Project Manager WO Bldg 22, Room 3240 301-796-4029
ESCORT INFORMATION (If different from Hosting Official)	N/A

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/s/

DIANA L WALKER
10/28/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 022225

GENERAL ADVICE

Organon USA Inc.
P.O. Box 2000, RY33-204
Rahway, NJ 07065

Attention: Dori L. Glassner
Director, Global Regulatory Affairs

Dear Ms. Glassner:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sugammadex Sodium Injection, 100 mg/mL.

The Division of Medication Error Prevention and Analysis (DMEPA) has the following comments on the Carton and Container labels for sugammadex:

1. All Container Labels and Carton Labeling

    a. Ensure that the term "TRADEMARK" is replaced by the proprietary name and revise it from appearing in all capital letters to appear in title case to improve readability (e.g., Trademark).

    b. Increase the size of the established name so that it is at least ½ the size of the proprietary name as set forth in 21 CFR 201.10(g)(2), which states that the established name should be displayed with size and prominence commensurate with the proprietary name taking into account all pertinent factors including typography, layout, contrast, and other printing features.

2. All Container labels (peel-off and vial)

    a. Relocate the word "injection" to appear on the same line as "(sugammadex [redacted] (b) (4)" to provide additional space for recommended label revisions.

    b. To provide further distinction between the two vial sizes, remove the proprietary and established name statements from the colored box. Only the strength statement should appear in the box, which uses a distinct color for each vial size.

    c. Remove the [redacted] (b) (4). Removal of this statement will provide greater space for the requested container label revisions. [redacted] (b) (4)

[redacted] (b) (4)

3. Peel-off Container Labels

   a. Relocate the concentration strength statement (100 mg/mL) to appear directly beneath the established name so that it appears in the primary viewing plane of the principal display panel. In its current location, the vial must be rotated to read the strength.

   b. Remove the total drug concentration statement (200 mg/2 mL or 500 mg/5 mL, as appropriate) from the peel-off section to reduce clutter and allow for display of other important information.

   c. Add the following directly beneath the concentration statement (100 mg/mL): "Total dose: ____mL" so that the total dosage volume contained in the dosing syringe may be transcribed on the peel off section of the label by the healthcare professional.

   d. Revise the route of administration on the label to read "For Intravenous Use Only" and place this statement in bolded font as the last line on the peel-off section of the label.

   e. The peel-off section of the container label should appear in line order as follows:

      Proprietary name
      Sugammadex [redacted] (b) (4) injection
      100 mg/mL
      Total dose: ____mL
      For Intravenous Use Only

4. Vial Container Labels

   a. Relocate the strength statement [e.g., 200 mg/ 2mL (100 mg/mL)] to appear directly beneath the established name and dosage form so that it appears in the primary viewing plane of the principal display panel. In its current location, the vial must be rotated to read the strength.

   b. Revise the route of administration on the vial label to read "For Intravenous Use Only."

   c. Revise the net quantity statement to read "2 mL single dose vial" or "5 mL single dose vial" as appropriate, if space permits.

   d. Relocate the "Rx only" statement to the bottom one-third of the label below the peel-off section as this distracts from important information on the principal display panel.

e. Remove the statement [redacted] (b) (4) as this contributes to clutter and distracts from important information on the principal display panel.

f. The vial container label may appear in line order as follows:

2 mL single dose vial or 5 mL single dose vial and NDC #
Proprietary name
Sugammadex [redacted] (b) (4) injection
200 mg/2 mL or 500 mg/5 mL
(100 mg/mL) (100 mg/mL)
For Intravenous Use Only
Rx Only
Storage: 25°C (77°F)
Protect from Light
Manufacturer statement

5. Carton Labeling

a. Ensure that the carton labeling uses a distinct trade dress color uniquely designated for each vial size on the corners and edges of the principal display, side, and back panels to further differentiate between the two vial sizes and help to minimize selection errors.

If you have any questions, call Diana L. Walker, Regulatory Project Manager, at (301) 796-4029.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

PARINDA JANI
10/02/2013

From: Walker, Diana
To: Glassner, D. (Dori)
Subject: NDA 22225 CMC labeling comments 27aug13
Date: Tuesday, August 27, 2013 5:55:50 PM

Dear Dori,

Per our teleconference today, we are sending written comments concerning the sugammadex established name, that were discussed during the call.

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)

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 non-proprietary 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).**

I will be out of the office from August 28 through September 3, but if you have any urgent questions, please send them to my supervisor Parinda Jani.

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
08/27/2013

From:	Walker, Diana
To:	Glassner, D. (Dori)
Subject:	NDA 22225 OSI Information Request 21aug13
Date:	Wednesday, August 21, 2013 8:29:10 AM
Importance:	High

Dear Dori,

I have the following information request from our Office of Scientific Investigations (OSI) team. Please respond to me via email as soon as possible, followed by an amendment to your NDA.

Regarding Site #2 (Ulrike Lorch in the UK) and the unblinding of some of the randomized subjects:
There was a DSMB for the study and it is not clear if they were made aware of the unblinding. Please submit all communications with the DSMB regarding this issue with Site #2 and all communications between the Sponsor/CRO and the site regarding this issue.

Thank you for your assistance.
Warm regards,
Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

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DIANA L WALKER
08/21/2013

From:	Walker, Diana
To:	Glassner, D. (Dori)
Subject:	NDA 22225 Container Labeling comments 15aug13
Date:	Thursday, August 15, 2013 10:43:05 AM

Dear Dori,

I have received the following comments from our CMC review team regarding your carton and container labeling. Please note that the DMEPA review team is still finalizing their review of your packaging labels, so additional comments pertaining to your carton and container labeling will likely be forthcoming in the next several weeks.

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."

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
08/15/2013

Walker, Diana

From: Walker, Diana
Sent: Wednesday, August 07, 2013 10:52 AM
To: Glassner, D. (Dori)
Subject: NDA 22225 Clinical Information Request 07August13

Importance: High

Dear Dori,

I have received an information request from the clinical reviewer of your NDA 22225. Please submit the following requested information to me via email, followed by an official submission to your NDA.

Provide the following information using the updated database, i.e., the pooled Phase 1-3 studies that were used in the 2012 submission, to provide the following:

- **Mean changes in systolic blood pressure from baseline in the pooled Phase 1-3 placebo-controlled trials**
- **Mean changes in systolic blood pressure from baseline in the pooled Phase 1-3 neostigmine-controlled trials**
- **Mean changes in diastolic blood pressure from baseline in the pooled Phase 1-3 placebo-controlled trials**
- **Mean changes in diastolic blood pressure from baseline in the pooled Phase 1-3 neostigmine-controlled trials**

Use the data to populate tables using the following format:

Time After Study Drug Administration (minutes)	Sugammadex [N=] Mean % (mean absolute)	Comparator [N=] Mean % (mean absolute)
2	% (mmHg)	% (mmHg)
5	% (mmHg)	% (mmHg)
10	% (mmHg)	% (mmHg)
30	% (mmHg)	% (mmHg)

In all, you should be sending us 4 tables for blood pressure.

Please do the same for heart rate. That will bring the total to 8 tables.

Please contact me if you have any questions about this request.

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

Reference ID: 3353703

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/s/

DIANA L WALKER
08/07/2013

From: Walker, Diana
To: Glassner, D. (Dori)
Subject: NDA 22225 Clinical Information Request 25july13
Date: Thursday, July 25, 2013 12:21:17 PM

Dear Dori,

I have received the following information request. Please submit the requested information to your NDA.

Please submit the postmarketing information that you provided in the line listings of CIOMS reports (submitted on June 21, 2013) as a SAS transport file.

Warm regards,
Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
07/30/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 022225

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Organon USA Inc.
c/o Merck Sharp & Dohme Corp.
P.O. Box 2000, RY33-204
Rahway, NJ 07065

Attention: Dori L. Glassner
Director, Global Regulatory Affairs

Dear Ms. Glassner:

Please refer to your Class 2 resubmission for your New Drug Application (NDA) dated December 19, 2012, and received December 20, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Sugammadex Sodium Injection, 100 mg/mL.

We also refer to your correspondence, dated and received April 17, 2013, requesting review of your proposed proprietary name, (b) (4) We have completed our review of the proposed proprietary name, (b) (4) and have concluded that it is acceptable.

The proposed proprietary name, (b) (4) will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your April 17, 2013, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Ms. Vaishali Jarral, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4248. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Diana Walker, at (301) 796-4029.

Sincerely,
{See appended electronic signature page}
Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
07/16/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22225 **INFORMATION REQUEST**

Organon USA, Inc.
Attention: Dori L. Glassner
Director, Worldwide Regulatory Affairs
P.O. Box 2000, RY33-204
Rahway, NJ 07065

Dear Ms. Glassner:

Please refer to your New Drug Application (NDA) dated October 30, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sugammadex sodium MK-8616/ SCH 900616, Injection, 100 mg/mL.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt response, in order to continue our evaluation of your NDA.

- The NDA does not contain stability data for drug product batches manufactured at production scales in Swords, Ireland. In accordance with the ICH Q1A, provide a post-approval commitment in Section 3.2.P.8.2 to place the first three production batches of each presentation on long term stability studies through the proposed shelf life and on accelerated studies for 6 months. In addition, provide the stability protocol for the studies.

If you have any questions, call LCDR Luz E Rivera, Regulatory Project Manager, at (301) 796 4013.

Sincerely,

{See appended electronic signature page}

Prasad Peri, PhD
Branch Chief, Branch VIII
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

PRASAD PERI
07/02/2013

From:	Walker, Diana
To:	Glassner, D. (Dori)
Subject:	NDA 22225 Clinical Information request 19jun13
Date:	Wednesday, June 19, 2013 1:17:14 PM
Importance:	High

Dear Dori,

I have received the following request from our clinical reviewer. Please respond as soon as possible with a submission to your NDA 022225. We request a response by Wednesday, June 26, 2013, or sooner if possible. (Note: if you can get it sooner, you are also welcome to combine this with the submission from the Information Request you are working on from earlier this week).

Currently, our reviewer is having to look through each CSR and in some cases cannot find the narratives, therefore, please provide the following:

Provide all the narratives and CRFs for deaths, SAEs, and discontinuations in a single file.

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
06/28/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22225 **INFORMATION REQUEST**

Organon USA, Inc.
Attention: Dori L. Glassner
Director, Worldwide Regulatory Affairs
P.O. Box 2000, RY33-204
Rahway, NJ 07065

Dear Ms. Glassner:

Please refer to your New Drug Application (NDA) dated October 30, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sugammadex sodium MK-8616/ SCH 900616, Injection, 100 mg/mL.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a response by **Friday, June 21, 2013**, in order to continue our evaluation of your NDA.

1. Your draft labeling states that [redacted] (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 "Declared amount of 100 mg/mL drug substance corresponds with 108.8 mg/mL Org 25969 (sodium salt) [redacted] (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.

2. The executed batch record for the compounding batch 827868001 shows that a potency of [redacted] (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.

3. Report potency of drug substance batches on release and on stability. Alternatively, demonstrate that potency does not change from batch to batch and on stability.

4. In the drug substance specification, the second compound of the [redacted] (b) (4) impurities in peak [redacted] (b) (4) is called [redacted] (b) (4). However, in Module 3.2.S.3.2, the compound is called [redacted] (b) (4) Make corrections as necessary.

If you have any questions, call LCDR Luz E Rivera, Regulatory Project Manager, at (301) 796 4013.

Sincerely,

{See appended electronic signature page}

Prasad Peri, PhD
Branch Chief, Branch VIII
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

PRASAD PERI
06/18/2013

From:	Walker, Diana
To:	Glassner, D. (Dori)
Subject:	NDA 22225 Clinical Information request 17jun13
Date:	Monday, June 17, 2013 4:31:30 PM
Importance:	High

Dear Dori,

I have received the following request from our clinical reviewer. Please respond to me via email as soon as possible followed by a submission to your NDA 022225. We request a response by Friday, June 21, 2013.

1. **Clarify the date that bradycardia was added to the Warnings and Precautions section and the Adverse Events section of the label?**
2. **Clarify which studies have had final study reports submitted to the agency but were not included in the most recent version of the ISS database.**
3. **Send a copy of all of the postmarketing reports/CIOMS forms that you have received to date.**

Please let me know if you need clarification of these questions.

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
06/18/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 022225

GENERAL ADVICE

Organon USA Inc.
126 E. Lincoln Avenue
P.O. Box 2000, RY33-204
Rahway, NJ 07065

Attention: Dori L. Glassner
Director, Global Regulatory Affairs

Dear Ms. Glassner:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sugammadex Sodium Injection, 100 mg/mL.

We also refer to your submission, dated and received February 27, 2013, containing a request that the Division seek input from the Office of Regulatory Policy on whether, (b) (4)

We have reviewed the referenced material and have the following comments:

1. We do not agree with your proposal because it would be inconsistent with our (b) (4)

2. Regarding the review of your currently proposed proprietary name:

   a. The Division of Medication Error Prevention and Analysis (DMEPA) will continue to review the recently submitted proposed proprietary name as expeditiously as resources allow.

   b. We also remind you that the proposed proprietary name, (b) (4) was previously deemed acceptable. You may choose to resubmit this name for consideration as an alternative approach to the review of your recently submitted proprietary name. However, because significant time has passed since (b) (4) was originally reviewed, the name would require a re-review and approval prior to use on any labels or labeling.

If you have any questions, call Diana L. Walker, Regulatory Project Manager, at (301) 796-4029.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

PARINDA JANI
05/02/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 022225

PROPRIETARY NAME REQUEST UNACCEPTABLE

Organon USA Inc.
c/o Merck Sharp & Dohme Corp.
PO Box 2000
RY33-204
Rahway, NJ 07065

ATTENTION: Dori L. Glassner
Director, Global Regulatory Affairs

Dear Ms. Glassner:

Please refer to your New Drug Application (NDA) dated December 19, 2012, received December 20, 2012, submitted under section 505(b)(1)of the Federal Food, Drug, and Cosmetic Act for Sugammadex Sodium Injection, 100 mg/mL.

We also refer to:

- Your correspondence dated January 14, 2013, and received January 15, 2013, requesting reconsideration of your proposed proprietary name, Bridion;
- Our January 23, 2013, teleconference with you clarifying the request for reconsideration of the proposed proprietary name, Bridion;
- Our email dated February 14, 2013, requesting additional information to support your January 15, 2013, request for reconsideration of your proposed proprietary name, Bridion; and
- Your correspondence dated and received February 21, 2013, amending your January 15, 2013, request for reconsideration.

We have completed our review of the information submitted in support of the proposed proprietary name, Bridion, and have concluded that your response has not addressed the safety concerns described in the letter dated June 7, 2012. Therefore, we continue to find the use of the proposed proprietary name, Bridion, unacceptable for the following reasons.

1. Bactrim concern:

The Bactrim/Bridion Failure Modes and Effects Analysis (FMEA) included in your submission has several shortcomings that undermine your finding that Bridion would not lead to confusion with Bactrim

if your proposed name were to be approved. The shortcomings identified in our evaluation of the FMEA include:

a) You did not consider that the Bactrim name continues to be used in prescribing and ordering sulfamethazole/trimethoprim IV formulations despite the fact that the Bactrim brand is no longer actively marketed. Sales data shows that an intravenous formulation of sulfamethoxazole and trimethoprim is presently sold by Teva Pharmaceuticals but has shown a steady, rapid decline in units prescribed since 2007 (source data: IMS Health). Literature indicates that the proprietary names of discontinued branded products continue long after market discontinuation, provided that generic formulations are available[1]. Hence, prescribers continue to order the intravenous formulation of sulfamethoxazole and trimethoprim as "Bactrim" although the brand is no longer marketed thus creating a risk for confusion between sulfamethoxazole/trimethoprim products and Bridion if it were to be approved. This is further supported by your survey responses where at least three pharmacists commented that "[Bactrim is] usually ordered by brand name and then filled with generic", "[Prescribers] tend to use the brand name [for IV Bactrim]", and "Filling with generic but physicians are writing for Bactrim."

b) You mischaracterize the expected ordering process for Bridion pertaining to a lack of hand-written orders for neuromuscular reversal agents. Specifically, you misrepresent the verbal ordering process and over-rely on Computerized Physician Order Entry (CPOE) implementation as a means of mitigating the risk of confusion between Bactrim and Bridion in hand-written orders.

   In your submission, you state that most hospitals and surgical centers have instituted electronic ordering systems alleviating the need for handwritten orders. Published literature indicates hat many, but not all hospitals have CPOE.[2] Furthermore, participants in your study also affirm that institutions continue to use written medication orders, as well as have written order protocols for CPOE downtimes or malfunction of CPOE systems."

   With respect to verbal ordering of medicines, in the case of urgent or emergency use, it is standard hospital policy for verbal orders to be transcribed onto the patient's medical record post administration. According to Joint Commission Standards and as recommended by the National Coordinating Council for Medication Error Reporting and Prevention (NCCMERP), all verbal orders should be reduced immediately to writing and signed by the individual receiving the order and be documented in the patient's medical record, reviewed, and countersigned by the prescriber as soon as possible within a timeframe designated by the organization, law and regulation.[3,4]

---

[1] Tu C, Taylor K, and Chai G. Use of proprietary names by prescribers for discontinued brand drug products with existing generic equivalents. *Drug Information Journal. 2012;46(6):677-682.*

[2] Jha A., DesRoches C., Campbell E., Donelan K.,Rao S., Ferris T., Shields A., Rosenbaum S., and D. Blumenthal, Use of Electronic Health Records in U.S. Hospitals**.** N Engl J Med 2009; 360:1628-1638, April 16, 2009

[3] National Coordinating Council for Medication Error Reporting and Prevention (NCCMERP). Recommendations to Reduce Medication Errors Associated with Verbal Medication Orders and Prescriptions. http://www nccmerp.org/council/council2001-02-20.html. Accessed February 12, 2013.

[4] Joint Commission. CAMH Update 2, September 2012. Record of Care, Treatment, and Services. RC.01.02.01 Element of Performance #4, Standard RC.02.03.07, RC.02.01.03 Element of Performance #8

c) You failed to analyze the potential for Bactrim and Bridion to be used within the same settings of care (such as the operating room, emergency department, and intensive care unit). Responses from your survey confirm that these settings should be included and expected for the use of your product. Additionally, medications may be ordered pre-operatively as substantiated by your survey responses, and thus a neuromuscular blockade reversal agent and an antibiotic may appear on an order form together.

2. Tridione concern

The Tridione/Bridion FMEA included in your submission also has several shortcomings that undermine your finding that Bridion would not lead to confusion with Tridione if your proposed name were to be approved. The shortcomings identified in our evaluation of the FMEA include:

a) You did not establish that these names are dissimilar in sound and spelling. In fact, the survey responses you collected and submitted describe the similarity of the names.

b) We are not convinced that historical sales data (or rather lack thereof) is a predictor of whether Tridione may be reintroduced to the market. The Tridione NDA remains active and the product may be reintroduced at any time.

c) Your FMEA overestimates the role of different dosage forms/route of administration (solution/IV versus tablet/po) in preventing errors between two similarly named products. Post-marketing reports of errors with other drug products refutes this assumption. There have been post-marketing cases of products with differing routes of administration being confused. One example of such confusion occurred with Cerebyx (an IV formulation) and Celebrex (an oral capsule). Another example of such confusion occurred with Advair (an oral inhalation product) and Advicor (a solid oral tablet). These post-marketing examples affirm that confusion may still occur between products with different dosage forms and routes of administration.

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Complete Submission for the Evaluation of Proprietary Names,* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Teena Thomas, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796 0549. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Diana Walker at (301) 796-4029.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
04/15/2013

From:	Walker, Diana
To:	Glassner, D. (Dori)
Subject:	NDA 22225 Clinical Information request 12apr13
Date:	Friday, April 12, 2013 11:11:57 AM
Importance:	High

Dear Dori,

I have received the following request from our clinical reviewer. **Please respond to me today via email if possible.** You can send your response to this information request officially to your NDA with your next submission, but we request an email response as soon as possible.

In regard to your March 1, 2013, submission of the ISS AE dataset, please respond to the following:
1) Are all AEs listed here in the safety evaluable population; if not, is there a flag to designate who is?
2) Are all AEs after sgdx, neo, pbo, etc. (also with a treatment phase if crossover)? If not, is there a column flag to designate AEs on/after treatment versus those before?

Please respond to this today as the clinical reviewer may need to request either a teleconference or another revision of the dataset if any answers to the second part of each question are "no".

Please let me know if you need clarification of these questions. If you are not able to respond to me via email today, please let me know when you plan to send a response.

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
04/12/2013

From: Walker, Diana
To: Glassner, D. (Dori)
Subject: NDA 22225 Clinical Inspection Information request 12Apr13
Date: Friday, April 12, 2013 11:23:41 AM
Importance: High

Dear Dori,

We have reviewed your proposal in the email below, and agree with your proposals; however, we also request that you continue to update us on your attempts to recover the actual site source documents.

We plan to consider the other sites listed in the application, and possibly select an alternative site for inspection. Additionally, we have the following information requests:

1. **Submit the whole site trial master file to your NDA for FDA inspection.**
2. **Provide the contact information for the Principal Investigator.**

Please let me know if you need clarification of these requests. Thank you for your assistance.

Regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

From: Glassner, D. (Dori) [mailto:dori.glassner@merck.com]
Sent: Thursday, April 11, 2013 2:29 PM
To: Walker, Diana
Subject: RE: NDA 22225 Clinical Inspection Information request 25mar13-update 11Apr13

Diana,
I wanted to provide you some further information on this.
We are continuing to work on several work streams to track down and obtain access to the study records, however, at this point we are not sure how long this may take.
Therefore, we think it would be a good idea to work on some other options with FDA in parallel and was wondering if it would be possible to have a teleconference with someone from OSI to discuss other options.
Options that we could recommend and would like to discuss are as follows:

- Merck could make our internal study documents/documentation (e.g. internal documents from our trial master file, monitoring records, a summary of the sponsor site audit) available to the FDA for inspection.
- The FDA could speak directly with the Principal Investigator (PI) from the site. We have contact information available for the PI.
- Could FDA inspect one of the other three sites from the study?

Regards,
Dori

From: Walker, Diana [mailto:Diana.Walker@fda.hhs.gov]
Sent: Monday, April 01, 2013 9:08 AM
To: Glassner, D. (Dori)
Subject: RE: NDA 22225 Clinical Inspection Information request 25mar13

Dear Dori,

I have received a response from our clinical investigations group. They said that we should aim for no later than the week of (b) (4) for the inspection.

Please let me know if you have any other questions, and if you can keep me up to date as to your progress, we can try to figure out all options if they ultimately refuse access to the records.

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

From: Glassner, D. (Dori) [mailto:dori.glassner@merck.com]
Sent: Thursday, March 28, 2013 2:38 PM
To: Walker, Diana
Subject: RE: NDA 22225 Clinical Inspection Information request 25mar13

Diana,
I wanted to provide you with an update of where we are with this.

I am not sure when the OSI staff spoke to these representatives from (b) (4), but since that time things have changed due to the bankruptcy. According to the information that we have been able to obtain: on the afternoon of (b) (4) all (b) (4) employees in (b) (4) were told they the company was shutting its doors and they were told to leave the buildings and the doors were locked behind them. As a result of this we were not able to get in contact the names provided below, although we did try all the phone numbers that were provided.

What we have been able to do is to contact the bankruptcy trustee and were informed that they will try to assist us, but it is unlikely that the records for the study would be released without approval from the bankruptcy court. The situation is very fluid and we are exploring all possible options including our own legal department.

The one question that I have been asked it what is the latest time when FDA would need to perform this inspection.

Regards,
Dori

From: Walker, Diana [mailto:Diana.Walker@fda.hhs.gov]
Sent: Monday, March 25, 2013 3:49 PM
To: Glassner, D. (Dori)
Subject: NDA 22225 Clinical Inspection Information request 25mar13
Importance: High

Dear Dori,

I have received the following request from our Office of Scientific Investigations (OSI) reviewer.

The OSI is attempting an inspection of the site in (b) (4) for NDA 22225. We are having a hard time tracking down the files and arranging the inspection for the (b) (4) site. We are requesting that Merck, as the NDA Sponsor, assist in arranging an inspection of the files.

As you know, (b) (4). Our Office of Regulatory Affairs (ORA) inspector called the (b) (4) point of contact who informed her that the business was closing. It has now filed for bankruptcy. (b) (4) (b) (4), indicated that the records pertaining to the study conducted under NDA 22225 are stored in a depository in (b) (4) The firm still owns/operates a clinical laboratory located within the same premises where the former (b) (4) site was located and they were willing to host the inspection at that facility. Now with the bankruptcy, that appears to no longer be possible.

This type of situation has happened in the past, and it is standard practice that the Sponsor should not take over the files for the site. An option that has been used in the past would be for Merck to hire a Contract Research Organization who can hold the files and host the inspection.

I am providing the names and phone #s of the (b) (4) officers that spoke with our inspector:

(b) (4)

We are requesting that you make these arrangements (or offer an alternative plan). Also, as you know, time is of the essence so this all needs to be arranged quickly.

Please let me know if you have questions, or would like to offer a plan for arranging for the site inspection, and I will find out more information from our OSI group as quickly as possible.

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
04/12/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 022225

REVIEW EXTENSION – MAJOR AMENDMENT

Organon USA, Inc.
126 E. Lincoln Avenue
P.O. Box 2000, RY33-204
Rahway, NJ 07065

Attention: Dori L. Glassner
Director, Worldwide Regulatory Affairs

Dear Ms. Glassner:

Please refer to your December 20, 2012, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sugammadex Sodium Injection, 100 mg/mL.

On March 1, 2013, we received your solicited major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is September 20, 2013.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017." If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by August 23, 2013.

If you have any questions, call Diana L. Walker, Regulatory Project Manager, at (301) 796-4029.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

PARINDA JANI
03/06/2013

From: Walker, Diana
To: "Glassner, D. (Dori)"
Subject: Follow-up - NDA 22225 Clinical Information Request dated 07Feb13 - 12Feb13
Date: Tuesday, February 12, 2013 3:15:00 PM

Dear Dori,

In general, the review team has conveyed to me that your proposed response below is not adequate. You will need to provide the datasets rather than having us construct them.

Here are the specific comments I have received from our reviewers:

We require a Demography dataset **for each study** and **integrated dataset**. Each Demography dataset must have only one entry (row) per subject in the study or integrated dataset. This must include AT LEAST the unique subject ID, but optimally has other demographic information.

Some of your studies appear to be missing datasets. We cannot find datasets for these two studies: P08370 and P08548. In addition, datasets used for the bleeding complications and re-occurrence of blockade analyses should be submitted. These are studies: INT00103441 and INT00095955.

Submission of the datasets and a detailed protocol for the Cleveland Study Report regarding anaphylactic reactions would be useful to verify the findings and permit exploratory analyses. However, this study does not involve sugammadex; therefore, submission of these items is encouraged but not required.

Please check your submission for other missing datasets and submit within 5 business days of this email.

Please let me know if you have any additional questions about these requests.

Regards,

Diana

Diana L. Walker, Ph.D.
Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

From: Glassner, D. (Dori) [mailto:dori.glassner@merck.com]
Sent: Monday, February 11, 2013 10:07 AM
To: Walker, Diana
Subject: RE: NDA 22225 Clinical Information Request 07Feb13

Diana,
Can you please share the attached with the reviewer to see if this adequately addresses the request or if additional datasets are still needed. Demographic data was included in the datasets

provided in the complete response.

I should have the response to the second request from Feb 7 either later today or tomorrow.
Dori

From: Walker, Diana [mailto:Diana.Walker@fda.hhs.gov]
Sent: Thursday, February 07, 2013 12:19 PM
To: Glassner, D. (Dori)
Subject: NDA 22225 Clinical Information Request 07Feb13
Importance: High

Dear Dori,

I have received the following information request from our clinical review team. Please respond to me via email as soon as possible, **but within five (5) business days**, followed by an official submission to your NDA. We require a timely response to the following in order to continue our review of your NDA:

We require a demography dataset (DM) with one entry for all unique subjects for each study. For your ISS and ISE, we also require a demography dataset that has one unique entry per patient.

Clarify how you handle patients that are in multiple studies in your ISS and ISE. For example, do you treat each subject as unique in each study or do you use the same identifier through studies. Provide a unique listing of subjects who are in more than one study and how they are identified in the different datasets (including ISS and ISE).

Please contact me as soon as possible if you require clarification of this request and I will be glad to assist you.

Regards,

Diana

Diana L. Walker, Ph.D.
Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

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DIANA L WALKER
03/05/2013

From:	Walker, Diana
To:	Glassner, D. (Dori)
Subject:	NDA 22225 Clinical Information Request 14Feb13
Date:	Thursday, February 14, 2013 1:43:50 PM
Importance:	High

Dear Dori,

I have received the following information request from our clinical review team.

Submit all ECG waveforms related to study 19.4.116 to the ECG warehouse at www.ecgwarehouse.com.

In terms of submitting anything to your NDA, nothing is required, but if you choose to submit a cover letter under General Correspondence to your NDA to document your response to this information request, you can definitely do so. If you would please send me an email once the files have been submitted so that I can alert the review team, it would be appreciated.

Please contact me as soon as possible if you require clarification of this request and I will be glad to assist you.

Regards,

Diana

Diana L. Walker, Ph.D.
Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

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DIANA L WALKER
03/05/2013

From:	Walker, Diana
To:	Glassner, D. (Dori)
Subject:	NDA 22225 Clinical Information Request 19Feb13
Date:	Tuesday, February 19, 2013 3:03:30 PM
Importance:	High

Dear Dori,

I have received the following information request from our clinical review team. Please respond to me as soon as possible via email, followed by an official submission to your NDA. Please respond to the following requests:

1. Confirm whether postmarketing reports of cardiac arrhythmias that involved patients with anaphylactic or hypersensitivity reactions were analyzed for both classes of adverse events. Also confirm whether this was the case for patients who experienced a bleeding-related adverse event.

2. Provide a unique patient identifier for each CIOMS report submitted in the NDA (this may be done by resubmitting the individual reports appended with the identifier) and provide a listing of when each of the CIOMS reports were submitted to the FDA and whether it was submitted under the IND or the NDA.

Please contact me as soon as possible if you require clarification of this request and I will be glad to assist you.

Regards,

Diana

Diana L. Walker, Ph.D.
Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
03/05/2013

From: Walker, Diana
To: "Glassner, D. (Dori)"
Subject: RE: Demography dataset submission was delivered via the gateway - follow-up 20Feb13
Date: Wednesday, February 20, 2013 3:57:00 PM
Importance: High

Dear Dori,

We have had a chance to look at the demography (DM) files that you submitted yesterday, February 19, 2013. Thank you for working so diligently to submit this information quickly. Unfortunately, we require the treatment arm to be one of the variables (columns) in this particular file type. We tried to manually join part of the basechar dataset to remedy this, however, we end up with a table that contains more than one row per subject.

Therefore, please resubmit this dataset with the treatment arms included. The treatment arm designation should include the dose information (for example, sugammadex 2 mg/kg or neostigmine 40 mcg/kg). Please confirm that each subject in these studies has received only one type of treatment.

Finally, it has come to my attention that there may be some issues with the eCTD submissions, and that you may be contacted directly by the eCTD staff. I don't have many details now, but if I find out more I will let you know.

Warm regards,

Diana

Diana L. Walker, Ph.D.
Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

From: Glassner, D. (Dori) [mailto:dori.glassner@merck.com]
Sent: Tuesday, February 19, 2013 2:12 PM
To: Walker, Diana
Subject: Demography dataset submission was delivered via the gateway

Diana,
I was just notified that the demography datasets submission was just delivered via the gateway. Since Dr Breder was anxious to receive this, I thought I would let you know so that you can keep an eye out for it. I am not sure how long it takes until you are notified.
Dori

From: Walker, Diana [mailto:Diana.Walker@fda.hhs.gov]
Sent: Tuesday, February 19, 2013 11:48 AM
To: Glassner, D. (Dori)
Subject: RE: NDA 22225: AC meeting telecon attendees

Dori,

Thanks so much for the update on the datasets. I did get the first submission already and have sent that on to the reviewers.

Regards,

Diana

Diana L. Walker, Ph.D.
Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

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DIANA L WALKER
03/05/2013

Thomas, Teena

From: Thomas, Teena
Sent: Thursday, February 14, 2013 10:48 AM
To: dori.glassner@merck.com
Cc: Bradley, Sean; Thomas, Teena; Jenkins, Darrell
Subject: Information request for (b) (4) NDA 022225

Dear Ms. Glassner,

We are currently reviewing your Request for Reconsideration of your proposed proprietary name, Bridion; and request additional information necessary to complete our review. Please submit your response via email to me followed by an amendment to your 14JAN13, Request for Reconsideration.

Please provide the following information:

1. The questionnaire given to or used by your safety evaluators to determine the answers to the questions posed to them for use in your research to support the use of Bridion.
2. Protocol and script used by the moderators during the research to support the use of Bridion
3. All verbatim responses and hazard scores determined by the study participants.

Let me know if you need clarification on this request.

Regards,

Teena

Teena Thomas, Pharm.D,CGP.
Safety Regulatory Project Manager
FDA, CDER
Office of Surveillance and Epidemiology
Bldg.22, Room 4435
10903 New Hampshire Ave.
Silver Spring, Maryland 20993-0002

Tel: 301.796.0549
E-mail : teena.thomas@fda.hhs.gov

Reference ID: 3264850

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/s/

TEENA THOMAS
02/21/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 022225

PROPRIETARY NAME REQUEST WITHDRAWN

Merck Sharp & Dohme Corp.
126 Lincoln Avenue
PO Box 2000
RY33-204
Rahway, NJ 07065

ATTENTION: Dori L. Glassner
Director, Global Regulatory Affairs

Dear Ms. Glassner:

Please refer to your New Drug Application (NDA) dated December 19, 2012, received December 20, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Sugammadex sodium injection, 100 mg/mL.

We acknowledge receipt of your January 14, 2013, correspondence, on January 14, 2013, notifying us that you are withdrawing your request for a review of the proposed proprietary name (b) (4). This proposed proprietary name request is considered withdrawn as of January 14, 2013.

We acknowledge receipt of your request for re-consideration for the proprietary name Bridion dated, January 15, 2013. We also refer to the January 23, 2013 teleconference with Merck clarifying the request for reconsideration of the proposed proprietary name Bridion.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Teena Thomas, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0549. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Diana Walker at (301) 796-4029.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
02/19/2013

MEMORANDUM	DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION CENTER FOR DRUG EVALUATION AND RESEARCH
MEETING DATE:	January 23, 2013
TIME:	4:00 PM
LOCATION:	WO Bldg 22, Rm 4311
APPLICATION:	NDA 022225
DRUG NAME:	Bridion (Sugammadex sodium injection)
TYPE OF MEETING:	Proprietary Name Review Teleconference (Bridion)
APPLICANT:	Merck
MEETING CHAIR:	Jamie Wilkins Parker, PharmD, Team Leader (TL), Division of Medication Error Prevention Analysis (DMEPA) Office of Surveillance and Epidemiology (OSE)
MEETING RECORDER:	Darrell Jenkins, Safety Regulatory Project Manager (SRPM), TL, OSE
FDA ATTENDEES:	Vicky Borders-Hemphill, PharmD, Safety Evaluator (SE), DMEPA Jamie Wilkins Parker, PharmD, DMEPA TL Darrell Jenkins, OSE SRPM, TL
SPONSOR ATTENDEES:	Lina Aljuburi, Ph.D. Director, US Regulatory Policy Dori Glassner Director, Regulatory Affairs Tamra Goodrow, PhD Executive Director, Regulatory Affairs Scott Korn, MD Vice-President, Regulatory Affairs

SUMMARY

The sponsor submitted a request for reconsideration of their proprietary tradename, Bridion on January 14, 2013, previously reviewed under the IND 68029. The name, Bridion, was considered unacceptable under the IND. The premise of the initial request for teleconference with Merck was due to the misunderstanding that the request for proprietary name reconsideration was submitted to their IND (although the name was initially denied under the IND) and is, in fact submitted to their NDA that is currently under review.

Further, the sponsor did not understand all the concerns from DMEPA with their reconsideration request. They understood the concerns from DMEPA with regard to the currently market product, Tridione, on which their name was denied under the regulations. However, their main point of contention is that the product will not be written for as an order in a health-care setting, and therefore would not be confused with the product, Bactrim, the other name on which their proposed proprietary name was initially denied.

During the meeting, DMEPA shared their preliminary concerns with the name Bridion which was also the subject of a teleconference on October 3, 2012, under IND 68029.

The sponsor acknowledged while they understood the concerns from DMEPA, they wished to proceed to have the name Bridion reconsidered and reviewed under their NDA 022225, as submitted in their submission dated January 14, 2013.

DMEPA acknowledged their request and will proceed with the sponsor's January 14, 2013, request for reconsideration and review of the tradename Bridion.

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/s/

TEENA THOMAS
02/13/2013

From:	Walker, Diana
To:	Glassner, D. (Dori)
Subject:	NDA 22225 Clinical Information Request 07Feb13
Date:	Thursday, February 07, 2013 12:19:07 PM
Importance:	High

Dear Dori,

I have received the following information request from our clinical review team. Please respond to me via email as soon as possible, **but within five (5) business days**, followed by an official submission to your NDA. We require a timely response to the following in order to continue our review of your NDA:

We require a demography dataset (DM) with one entry for all unique subjects for each study. For your ISS and ISE, we also require a demography dataset that has one unique entry per patient.

Clarify how you handle patients that are in multiple studies in your ISS and ISE. For example, do you treat each subject as unique in each study or do you use the same identifier through studies. Provide a unique listing of subjects who are in more than one study and how they are identified in the different datasets (including ISS and ISE).

Please contact me as soon as possible if you require clarification of this request and I will be glad to assist you.

Regards,

Diana

Diana L. Walker, Ph.D.
Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
02/07/2013

From: Walker, Diana
To: "Glassner, D. (Dori)"
Subject: NDA 22225 Clinical Information Request #2 07Feb13
Date: Thursday, February 07, 2013 2:12:00 PM
Importance: High

Dear Dori,

I have received the following information request from our clinical review team. Please respond to me via email as soon as possible, **but within five (5) business days**, followed by an official submission to your NDA. We require a timely response to the following in order to continue our review of your NDA:

The data sets, in SAS transport format, for each of the studies submitted were to have been included in the Complete Response submission to your NDA 22225. The data sets for study 19.4.304 could not be found. Provide the location for the data sets for each of the studies in the submission and submit the sets for any that have not already been provided.

Please contact me as soon as possible if you require clarification of this request and I will be glad to assist you.

Regards,

Diana

Diana L. Walker, Ph.D.
Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
02/07/2013

From:	Walker, Diana
To:	Glassner, D. (Dori)
Subject:	NDA 22225 Sugammadex Clinical Information Request follow-up 04Feb13
Date:	Monday, February 04, 2013 3:26:22 PM
Importance:	High

Dear Dori,

We have reviewed your response to our information request dated January 15, 2013. Based on your response, we are clarifying our original request, since we require information concerning the protocol changes for all of the clinical studies, regardless of the IND status. Please submit your response to me via email, followed by an official response to your NDA. Please respond to the request below:

For each of the new clinical studies reported in the Complete Response submission, whether conducted under an IND or not, please supply the following information:

- **Dates for each amendment to the protocol**
- **Date first subject was enrolled**
- **Date last subject completed the study**

Regards,

Diana

Diana L. Walker, Ph.D.
Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

From: Glassner, D. (Dori) [mailto:dori.glassner@merck.com]
Sent: Wednesday, January 16, 2013 8:11 AM
To: Walker, Diana
Subject: RE: NDA 22225 Sugammadex Clinical Information Request 15Jan13

Diana,
Attached is the requested information.
I have requested a response to your second email and will provide the response by email once I receive it. I will then provide the official submission to the NDA for both responses.
Any questions, please let me know.
Dori

From: Walker, Diana [mailto:Diana.Walker@fda.hhs.gov]
Sent: Tuesday, January 15, 2013 1:37 PM
To: Glassner, D. (Dori)
Subject: NDA 22225 Suggamadex Clinical Information Request 15Jan13

Dear Dori,

I have received an information request from our clinical review team. Please respond to the following request for information:

For each of the new clinical studies reported in the Complete Response submission, provide a list of the submission dates for each protocol and amendment to the protocol.

Warm regards,

Diana

Diana L. Walker, Ph.D.
Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

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DIANA L WALKER
02/04/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22225 **INFORMATION REQUEST**

Organon USA, Inc.
Attention: Dori L. Glassner
Director, Worldwide Regulatory Affairs
126 E. Lincoln Avenue, P.O. Box 2000, RY33-204
Rahway, NJ 07065

Dear Ms. Glassner:

Please refer to your New Drug Application (NDA) dated October 30, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for sugammadex sodium Injection, 100 mg/mL.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a response in order to continue our evaluation of your NDA.

(b) (4)

If you have any questions, call LCDR Luz E Rivera, Regulatory Project Manager, at (301) 796 4013.

Sincerely,

{See appended electronic signature page}

Prasad Peri, PhD
Branch Chief, Branch VIII
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

PRASAD PERI
02/04/2013

From:	Walker, Diana
To:	Glassner, D. (Dori)
Subject:	NDA 22225 Suggamadex Clinical Information Request 15Jan13
Date:	Tuesday, January 15, 2013 1:36:52 PM

Dear Dori,

I have received an information request from our clinical review team. Please respond to the following request for information:

For each of the new clinical studies reported in the Complete Response submission, provide a list of the submission dates for each protocol and amendment to the protocol.

Warm regards,

Diana

Diana L. Walker, Ph.D.
Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
01/15/2013

From: Walker, Diana
To: Glassner, D. (Dori)
Subject: NDA 22225 Suggamadex Clinical Information Request #2 15Jan13
Date: Tuesday, January 15, 2013 3:54:01 PM

Dear Dori,

I have received an additional request for clinical information. Please submit this to me via email, followed by an amendment to your NDA. You can send your response to the previous clinical information request for 15Jan13 in the same amendment to your NDA, if desired.

Please respond to the following information request:

In the study report for Study 19.4.304, section 7.13 on page 53 of describes "Changes from the pre-specified statistical analysis." Clarify whether these were post-hoc changes. If not, specify the date that the protocol was modified to incorporate the changes. We are specifically interested in the modification of the analysis of the primary efficacy variable. The use of the additive ANOVA assessment does not appear to be in Appendix D where other amendments are included.

Please contact me if you need clarification on this request.

Warm regards,

Diana

Diana L. Walker, Ph.D.
Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
01/15/2013

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

MEETING DATE: January 9, 2013
TIME: 12:00 PM
LOCATION: WO Bldg 22, Rm 4311
APPLICATION: NDA 22225
DRUG NAME: (b) (4) (sugammadex sodium injection)
TYPE OF MEETING: Proprietary Name Review Teleconference (b) (4)

APPLICANT: Merck Sharp & Dohme Corp

MEETING CHAIR: Jamie Wilkins Parker, PharmD (DMEPA Team Leader)

MEETING RECORDER: Teena Thomas, Safety Regulatory Project Manager, OSE

FDA ATTENDEES:
Vicky Borders-Hemphill, PharmD
(DMEPA Safety Evaluator)
Jamie Wilkins Parker, PharmD (DMEPA Team Leader)
Teena Thomas, (OSE PM DAAAP)
Franklin Stephenson, (OSE PM Team Leader)
Patricia Dryden (Pharmacy Student)

SPONSOR ATTENDEES:
Scott Korn, MD, VP, Regulatory Affairs
Tamra Goodrow, PhD, Executive Director, Regulatory Affairs
Dori Glassner, Director, Regulatory Affairs
Lina Aljuburi, Director, US Regulatory Policy
Tiffany Woo, Director, Clinical Research
Bach-Yen Nguyen, MD, Executive Director, Project Leadership
Robert Przybylko, Associate Director, Global Trademark Development

Sophie Anger, Director, Trademark Legal
Thomas Hall, Associate VP, Portfolio Management and Strategy

Background:
DMEPA requested this teleconference to notify you of our safety concerns with the proposed proprietary name, (b) (4)

Discussion:

1. **USAN stem**

During the initial steps of the proprietary name review process, the DMEPA initial search (b) (4)

(b) (4)

2. **Bridion versus** (b) (4)

In June 2012, we evaluated the proposed proprietary name Bridion for your product and found it unacceptable due to orthographic similarity and overlapping product characteristics with Bactrim (Sulfamethoxazole and Trimethoprim) as well as due to similarities in spelling and pronunciation to the currently marketed product Tridione (Trimethadione). (b) (4) .

Regulatory Options:

1) Wait for DMEPA to complete our review of (b) (4) by our OSE PDUFA goal date of 3/21/2013 and issue a denial letter.
2) Withdraw the proposed name (b) (4) and submit an alternate name for review. In order to initiate the safety review of an alternate proprietary name, a new complete request for proprietary name review must be submitted. The safety review of this alternate name will not be initiated until the new request is received.

Agenda:

Introduction: Merck attendees followed by FDA attendees

DMEPA provided the background and the reasons for the teleconference and provided Merck with some options to consider

Merck clarified their concerns regarding the review clock

Merck inquired about the difference between a formal dispute resolution and request for reconsideration and DMEPA clarified them.

The teleconference ended within 15 minutes

Action items:

Merck may consider to submit request for reconsideration of BRIDION or withdraw the name (b) (4) **and submit a new Proprietary name for review.**

Merck is to inform OSE project manager in a week about their decision

---

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/s/

TEENA THOMAS
01/14/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 022225

ACKNOWLEDGE –
CLASS 2 RESPONSE

Organon USA, Inc.
126 E. Lincoln Avenue
P.O. Box 2000, RY33-204
Rahway, NJ 07065

Attention: Dori L. Glassner
Director, Worldwide Regulatory Affairs

Dear Ms. Glassner:

We acknowledge receipt on December 20, 2012, of your December 19, 2012, resubmission of your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sugammadex Sodium Injection, 100 mg/mL.

We consider this a complete, class 2 response to our July 31, 2008, action letter. Therefore, the user fee goal date is June 20, 2013.

If you have any questions, call me at (301) 796-4029.

Sincerely,

{See appended electronic signature page}

Diana L. Walker, Ph.D.
Sr. Regulatory Project Manager
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

DIANA L WALKER
01/03/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 068029

MEETING MINUTES

Merck Sharpe & Dohme Group
PO Box 2000, RY33-204
Rahway, NJ 07065

Attention: Dori Glassner
Director, Worldwide Regulatory Affairs

Dear Ms. Glassner:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for sugammadex sodium injection.

We also refer to the telecon between representatives of your firm and the FDA on June 14, 2012. The purpose of the meeting was to discuss the resubmission of your NDA.

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1258.

Sincerely,

{See appended electronic signature page}

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: Guidance on Resubmission
Meeting Date and Time: June 14, 2012, 10:30 am
Application Number: IND 068029
Product Name: sugammadex sodium
Indication: **reversal of neuromuscular blockade**
Sponsor/Applicant Name: Merck Sharpe & Dohme Group
Meeting Chair: Christopher Breder, MD, PhD; Clinical Team Leader, DAAAP
Meeting Recorder: Allison Meyer, Sr. Regulatory Project Manager

FDA ATTENDEES

Bob A. Rappaport, MD	Director
Rigoberto Roca, MD	Deputy Director
Christopher Breder, MD, PhD	Clinical Team Leader
Arthur Simone, MD, PhD	Clinical Reviewer
Xiaobin Shen, PhD	CMC Reviewer
Adam Wasserman, PhD	Supervisor, Pharmacology/Toxicology
Zengjun Xu, PhD	Pharmacology/Toxicology Reviewer
Yun Xu, PhD	Clinical Pharmacology Team Leader
Allison Meyer	Sr. Regulatory Health Project Manager

SPONSOR ATTENDEES

Richard Briscoe, PhD	Therapeutic Area Lead, Toxicology
Ibia Ekopimo, MD, MPH	Director and Regulatory Policy Lead
Hein Fennema, PhD	Head, Late Stage Statistics, Oss
Dori Glassner	Director, Worldwide Regulatory Affairs
Tamra Goodrow, PhD	Senior Director, Worldwide Regulatory Affairs
David Gutstein, MD	Senior Director, Clinical Pharmacology
Pieter-Jan de Kam, PhD	Director, Clinical Research
Marie-Jose van Lierop, PhD	PK-PD Scientist
Robert J. Meyer, MD	Vice President, Global Regulatory Strategy, Policy and Safety
David Michelson, MD	Vice President, Clinical Neuroscience and Ophthalmology
Glen Miller, DVM, PhD	Distinguished Senior Investigator, Global Pathology; Safety Assessment, Laboratory Animal Resources
Bach-Yen Nguyen, MD	Senior Project Leader
Cynthia Silber, MD	Director, Clinical Risk Management
Armin Szegedi, MD, PhD	Clinical Lead
Tiffany Woo	Program Lead, Clinical Scientist

Reference ID: 3160858

1.0 BACKGROUND

On June 14, 2012, the Sponsor received the Division's responses to the questions posed in their meeting package. The questions are presented below in *italicized* text, Agency responses prepared prior to the meeting are **bolded**, and the discussion is presented in normal text. The purpose of this meeting was to discuss the contents of the NDA resubmission.

2. DISCUSSION

Clinical Comment
At the time the Not Approvable letter was issued on July 31, 2008, it was anticipated that only the studies needed to address the deficiencies would be conducted and a Complete Response would be submitted to the agency within a couple of years' time. However, you indicate that, in the interim, a number of additional efficacy studies have been conducted and the size of the safety database has doubled. Furthermore, in the interim, a substantial number of safety reports have been submitted regarding cardiac adverse events following the administration of sugammadex. Therefore, with the submission of the Complete Response, the Division will need to not only focus its attention on the data provided to address the deficiencies but to assess the combination of new and previously submitted efficacy data to determine whether any modifications of the indications or dosing paradigms are warranted and to reanalyze the combination of new and previously submitted safety data to determine whether the risk profile has changed in light of the new information. Submission of such substantial amounts of new efficacy and safety data, in the absence of a previous finding of safety and efficacy for a specific indication and dosing paradigm, will require that you reintegrate the efficacy and safety findings to allow a benefit risk analysis that incorporates all the available clinical data to date.

The responses to the clinical questions that follow incorporate the expectation that the new data will be combined with the old and new analyses will be performed.

Question 1: Does the Agency agree with the proposal on how to present the updated quality changes since the time of the original NDA in the NDA resubmission?

FDA Response: Your proposal appears to be acceptable. Note that all cGMP facilities should be ready for Agency inspection at the time of submission.

Discussion: There was no additional discussion on this question.

Question 2: Does the Agency agree with the proposed location and format for the new nonclinical data?

FDA Response: No. Modules 2.4 and 2.6 need to be updated to include and integrate the data of the nonclinical studies conducted to address the Agency's comments in the Not Approvable Letter.

Reference ID: 3160858

Discussion: The Sponsor proposed to amend Sections 2.4 and 2.6 with the new studies being integrated into the sections based on study type. The previous studies will be included as well. The Division agreed.

Question 3: …The complete ICH E3-compliant Clinical Study Reports for all new clinical studies conducted since the original NDA submission will also be provided in Module 5. An updated Module 5.2 will also be provided.

a. *Does the Agency agree with the proposed overall approach to updating the clinical section of the resubmission.*

FDA Response: As sugammadex has not been approved by the FDA and since from the time the Not Approvable letter was issued 20 additional clinical studies have been conducted and the safety database has been substantially increased, the analyses performed to generate the integrated summaries of safety and efficacy need to be repeated using all data generated to date.

b. *Does the Agency agree with the proposal for not updating Modules 2.7.1, 2.7.2, 2.7.3, and 2.7.4?*

FDA Response: The critical analyses of the efficacy data in the Overview of Efficacy (section 2.5.4) and Safety (section 2.5.5) need to be repeated to incorporate the new data.

Similarly, section 2.7.3 needs to be updated to include the new efficacy data obtained since the NDA was submitted, as do the Comparison and Analyses of Results Across Studies (section 2.7.3.3), Analysis of Clinical Information Relevant to Dosing Recommendations (section 2.7.3.4) and Persistence of Efficacy and/or Tolerance Effects (section 2.7.3.5). These sections will be important in performing the benefit risk analysis.

Discussion: The Sponsor stated that a concise presentation of efficacy data will be presented in Section 2.5 by means of a forest plot. Studies of the 2 mg and the 4 mg doses will be treated separately with the primary endpoint, recovery speed, presented for individual studies and for pooled data based on sugammadex dose. The Sponsor will include updated data for the new study, as well as the old data and overall recovery data. This will be supported with tables and summary statistics as the basis for the risk:benefit analysis. There will be no new data in section 2.7.3. Everything will be included in Module 2.5. The Division stated that the Sponsor should provide a more granular description of how it intends to incorporate new information into the modules 2 and 5 of the NDA to allow feedback prior to the resubmission.

Question 4: Does the Agency agree with the proposed content of supplementary Module 2.5?

FDA Response: The clinical efficacy and safety sections of Module 2.5 should be revised to incorporate the new data obtained since the NDA submission, rather than supplemented to reflect the new data. A single benefit risk analysis should be

Reference ID: 3160858

performed on all data available to date, rather than two analyses, i.e., the original analysis of the previously submitted data and a separate analysis on the data obtained since then.

Discussion: There was no additional discussion on this question.

Question 5a: Does the Agency agree with the proposed content and organization of the Safety Update?

FDA Response: The proposed tiered approach to presenting the data specific to the deficiencies in the Not Approvable letter is acceptable. You should note that a substantial number of cardiac arrhythmias have been reported to the IND since the completion of the NDA review. Analyzing the "combined" safety dataset related to these adverse events should be a point of focus in the new integrated summary of safety, as well as analyses related to hypersensitivity/anaphylaxis and coagulation/bleeding.

Discussion: The Sponsor stated that there has been no signal of cardiac arrhythmias in the post-marketing period for the countries that have already approved sugammadex. An analysis of cardiac arrhythmias and hypersensitivity will be provided upon resubmission. The Division noted that numerous safety reports have been submitted to the IND describing cardiac adverse events, mostly arrhythmias, and a number of reports describing allergic reactions. An updated analysis of these classes of adverse events needs to be submitted to the NDA. The Sponsor asked if the Division was interested in a specific type of arrhythmia. The Division stated that all types of arrhythmias should be included and that the analysis should also include evaluation of those arrhythmias that were considered as life threatening versus non-life threatening, and those requiring treatment versus no treatment needed.

Question 5b: Does the Agency agree with the proposal to define "combined" safety data as new safety data since the original NDA submission combined with the original NDA safety data?

FDA Response: It is acceptable to combine the new data with that previously submitted to the NDA, without tabulating the "new data" only, provided:

- **The tabulations that contain new data are readily identifiable from those that do not.**
- **The safety database is designed to easily discern the "new data" from the "old data."**

Discussion: The Sponsor stated that the resubmission will retain the table from the original submission in the ISS. However, additional tables from the new analysis will be included so the table numbers will change. The Division noted that the size of the safety database has doubled and all new information needs to be integrated. The unchanged tables should be identified as such.

Question 6: The Sponsor is planning to submit SAS datasets, annotated CRFs, and a define file for all clinical studies included in the resubmission that were not previously submitted, as

Reference ID: 3160858

well as integrated SAS datasets across all clinical studies that were used for new analyses, also including a define file. Does the Agency agree with this approach?

FDA Response: Yes.

Discussion: There was no additional discussion on this question.

Question 7: The Not Approvable Letter requests "English translations of the current approved foreign labeling not previously submitted" be included as part of the Safety Update. Sugammadex is currently approved in 71 countries (which includes the 29 countries of the EU/EEA). We proposed to provide the English versions of the labels only for the major markets where sugammadex is approved (e.g. the EU, Japan and Australia). Does the Agency concur?

FDA Response: This approach is acceptable provided any differences in indications, dosing and administration, adverse events, warnings and precautions that exist in labels not included in the submission are identified and described in the new submission.

Discussion: There was no additional discussion on this question.

Question 8: Does the Agency agree that the addition of these additional patients and events as proposed is appropriate and will better enable the study to meaningfully inform bleeding risks in the setting of sugammadex treatment?

FDA Response: The planned enrollment of 800 patients has been reached, but only 26 events have been observed. Your rationale for the observed rate being lower than the expected rate of events is clear. You plan to enroll subjects until either the planned number of events (33 total, blinded) are observed, or an additional 400 patients are enrolled, whichever occurs first, is acceptable.

Discussion: The Sponsor provided an update indicating that, after adjudication, there were 30 qualifying bleeding events and that 900 patients have been recruited thus far. The 30 qualified events represented 55% of the reported cases. The difference is attributed, in part, to differences in opinion as to whether the observed bleeding was to be expected. Currently, 1200 patients are targeted for enrollment, but given the current rates, it is projected that 33 qualified events will not be reached. If a sensitivity analysis is added the number of bleeding events may approximate what is anticipated. The Division stated that this is acceptable and upon resubmission the Sponsor will need to include all results, case report forms, and narratives.

The Sponsor stated that they would like to amend the protocol so that the 7-week follow-up period can be changed to a 2-week follow-up phone call. The Division asked when the majority of events were occurring. The Sponsor stated that 85% of the events occurred within 2 weeks, 6 events occurred outside that window with one event at 4 weeks. The Division stated that the Sponsor should submit a rationale for their proposal to change the follow-up period that incorporates the PK/PD profiles for the product, the adverse event data

Reference ID: 3160858

related to coagulation and bleeding, along with the relevant case report forms and narratives. The Division stated that we would need to know the basis for the bleeding events before rendering a decision. Only the adverse events related to clotting and bleeding issues from less than 2 weeks to the end of follow-up need to be included in the submission.

ADDITIONAL DISCUSSION

The Sponsor inquired if the Division was intending on having a second advisory committee meeting upon resubmission. The Division replied that there will be another advisory committee meeting.

ACTION ITEMS

1. The Sponsor will submit their proposal to amend the follow-up period including the pharmacodynamic reasons, data and narratives.

2. The Sponsor will provide a granular table to map out sections 2.5 and 2.7 of the NDA resubmission for proposal.

Reference ID: 3160858

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/s/

ALLISON MEYER
07/18/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 022225

PROPRIETARY NAME REQUEST WITHDRAWN

Organon USA, Inc.
126 E. Lincoln Avenue
P.O. Box 2000, RY33-204
Rahway, NJ 07065

ATTENTION: Dori L. Glassner
Director, Worldwide Regulatory Affairs

Dear Ms. Glassner:

Please refer to your New Drug Application (NDA) resubmission dated October 30, 2007, received October 31, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sugammadex Sodium Injection, 100 mg/mL.

We acknowledge receipt of your December 19, 2011 correspondence, on December 20, 2011, notifying us that you are withdrawing your request for a review of the proposed proprietary name (b) (4) This proposed proprietary name request is considered withdrawn as of December 19, 2011.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Danyal Chaudhry, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3813. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Allison Meyer at (301) 796-1258.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

AZEEM D CHAUDHRY
12/23/2011

CAROL A HOLQUIST
12/23/2011

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/s/

SARA E STRADLEY on behalf of PARINDA JANI
09/06/2011

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 22-225

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

Attention: Dori Glassner
Director and Liaison, Global Regulatory Affairs

Dear Ms. Glassner:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for sugammadex sodium injection.

Attached are the Division's responses to the questions from your meeting package for our upcoming post-action teleconference, scheduled for July 23, 2009, to discuss QT issues discovered during the first cycle review of sugammadex sodium.

The previously agreed upon time is still set aside to meet with you, but, if you would like to either cancel the meeting, because you feel all your questions have been answered to your satisfaction, or re-focus the meeting (i.e., only focus on items which you feel require additional clarification), that would be acceptable to the Division as well.

We will be happy to provide clarification on any of the Division's responses, but **WILL NOT entertain any NEW questions, topics or review additional data** (there is simply not enough time prior to the meeting for the team to review such materials). Please let me know if you would like to change anything about our forthcoming meeting.

If you have any questions, please call me at 301-796-2205.

Sincerely,

{See appended electronic signature page}

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Questions for Discussion

1. *Our analysis of the placebo-controlled studies with an ECG assessment included in the document entitled "Cardiac Safety of Sugammadex" shows that for two of the three studies that generated the majority of SAE's (studies 19.4.205 and 19.4.206, 17/18 SAE's), there is an imbalance in group size between patients receiving placebo vs patients that received sugammadex (37 vs 6 patients in study 19.4.205 and 157 vs 16 patients in study 19.4.206). However, in the third study (the cardiac study 19.4.309), with a more balanced group size for the two sugammadex groups (2 and 4 mg/kg) and the placebo group (each group 40 patients), there is no increased incidence of QTc prolongation and/or other (serious) cardiac events in the sugammadex groups.*
    a. *Could the Agency please provide the analysis that has led to the conclusion that there is a "three-fold greater incidence of QTc prolongation in sugammadex treated subjects than in placebo-treated subjects that rose to a level of a SAE, 3% vs 1%, respectively"?*
    b. *Could the Agency provide an explanation on how these findings in the Phase 2 and Phase 3 clinical studies lead to questioning the findings with respect to the effect of sugammadex on QTc in two thorough QTc studies, two meta analyses (reports 19.4.003 and 19.4.005) as well as the cardiologic evaluation of the study in cardiac patients (19.4.309)?*
    c. *Could the Agency please provide/tabulate the cardiac events that were considered and the analysis that was performed to conclude that "other serious cardiac adverse events occurred more frequently in sugammadex-treated subjects than in either placebo- or neostigmine treated subjects"?*
    d. *Are there events other than those presented during the Advisory Committee meeting that were considered? The slides from the Advisory Committee meeting are reproduced on the following page.*
    e. *Could the Agency identify these cases (subjects) and indicate for which of these cases the Agency considers the causal relationship to be "unclear"?*

FDA Response: Following internal discussions regarding the thorough QTc studies, ECG morphology data submitted in the NDA, and the information provided in your submissions dated June 22 and July 2, 2009, the Division concurs with your position that sugammadex sodium is not likely to pose an increased risk for QT prolongation or arrhythmias in the surgical setting. Therefore, at the present time, it is not necessary to conduct a study of the frequency and severity of cardiac arrhythmias and QTc prolongation as described in the "Not Approvable" letter dated July 31, 2008.

If sugammadex were to be approved, cardiac adverse events observed in the clinical trials will be included in the label and monitoring for these events in the post-marketing period will be continued.

2. *The meeting minutes for the End of Review meeting state "The Sponsor plans tosubmit a meeting request to discuss issues concerning drug-drug interactions and the QTc prolongation events observed with sugammadex." Can the Agency please explain the phrase "drug-drug interactions and the QTc prolongation events observed with sugammadex." since "drug-drug interactions" was not indicated in any previous communication? Previous*

communication referred to "...frequency and severity of cardiac arrhythmias and QTc prolongation occurring in patients receiving sugammadex versus those receiving other NMBA reversal agents and those not receiving reversal agents but who were administered an NMBA."

FDA Response: At the end of the post-action meeting, the Division indicated that further discussion regarding the issues of (a) cardiac safety and (b) drug-drug interactions for sugammadex and agents used in the perioperative setting that affect bleeding and coagulation would be possible. The latter topic arose during the discussion of Question 6 and the interaction of sugammadex with coagulation Factor 10a. The Division stated that, to have its concerns fully addressed, data regarding the mechanism of action, the dose response, the pharmacodynamic effect and possible interactions between sugammadex and other drugs affecting coagulation (e.g., heparin, warfarin, aspirin, and clopidogrel bisulfate) would need to be submitted.

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/s/

Allison Meyer
7/23/2009 10:26:57 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-225

Organon International
56 Livingston Ave.
Roseland, NJ 07068

Attention: Dori Glassner
Director and Liaison, Global Regulatory Affairs

Dear Ms. Glassner:

Please refer to your New Drug Application (NDA) file submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for sugammadex sodium injection.

We also refer to your March 23, 2009, correspondence, received March 24, 2009, requesting an type C meeting to discuss the request for the study of the frequency and severity of cardiac arrythmias and QT prolongation. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C meeting.

The meeting is scheduled as follows:

Date: **July 23, 2009**
Time: **10:00 AM (EST)**
Call-in Number: **to be determined**

CDER Participants: Bob A. Rappaport, MD, Division Director
Rigoberto Roca, MD, Deputy Division Director
Bindi Nikhar, MD, Clinical Team Leader
Art Simone, MD, Clinical Reviewer
Adam Wasserman, PhD, Pharmacology Toxicology Supervisor
Alex Xu, PhD, Pharmacology Toxicology Reviewer
Danae Christodoulou, PhD, Pharmaceutical Assessment Lead
Ali Al Hakim, PhD, Branch Chief, Division of Pre-Marketing Assessment
Dionne Price, PhD, Statistical Team Leader
Suresh Doddapaneni, PhD, Clinical Pharmacology Team Leader
Lei Zhang, PhD, Clinical Pharmacology Team Reviewer
Allison Meyer, Sr. Regulatory Health Project Manager

Provide the background information for this meeting (three copies to the NDA) to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia
and Rheumatology Products
5901-B Ammendale Rd.
Beltsville, MD 20705-1266

Provide 15 desk copies to me at the following address:

Allison Meyer
Food and Drug Administration
10903 New Hampshire Ave.
Bldg.22, Room 3176
Silver Spring, MD 20903-0002

If the materials presented in the information package are inadequate to justify holding a meeting, or if we do not receive the package by June 23, 2009, we may cancel or reschedule the meeting.

If you have any questions, call me at (301) 796-1258.

Sincerely,

{See appended electronic signature page}

Allison Meyer
Sr. Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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Allison Meyer
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-225

Organon USA Inc.
56 Livingston Avenue
Roseland, NJ 07068

Attention: Dori Glassner
Director, Regulatory Affairs

Dear Ms. Glassner:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for sugammadex sodium injection.

We also refer to the meeting between representatives of your firm and the FDA on December 1, 2008. The purpose of the meeting was to discuss deficiencies identified in the Agency's Not Approvable letter dated July 31, 2008.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me, at (301) 796-1258.

Sincerely,

{See appended electronic signature page}

Allison Meyer
Regulatory Project Manager
Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: December 1, 2008
TIME: 12:00 PM
LOCATION: White Oak
APPLICATION: NDA 22-225
DRUG NAME: Sugammadex
TYPE OF MEETING: Type A

MEETING CHAIR: Curtis Rosebraugh, M.D., M.P.H.
Director, Office of Drug Evaluation II

MEETING RECORDER: Allison Meyer
Project Manager

ATTENDEES:

FDA Attendees	Title
Curtis Rosebraugh, MD, MPH	Director, Office of Drug Evaluation II (ODE II)
Bob A. Rappaport, MD	Division Director
Rigoberto Roca, MD	Deputy Division Director
Bindi Nikhar, MD	Clinical Team Leader
Arthur Simone, MD, PhD	Medical Officer
Adam Wasserman, PhD	Supervisory Pharmacologist
Alex Xu, PhD	Pharmacology/Toxicology Reviewer
Danae Christodoulou, PhD	Pharmaceutical Assessment Lead, ODDQA
Dionne Price, PhD	Team Leader, Biostatistics
Thomas Permutt, PhD	Director, Office of Biostatistics II
Lei K Zhang, PhD	Clinical Pharmacology Reviewer
Badrul Chowdhury, MD	Director, Division of Pulmonary and Allergy Products
Sally Seymour, MD	Clinical Team Leader, DPAP
Susan Limb, MD	Clinical Reviewer, DPAP
Ayanna Augustus, PhD	Regulatory Project Manager
Allison Meyer	Regulatory Project Manager
Gemma Kuijpers, PhD	Pharmacology/Toxicology Reviewer, DMEP

EXTERNAL CONSTITUENT ATTENDEES:

Sponsor Attendees	Title
Patrick Boen, MD	Global Senior Medical Director
Chris Carter, MD	Vice President, Project Co-Lead
Constance Cullen, PhD	Director Preclinical and Clinical Bioanalytics
Diels van den Dobbelsteen, PhD	Principal Toxicologist
Robert Fick, MD	Senior Director, Experimental Pathology, Pharmacology & Discovery Medicine
Ronald Garutti, MD	Group Vice President, Head, GRA
Dori Glassner	Director, Regulatory Affairs
Thomas Haverty, MD	Group Vice President, Head, Global Clinical Research
Emiel van Heumen, MD	Medical Advisor
Marty Huber, MD	Vice President, Head Global Pharmacovigilance
Thomas Koestler, PhD	Executive Vice President, and President R&D
Robert Kowalski, PharmD	Vice President, Regulatory Affairs, North America & Japan
Jerrold Levy, MD	Professor & Deputy Chair for Research, Emory University
Frank van Meel, PhD	Project Co-Lead
Ronald Miller, MD	Professor and Chair, Dept. of Anesthesia, Univ. of CA
Elmer Mirro, DVM, PhD	Global Scientific Advisor, Drug Safety and Metabolism
David Nicholson, PhD	Senior Vice President, Head, Global Project Management
Pierre Peeters, PhD	Executive Director Clinical Pharmacology & Kinetics
Sharon Olmstead	Vice President, Regulatory Policy and Intelligence
Tiffany Woo	Director, Clinical Development, Anesthesia

BACKGROUND:

The purpose of the meeting was to discuss the deficiencies identified in the Not Approvable letter dated July 31, 2008, and to discuss a path forward.

The Sponsor's questions are presented below in italics, followed by the Division's response in bold. A record of the discussion that occurred during the meeting is presented in normal text.

<u>Agency Comments and Responses to Questions:</u>

After brief introductions, the Sponsor opened the discussion by indicating their intent to focus primarily on the hypersensitivity and coagulation issues concerning sugammadex. The Sponsor regarded the benefit:risk ratio for sugammadex as favorable. The Sponsor believes that the product addresses an unmet medical need and would be the only agent to offer complete and immediate reversal of neuromuscular blockade. The Sponsor expressed surprise at the number

of issues identified in the Not Approvable letter; especially considering the unanimous decision by the Advisory Committee (AC) at the meeting held on March 11, 2008, recommending approval for sugammadex, and the approval of the product in the European Union and Australia. Although the Sponsor acknowledged that the AC did not contain an allergist or an immunologist, they believed that the issues surrounding sugammadex safety and efficacy were thoroughly discussed by the anesthesiologists on the committee.

Dr. Rappaport stated that a detailed discussion of the deficiencies in the application did not occur at the AC meeting, given the priority review timeline and the need to schedule an AC meeting for this application within that timeline. The hypersensitivity issues observed with sugammadex were identified at a point in the review cycle where they could not be adequately presented and discussed at the AC meeting as we had not received input from our own experts.

The Sponsor mentioned that progress was made with their coagulation parameter trial and indicated that they plan to submit this data for review to the Division. The Sponsor has also developed an IgE/IgG detection assay, which they believe supports the position that an immunoglobulin mediated reaction is not the mechanism of action underlying the hypersensitivity reactions observed in the six cases discussed in the Not Approvable letter.

Question 1:

Given the priority review, unmet medical need and unanimous recommendation for approval from the Advisory Committee, please explain why the Agency did not approve Sugammadex with a REMS?

FDA Response:

The NDA was not approved because there was insufficient data to fully assess safety and, therefore, to perform an adequate benefit-risk analysis. As indicated in the Not Approvable Letter dated July 31, 2008, it was not possible to fully asses the risk of anaphylaxis either at the time of initial exposure to Sugammadex or upon repeat exposure, and it was not possible to determine the nature and extent of the effects of Sugammadex on either coagulation parameters or laboratory measurements thereof.

These two aspects of safety, risk of anaphylaxis and impact on coagulation, were critical for completing the benefit-risk analysis based on the nature of the product's use in the perioperative period and the extent of exposure for the general population. (b) (4)

The granting of the priority review did not alter the requirements for providing evidence of safety and efficacy and did not affect the standards by which the regulatory decision to approve or not approve was reached; it merely abbreviated the review cycle. The "unmet medical need" of "immediate reversal" was the basis for granting the priority review; however, the arguable benefit of an immediate-acting reversal agent was outweighed by the concerns for lack of information regarding the risk of anaphylactic reactions and impact of Sugammadex on coagulation in the benefit-risk analysis that was conducted with the data submitted.

Discussion:

(b) (4)

The data provided in the NDA were inadequate to fully characterize the risk profile of the product.

Question 2:

The action letter states "Sugammadex sodium caused anaphylaxis in approximately 1% of healthy subjects exposed to a single dose of the drug. Some patients exposed to Sugammadex sodium in the setting of anesthesia also had reactions suggestive of a Type I hypersensitivity reaction on first exposure." Please identify these subjects/patients.

FDA Response

Two of the 209 healthy subjects (1%) in the clinical safety database were identified as cases of anaphylaxis: Cases 106101008 and 105101030. The following cases did not meet full criteria of anaphylaxis but had symptoms suggestive of Type I hypersensitivity reactions: 105101028, 109101073, 115101008, and 105101001.

Discussion:

The Sponsor asked for clarification regarding the significance of the hypersensitivity reactions observed in six subjects (volunteers not patients), noting that the total number observed seemed trivial. Although anaphylaxis is a serious event, the Sponsor did not consider the hypersensitivity observed in the six subjects serious, as the reactions were self-limited and only one case required further treatment with an antihistamine. Dr. Rosebraugh stated that the number of cases reported was relatively high considering the size of the safety database and it was concerning, given the widespread exposure expected should the product be approved. He indicated that other products have been denied approval based on one case of Hy's Law. Dr. Rosebraugh further stated that the Sponsor needed to focus the discussion on how to fully assess the hypersensitivity risk, not whether the hypersensitivity signal exists. Dr. Limb stated that sugammadex was given the benefit of the doubt in that only cases from healthy volunteers were counted, since these cases were free of confounding factors present in the operating room setting. Two subjects out of 200 healthy volunteers had anaphylaxis to sugammadex, resulting in a frequency of 1%.This rate of anaphylaxis is a relatively high rate of anaphylaxis for a non-biologic drug product. In light of these findings, the Division did not consider the number of cases of hypersensitivity trivial.

The Sponsor stated that there is disagreement within the scientific community regarding the definition of anaphylaxis. The Sponsor did not deem the six cases highlighted as serious because the subjects did not require medical intervention of any consequence and the conditions were self-limiting. Dr. Chowdhury stated that the definition of anaphylaxis is not as unclear as the Sponsor suggested. There are diagnostic criteria put forth by the Symposium on the Definition and Management of Anaphylaxis. Whether the individual signs and symptoms observed were serious or self-limited is secondary to the real-life concern about the risk of more severe reaction in these patients upon readministration of sugammadex. On this basis, all of the hypersensitivity reactions observed for sugammadex are taken seriously. This concern needs to be addressed by a formal study of repeat exposure.

Question 3:

The Sponsor has sera from 7 of the previously identified cases of possible hypersensitivity, and we are in the process of analyzing these samples in a well controlled, validated ELISA format.

a. (b) (4) *Does the Agency concur?*

b. In a continuing effort to elucidate a mechanism we propose additional studies to be conducted in parallel, i.e. direct (non-IgE/non-IgG) mediated release from basophils, mast cells and non-cellular, humoral mechanisms as outlined in Figure 1 below. Does the Agency concur with this experimental approach?

Figure 1: Decision Tree

to identify mechanism of action for sugammadex clinical hypersensitivity reactions

(b) (4)

FDA Response:

We encourage you to explore both IgE/IgG-mediated and non-IgE/IgG mediated mechanisms, as proposed in Figure 1. However, we do not agree that (b) (4) **.**

Discussion:

The Sponsor stated that since February 11, 2008, all six subjects that developed hypersensitivity have been enrolled in a skin prick study and blood samples from these subjects have been preserved for further analysis. The Sponsor expressed their belief that the mechanism underlying the hypersensitivity reactions was likely non-specific mast cell release, as the six cases of hypersensitivity did not develop IgE/IgG antibodies. In addition, the Sponsor reiterated their

assertion that these six cases do not represent anaphylaxis, as the cases did not develop adverse pulmonary complications, were self limited, and only occurred at the higher doses. The Division stated that although the Sponsor's assay results may indicate that an IgE/IgG-mediated mechanism is unlikely, these results do not obviate the need for a clinical study. The Sponsor should continue to explore all possible mechanisms, as an insight into the underlying mechanism may be helpful for patient screening and risk management. The Division reminded the Sponsor of the deaths associated with reactions to heparin that weren't IgG/IgE mediated and noted how elucidation of the underlying mechanism lead to a strategy to minimize the risk.

The Sponsor stated that sugammadex is given at the end of surgery and not during the induction period when confounding effects from multiple drugs can complicate the diagnosis of anaphylaxis. The sponsor also stated that 90% of anaphylaxis reactions caused by drug allergies develop 10 to15 minutes following exposure, with some reactions developing up to one hour later. The Sponsor believes any reactions that develop following administration of sugammadex at the end of surgery will be detected quickly during the post-operative recovery period when patients are closely monitored. The lack of hypersensitivity reactions observed in the 1845 patients who received sugammadex at the perioperative period suggest a low risk for development of anaphylaxis in a larger patient population; therefore, the Sponsor concluded that a Phase 4 post-marketing observational study would be safe and feasible. Dr. Chowdhury stated that many experts feel that peri-operative anaphylaxis is difficult to diagnose. Furthermore, drug-induced anaphylaxis does not always occur immediately, but can occur well beyond 1 hour following exposure, including after a patient has been discharged from a hospital. Moreover, Dr. Chowdhury stated that potential peri-operative cases of anaphylaxis were identified from the clinical trial database but were excluded on the basis of confounding factors.

Question 4:

The Agency has requested repeat exposure data in man for sugammadex specifically addressing the nature and frequency of anaphylaxis and other hypersensitivity reactions. Currently, we have significant nonclinical repeated exposure data in 28 monkeys (2-10 intravenous exposures, mean interval 13 weeks, vast majority of intervals > 5-6 weeks), 46 dogs (daily intravenous exposure for 3 to 4 weeks) and 292 rat (daily intravenous or subcutaneous dosing for 4 weeks) and multiple exposure in 201 healthy volunteers from 6 clinical trials with mean (min-max) time interval between first and last exposure of 15 (3-22) days. We believe these data are sufficient to assess whether there is an increased risk of hypersensitivity upon repeated exposure. Can the Agency provide further explanation of why they have requested a multiple exposure trial? What additional information would this trial provide? What is the hypothesis to be tested in such a study and what would be the endpoint(s)?

FDA Response

The strength of animal data to support repeat exposure in man is limited given the lack of a good animal model for anaphylaxis. Controlled data in humans is required. The original clinical program did not formally assess the safety of repeat exposure at time intervals sufficient to permit formation of drug-specific IgE in an adequate number of patients. A formal study is recommended to assess the rates of sensitization and hypersensitivity reactions that may be anticipated with widespread use, when individual patients may receive multiple doses of sugammadex over a lifetime. Further study of the clinical

features of these reactions may help elucidate the underlying mechanism as well as facilitate the development of predictive screening tests.

Discussion:

The Sponsor stated that they have assay results that suggest mast cell degradation, a non-specific cell-mediated event, may be the mechanism for the hypersensitivity reactions reported. The Division stated that while this information may be useful, a clinical study of repeat exposure was required. The Division informed the Sponsor that all new data demonstrating the benefits and risk of sugammadex will be presented at an advisory committee meeting consisting of a panel of expert anesthesiologists and allergists for public vetting.

The Sponsor requested clarity regarding the advantages of the Division's request to conduct a controlled clinical trial to assess the risk of sugammadex to patients. The Sponsor proposed establishing a registry in Europe to capture hypersensitivity cases, within a week of occurrence, for all products used in the surgical setting, including sugammadex. The Sponsor considered this the best approach to assess risk of sugammadex while recording potential signals and serious outcomes that require intervention and a prolonged hospital stay. The Division stated that registry data would not be an adequate substitute for a prospective clinical trial of repeat exposure. The Division asked the Sponsor if they had conducted a repeat exposure study to which they responded that they had not. The Division informed the Sponsor of the need to consider the effects of sugammadex on multiple organ systems and stated that repeat exposure in healthy volunteers is the best way to assess the risk. Dr. Chowdhury stated that a controlled setting would allow for multiple sample collections of tryptase and other markers of allergic reactions as well as serial physical observations. The Division also mentioned that data collected from patients in a clinical setting is confounded by comorbidities, polypharmacy and physiological responses to the surgical procedure. The Division recommended that study subjects be exposed to the highest to-be-labeled-dose of 16 mg/kg in the repeat exposure study. In addition, the Sponsor should enroll enough healthy volunteers (in the range of several hundred) to effectively evaluate the risk.

Question 5:

When conducting immunization protocols, it is standard practice to administer a prime dose of immunogen and consecutive boosting dosages at weekly intervals to evoke a B-cell mediated specific Ig response. According to abundant data in the literature, specific Ig serum-titers reach peak values within 2-3 weeks following a boost dose administration. Can the Agency please provide their rationale for requesting a 5-6 weeks dosing interval for a multiple dose trial with sugammadex?

FDA Response

The applicability of a typical immunization protocol is questionable, as the kinetics of drug-specific IgE production in drug allergy are not fully understood. Immunization protocols are typically focused on non-IgE antibody responses and based on more immunogenic molecules. There is not much literature characterizing the time course of specific IgE formation in human drug allergy. An interval of 5-6 weeks is likely to be an adequate time period to permit development of a specific IgE response, as previously noted by the Applicant's own consultant, Dr. William Busse, during the June 20, 2008

teleconference. Shorter time intervals with more intense dosing regimens may also suffice. The design of the multiple dose trial is at the Applicant's discretion; submit whatever data is needed to support the time interval and study design selected.

Discussion

The Sponsor requested clarification regarding which exposure interval would be appropriate and proposed repeat exposure four weeks following initial administration. The Division stated that the study should include multiple exposures (e.g., 3-4 times over a 4-6 week period). The Division advised the Sponsor to develop a protocol and submit it to the IND for review.

Question 6:

The action letter states "In a comparison of hemorrhagic adverse events between placebo- and sugammadex-treated subjects, which were not included in protocol specified safety assessments, fewer events were observed in the placebo-treated groups. A difference in these events persisted when the comparison was further refined." Could the Agency please provide the details of how the clinical safety data (hemorrhagic adverse events) were analyzed, including the details on the further refinement of these analyses?

FDA Response

The data analysis to which you refer was the one you performed and described on pages 38 and 39 of the Risk Management Plan submitted in the NDA. You correctly identified the effect of sugammadex on values for laboratory parameters of blood coagulation time (APTT, PT (INR), PT) as "important missing information" in this document.

As the trials were not designed to assess treatment-related differences in bleeding and bleeding-related events were not actively assessed, the *in-vitro* findings that sugammadex affected coagulation parameters combined with the *post-hoc* analysis finding of differences in bleeding-related adverse events between treatment groups presented several safety issues that could not be adequately addressed with the available information. These issues were of a magnitude that precluded a thorough benefit-risk analysis and included the following:

- **The mechanism by which sugammadex affects PT, aPTT and the INR are unknown.**
- **The in-vitro assessment of coagulation parameters considered the effects of sugammadex alone. The effect of the sugammadex-NMBA complex was not assessed and neither was the overall effect of sugammadex use in conjunction with other anesthetic agents and commonly administered medications used during the perioperative period on these parameters.**
- **The magnitude and duration of the effect of sugammadex on coagulation parameters were not reported or assessed.**

Discussion

The Sponsor stated that they have conducted a study (Trial 115) to assess coagulation parameters and observed mild transient results for APT/PT. The Sponsor observed a 0.1 unit increase in INR and a 0.3 increase at 16 mg/kg. The Sponsor indicated that sugammadex was interacting with Factor 10a, but not in a clinically relevant manner that would translate into a bleeding risk.

The Division stated that to have its concerns fully addressed, data regarding the mechanism of action, the dose response, the pharmacodynamic effect and possible interactions between sugammadex and other drugs affecting coagulation (e.g., heparin, warfarin, aspirin, and clopidogrel bisulfate) would need to be submitted. The Sponsor stated that they observed a 30-minute increase in INR at the 16 mg/kg does. The Sponsor reported that they observed additive effects with Vitamin K. The Division advised the Sponsor to submit this new information to the IND for review.

Question 7:

Would a clinical trial studying coagulation in patients undergoing surgical procedures still be required provided the mechanism underlying the effect of prolongation of aPTT and PT(INR) is adequately clarified and shown to be of no clinical relevance based on:
- *mechanistic data of in vitro studies explaining the in vitro spiking effect,*
- *possibly, studies in appropriate nonclinical models of bleeding, and*
- *data on coagulation parameters in a healthy volunteer trial? If yes, why?*

FDA Response:
These studies may provide a substantial understanding of the effects of sugammadex on coagulation and may help limit the data needed from a clinical study to complete the benefit-risk analysis. However, as described in the response to question 6 above, the effects of sugammadex when it binds with non-NMBA moieties and the impact that has on post-administration bleeding will not likely be addressed by these studies.

There is a concern that the effects of sugammadex on coagulation may present differently when used as intended in the clinical setting compared to carefully controlled studies that do not expose subjects to all the medications typically used in the perioperative period.

No Discussion

Question 8:

Please clarify why the Agency is requesting additional data on growth plate morphology since the Sponsor believes that growth plate morphology has been adequately studied histologically based on longitudinal transsections of femur through the epiphyseal disc in amongst others two 4-week toxicity studies in young adult rats and one 4-week toxicity studies in juvenile rats including delayed effects/recovery upon up to 8 weeks post-dosing. No drug-related adverse histopathological effects on growth plate morphology have been observed. This is in line with the only slight longitudinal growth reduction of rat femur and ulna being secondary to slight general body growth reduction in the juvenile rat. Would the Agency like to review histology slides or photographs and/or would the Agency prefer juvenile rat femur and ulna growth data expressed per body weight change as a means to demonstrate that there is a large safety margin before longitudinal growth is reduced by a specific effect on bone growth?

FDA Response:
Based on our review, the relationship between the reduction in the length of the femur and ulna and the body weight decrease in the 4-week juvenile rat study is not clear. It is recommended you submit your additional data analysis including rat femur and ulna

growth data expressed per body weight change in order to support your conclusion that the effect on longitudinal growth was secondary to body weight reduction.

Submission of photomicrographs and morphometric analysis of the femoral growth plate from animals treated in the 4-week juvenile rat study may assist in understanding the growth effects of sugammadex and is encouraged.

No Discussion

Question 9:

Given the technical difficulty of sectioning undecalcified bone and the limitations in the resolution of micro-autoradiography as applied in report INT00029186 defining the exact binding site by this technique is not possible. However, binding to the anorganic extracellular matrix is most likely. This is based on structural analogy to other agents such as bisphosphonates, EDTA and tetracycline, as explained in section 5.1 of Position Paper: Retention and effects of Org 25969 in bone and teeth (R&D release report INT00047251) and by absence of binding to collagen containing structures such as cartilage. For the agents above it is known that incorporation occurs during mineralization of bone and the results of the microautoradiography study in rat bone are in line with this.

a. The photographs in the report of the micro-autoradiography may not be ideal for providing visual information regarding the binding site of sugammadex to bone. Therefore, would the Agency like to review slides or does the Agency consider the technique insufficient to reveal the location of binding?

b. Can the Agency further clarify which "errors in description" have been noted in the submitted materials that may have caused confusion in the review?

FDA Response:
The microautoradiography study provided relevant information on the location of sugammadex in long and flat bones in young adult rats. However, as you indicated, the data are not adequate to determine the exact binding site(s) of sugammadex. In addition, the value of the study was suboptimal due to small sample size, presence of label in control scapula from untreated rat (Fig.1), errors in figure legends (i.e. growth plate not identifiable in Figs. 1, 2, 5, 7, trabeculae not observed in Figs. 3, 5, 7) and inadequate quality of micrograph of femur growth plate area (Fig. 6). Submission of adequate low and high power micrographs particularly of the femoral metaphyseal area is requested to resolve this issue.

No Discussion

Question 10:

As sugammadex (Org 25969 and Org 48302) is not genotoxic, no continuous stimulation of the parathyroid gland will be present under the proposed conditions of use, its binding to bone is reversible, the estimated levels of human exposure is in the range 2.25, 4.5 or 18 µg/g bone (report INT00047251) and the accumulation factor is limited as there is also a phase of rather rapid release from bone (initial half-life in rat bone approx. 3 weeks), the Sponsor regards the risk for tumor formation negligible even for the pediatric population. Does the Agency have any

specific considerations or observations regarding sugammadex triggering their concern for carcinogenic potential?

FDA Response:
The principal reasons for concern relate to the increased propensity for sugammadex deposition along with long retention (potentially years) expected in bones of pediatric patients. This, combined with the absence of definitive information on the binding site of sugammadex and long-term nonclinical studies is the foundation of the request for further information prior to an approval for use in pediatric patients. Demonstration of binding to hydroxylapatite as well as submission of bone metabolism and histopathology data from the requested juvenile rat study with extended duration of follow-up would address this concern.

Discussion

The Sponsor requested clarification on what data is need to demonstrate binding of sugammadex to hydroxylapatite. The Division stated that there are *in vitro* binding assays that can be used to detect binding of sugammadex to hydroxylapatite. These assays have been established and published in the literature.

Question 11:
The action letter states: "Additional studies to address the potential local effects in bone, such as in vitro bone resorption assay (45Ca release), assessment of bone turnover markers, hydroxyl apatite crystal growth and dissolution assay, and effect of in vitro bone decalcification on sugammadex retention."

a. In an extensive package of nonclinical in vivo studies the actual result on bone and tooth physiology has been investigated in detail and a wide safety margin has been demonstrated for all relevant endpoints in bone and teeth. In addition, the Sponsor intends to conduct additional nonclinical studies with sugammadex to evaluate the effect on bone fracture repair and to evaluate the effect on bone in the juvenile rat using an intermittent dosing regimen and an extended follow-up period to further assess effects on bone. Could the Agency please clarify why and how the suggested additional studies to address the potential effects of bone recommended under 'Other studies' are considered important in the risk assessment based on an extensive package of nonclinical in vivo studies already available, which already demonstrate a wide safety margin?

b. Could the Agency please explain what is meant by "effect of in vitro bone decalcification on sugammadex retention?"

FDA Response:

The mechanism of action underlying the bone effects of sugammadex observed in nonclinical studies is not clear. It is possible that sugammadex binds to hydroxyapatite but no direct evidence for this hypothesis was provided. The Division believes that characterization of the binding of sugammadex to the bone mineral matrix constituents and its effects on bone cell activity would contribute to the understanding of its bone

retention and help determine the relevance of the animal bone findings, respectively. Data can also be used to address long term bone toxicity concerns.

"Effect of in vitro bone decalcification on sugammadex retention" would mean an in vitro assay to determine the release of sugammadex from bone as a result of bone decalcification.

No Discussion

Question 12:

In the action letter, the Agency specifically requests to study the frequency and severity of cardiac arrhythmias and QTc prolongation occurring in patients receiving sugammadex versus those receiving other NMBA reversal agents and those not receiving reversal agents but who were administered an NMBA during their surgical procedure. The cardiac effects of sugammadex have been thoroughly investigated and reported in the NDA as follows:

• Two thorough QTc trials (19.4.109 and 19.4.105) have been conducted as per ICH E14 guideline. These trials not only studied the effect of therapeutic and supra-therapeutic doses of sugammadex alone on QTc, but also the rocuronium/sugammadex and vecuronium/sugammadex complex at the request of the Agency. Both thorough QTc trials were negative according to the ICH-E14 criteria.

• Patient ECG data have routinely been collected in Phase 2 studies (Trials 19.4.003 and 19.4.005) as well as in Trial 19.4.309 (cardiac) which provided further support for the absence of a relation between sugammadex and QTc prolongation in a patient setting.

• Pooling of the sugammadex data and a comparison to both placebo and neostigmine showed no clinically relevant effects of sugammadex on blood pressure, heart rate, pulse rate, respiratory rate or body temperature. Pooled electrocardiographic data were also rigorously analyzed for treatment-related abnormalities, and the results were consistent with conclusions of the two thorough QTc trials (19.4.109 and 19.4.105). The analyses of pooled ECG data show that sugammadex has limited effects on the electrocardiogram of subjects regardless of the NMBA administered (rocuronium, vecuronium, pancuronium, or no NMBA).

Furthermore, it is the Sponsors' understanding that expanded ECG safety evaluation during later stages of drug development is only required if the thorough QTc study is positive or if the thorough QTc study is negative but the available nonclinical data are strongly positive (ICH-E14). We believe based on the above data an expanded ECG safety evaluation is not warranted. Considering these extensive healthy volunteer and patient data demonstrating the beneficial cardiac safety pattern of sugammadex, which results or data from the sugammadex database support the Agency's request to investigate the frequency and severity of QTc prolongations and arrhythmias of sugammadex versus those receiving other NMBA reversal agents in a patient trial (and thereby deviating from the ICH guidance)?

FDA Response

While the data from the QTc studies indicated sugammadex does not prolong the QT interval, the clinical setting in which those studies took place was substantially different from the operating room setting in which the product will ultimately be used, i.e., subjects

in the QTc studies were not undergoing surgical procedures. That difference appeared to have a substantial effect on the ECG based on the safety data generated in the clinical trials. Specifically, it is not clear why there was a three-fold greater incidence of QTc prolongation in sugammadex-treated subjects than in placebo-treated subjects that rose to the level of a serious adverse event (SAE), 3% versus 1%, respectively. In addition to QTc prolongation, other serious cardiac adverse events occurred more frequently in sugammadex-treated subjects than in either placebo- or neostigmine-treated subjects, despite your ECG morphology assessment with findings suggesting no substantial difference. These other serious cardiac adverse events included atrial fibrillation, cardiac arrest, cardiogenic shock, electro-mechanical disjunction, myocardial infarction and ventricular tachycardia. Although it was not possible to show cause and effect for these SAEs, the greater frequency with which they occurred in sugammadex-treated subjects than those in other treatment arms in randomized studies raised a safety concern. Therefore, further study was required, and the study should be powered to detect differences for these adverse events based on findings from the clinical trials submitted in the NDA.

It was noted that none of these cardiac adverse events occurred in a manner that appeared to be dose related and most occurred while subjects were being monitored as part of their anesthetic care, i.e., intraoperatively or in the Post Anesthesia Care Unit, where the monitoring and readily available treatments would favor a positive outcome. Therefore, the decision was made that, while these sugammadex-related effects required further evaluation, such a study could be conducted as a post-marketing commitment.

No Discussion

Question 13:

In the first sugammadex thorough QTc study (19.4.105), the Sponsor attempted to include an additional arm with a therapeutic dose of neostigmine (50 µg/kg) combined with 10 µg/kg glycopyrrolate. During the review of this thorough QTc protocol, the Agency questioned the need for adding this NMBA reversal agent arm. The combination of neostigmine/glycopyrrolate is commonly used as NMBA reversal agent, and based on a literature search this combination is associated with maximum mean QTc prolongations of approximately 30 ms and severe cardiac arrhythmias [1-3]. Therefore, can the Agency please explain their rationale for the current request to evaluate QTc prolongation (and cardiac arrhythmias) for other NMBA reversal agents and which specific agents are of interest to the Agency?

FDA Response: Based on the safety data provided in the NDA, sugammadex use resulted in a three-fold increase in the incidents of QTc prolongation, which rose to the level of a serious adverse event, compared to placebo. The reasons for such a difference are not known. In addition, as noted in the response to the question above, other serious cardiac adverse events occurred more frequently in sugammadex-treated subjects than in either placebo- or neostigmine-treated subjects. Here too, the reasons for such differences are unknown. Therefore, to adequately assess the role of the reversal agent and to provide a clinically relevant context for interpreting the findings, the recommendation was made that a study be conducted to evaluate the frequency and severity of cardiac arrhythmias and QTc prolongation occurring in patients receiving sugammadex versus those receiving other NMBA reversal agents and those not receiving reversal agents but who were administered

an NMBA during their surgical procedure. Powering this study to detect differences for these adverse events based on the findings from the clinical trials submitted in the NDA will permit a determination of the role of the reversal agents, if any, in these cardiac events and of whether sugammadex differs significantly from other reversal agents in this regard. The Agency recognizes that neostigmine administered in combination with glycopyrrolate is the most commonly used NMBA reversal agent in the United States and appreciates the concern for the cardiac effects of these two agents; however, the results from the clinical trials for sugammadex, suggest that sugammadex poses a greater risk in this regard. Therefore, a study comparing the two reversal agents would not be unethical and would provide resolution to the extent of risk associated with each method of reversal. The use of a placebo- treatment arm would provide assay sensitivity.

No Discussion

Question 14:

At the time of the pre-IND meeting, the Division stated that "A study specifically focused on patients with hepatic insufficiency is not required; however patients with hepatic impairment should not be excluded." Therefore, we removed hepatic impairment from the exclusion criteria for most, if not all trials. Additionally, a hepatic study was not discussed or requested at the End of Phase 2 meeting. Please indicate what concern(s) prompted the request for a study in hepatically impaired patients.

FDA Response

Although hepatic impairment is not likely to affect PK of sugammadex as it is mainly eliminated in the kidney, hepatic impairment would affect PK of rocuronium or vecuronium. The reversal of rocuronium-or vecuronim-induced neuromuscular blockade (NMB) by sugammadex in hepatic impairment patients is anticipated to be longer than patients with normal hepatic function. (b) (4) **he recovery times were derived based on the assumption that similar changes in the pharmacokinetics of sugammadex might be seen based on the findings of a study which evaluated the changes in pharmacokinetics of rocuronium in subjects with hepatic impairment. Because changes in the pharmacokinetics of sugammadex in patients with hepatic impairment are not expected, the assumptions of similar impact of hepatic impairment on the pharmacokinetics of sugammadex as observed for rocuronium might not be valid.** (b) (4) **we would recommend that you conduct a PK-PD study in patients with hepatic impairment.**

No Discussion

ACTION ITEMS:

1) The Sponsor agreed to submit a repeat dose study protocol that will assess risk of anaphylaxis in several hundred healthy volunteers exposed to sugammadex.

2) The Sponsor plans to submit a package addressing the effects of sugammadex on coagulation parameters.

3) The Sponsor plans to submit a meeting request to discuss issues concerning drug-drug interactions and the QTc prolongation events observed with Sugammadex.

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/s/

Allison Meyer
12/29/2008 12:08:59 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-225

Organon USA Inc.
56 Livingston Avenue
Roseland, NJ 07068

Attention: Dori Glassner
Director, Regulatory Affairs

Dear Ms. Glassner:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for sugammadex sodium injection.

Attached are the Division's responses to the questions from your October 10, 2008, meeting package for our upcoming meeting, scheduled for December 1, 2008, to discuss issues related to the Not Approvable letter.

The previously agreed upon time is still set aside to meet with you, but, if you would like to either cancel the meeting, because you feel all your questions have been answered to your satisfaction, or re-focus the meeting (i.e., only focus on items which you feel require additional clarification), that would be acceptable to the Division as well. Alternatively, you can change the format of the meeting from face-to-face to teleconference. If you decide to change the format of the meeting, please contact us promptly by phone or e-mail.

We will be happy to provide clarification on any of the Division's responses, but **WILL NOT entertain any NEW questions, topics or review additional data** (there is simply not enough time prior to the meeting for the team to review such materials). Please let me know if you would like to change anything about our forthcoming meeting.

If you have any questions, call me at 301-796-1258.

Sincerely,

{See appended electronic signature page}

Allison Meyer
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

Questions for Discussion

General:
1. Given the priority review, unmet medical need and unanimous recommendation for approval from the Advisory Committee, please explain why the Agency did not approve sugammadex with a REMS?

FDA Response: The NDA was not approved because there was insufficient data to fully assess safety and, therefore, to perform an adequate benefit-risk analysis. As indicated in the Not Approvable Letter dated July 31, 2008, it was not possible to fully asses the risk of anaphylaxis either at the time of initial exposure to sugammadex or upon repeat exposure, and it was not possible to determine the nature and extent of the effects of sugammadex on either coagulation parameters or laboratory measurements thereof.

These two aspects of safety, risk of anaphylaxis and impact on coagulation, were critical for completing the benefit-risk analysis based on the nature of the product's use in the perioperative period and the extent of exposure for the general population. (b) (4)

The granting of the priority review did not alter the requirements for providing evidence of safety and efficacy and did not affect the standards by which the regulatory decision to approve or not approve was reached; it merely abbreviated the review cycle. The "unmet medical need" of "immediate reversal" was the basis for granting the priority review; however, the arguable benefit of an immediate-acting reversal agent was outweighed by the concerns for lack of information regarding the risk of anaphylactic reactions and impact of sugammadex on coagulation in the benefit-risk analysis that was conducted with the data submitted.

Hypersensitivity (point #1 action letter)
2. The action letter states *"Sugammadex sodium caused anaphylaxis in approximately 1% of healthy subjects exposed to a single dose of the drug. Some patients exposed to sugammadex sodium in the setting of anesthesia also had reactions suggestive of a Type I hypersensitivity reaction on first exposure."* Please identify these subjects/patients.

FDA Response: Two of the 209 healthy subjects (1%) in the clinical safety database were identified as cases of anaphylaxis: Cases 106101008 and 105101030. The following cases did not meet full criteria of anaphylaxis but had symptoms suggestive of Type I hypersensitivity reactions: 105101028, 109101073, 115101008, and 105101001.

3. The Sponsor has sera from 7 of the previously identified cases of possible hypersensitivity, and we are in the process of analyzing these samples in a well controlled, validated ELISA format.

a. (b) (4)

(b) (4)

b. In a continuing effort to elucidate a mechanism we propose additional studies to be conducted in parallel, i.e. direct (non-IgE/non-IgG) mediated release from basophils, mast cells and non-cellular, humoral mechanisms as outlined in Figure 1 below. Does the Agency concur with this experimental approach?

FDA Response:

Figure 1: Decision Tree

to identify mechanism of action for sugammadex clinical hypersensitivity reactions

(b) (4)

We encourage you to explore both IgE/IgG-mediated and non-IgE/IgG mediated mechanisms, as proposed in Figure 1. (b) (4)

4. The Agency has requested repeat exposure data in man for sugammadex specifically addressing the nature and frequency of anaphylaxis and other hypersensitivity reactions. Currently, we have significant nonclinical repeated exposure data in 28 monkeys (2-10 intravenous exposures, mean interval 13 weeks, vast majority of intervals > 5-6 weeks), 46 dogs (daily intravenous exposure for 3 to 4 weeks) and 292 rat (daily intravenous or subcutaneous dosing for 4 weeks) and multiple exposure in 201 healthy volunteers from 6 clinical trials with mean (min-max) time interval between first and last exposure of 15 (3-22) days. We believe these data are sufficient to assess whether there is an increased risk of hypersensitivity upon repeated exposure. Can the Agency provide further explanation of why they have requested a multiple exposure trial? What additional information would this trial provide? What is the hypothesis to be tested in such a study and what would be the endpoint(s)?

FDA Response: The strength of animal data to support repeat exposure in man is limited given the lack of a good animal model for anaphylaxis. Controlled data in humans is

required. The original clinical program did not formally assess the safety of repeat exposure at time intervals sufficient to permit formation of drug-specific IgE in an adequate number of patients. A formal study is recommended to assess the rates of sensitization and hypersensitivity reactions that may be anticipated with widespread use, when individual patients may receive multiple doses of sugammadex over a lifetime. Further study of the clinical features of these reactions may help elucidate the underlying mechanism as well as facilitate the development of predictive screening tests.

5. When conducting immunization protocols, it is standard practice to administer a prime dose of immunogen and consecutive boosting dosages at weekly intervals to evoke a B-cell mediated specific Ig response. According to abundant data in the literature, specific Ig serum-titers reach peak values within 2-3 weeks following a boost dose administration. Can the Agency please provide their rationale for requesting a 5-6 weeks dosing interval for a multiple dose trial with sugammadex?
Coagulation (point #2 action letter)

FDA Response: The applicability of a typical immunization protocol is questionable, as the kinetics of drug-specific IgE production in drug allergy are not fully understood. Immunization protocols are typically focused on non-IgE antibody responses and based on more immunogenic molecules. There is not much literature characterizing the time course of specific IgE formation in human drug allergy. An interval of 5-6 weeks is likely to be an adequate time period to permit development of a specific IgE response, as previously noted by the Applicant's own consultant, Dr. William Busse, during the June 20, 2008 teleconference. Shorter time intervals with more intense dosing regimens may also suffice. The design of the multiple dose trial is at the Applicant's discretion; submit whatever data is needed to support the time interval and study design selected.

6. The action letter states *"In a comparison of hemorrhagic adverse events between placebo- and sugammadex-treated subjects, which were not included in protocol specified safety assessments, fewer events were observed in the placebo-treated groups. A difference in these events persisted when the comparison was further refined."* Could the Agency please provide the details of how the clinical safety data (hemorrhagic adverse events) were analyzed, including the details on the further refinement of these analyses?

FDA Response:
The data analysis to which you refer was the one you performed and described on pages 38 and 39 of the Risk Management Plan submitted in the NDA. You correctly identified the effect of sugammadex on values for laboratory parameters of blood coagulation time (APTT, PT (INR), PT) as "important missing information" in this document.

As the trials were not designed to assess treatment-related differences in bleeding and bleeding-related events were not actively assessed, the *in-vitro* findings that sugammadex affected coagulation parameters combined with the *post-hoc* analysis finding of differences in bleeding-related adverse events between treatment groups presented several safety issues that could not be adequately addressed with the available information. These issues were of a magnitude that precluded a thorough benefit-risk analysis and included the following:

- **The mechanism by which sugammadex affects PT, aPTT and the INR are unknown.**

- **The in-vitro assessment of coagulation parameters considered the effects of sugammadex alone. The effect of the sugammadex-NMBA complex was not assessed and neither was the overall effect of sugammadex use in conjunction with other anesthetic agents and commonly administered medications used during the perioperative period on these parameters.**
- **The magnitude and duration of the effect of sugammadex on coagulation parameters were not reported or assessed.**

7. Would a clinical trial studying coagulation in patients undergoing surgical procedures still be required provided the mechanism underlying the effect of prolongation of aPTT and PT(INR) is adequately clarified and shown to be of no clinical relevance based on:
• mechanistic data of in vitro studies explaining the *in vitro* spiking effect,
• possibly, studies in appropriate nonclinical models of bleeding, and
• data on coagulation parameters in a healthy volunteer trial? If yes, why?

FDA Response:
These studies may provide a substantial understanding of the effects of sugammadex on coagulation and may help limit the data needed from a clinical study to complete the benefit-risk analysis. However, as described in the response to question 6 above, the effects of sugammadex when it binds with non-NMBA moieties and the impact that has on post-administration bleeding will not likely be addressed by these studies.

There is a concern that the effects of sugammadex on coagulation may present differently when used as intended in the clinical setting compared to carefully controlled studies that do not expose subjects to all the medications typically used in the perioperative period.

Pediatrics (Points # 2, 4 and 5 action letter)

8. Please clarify why the Agency is requesting additional data on growth plate morphology since the Sponsor believes that growth plate morphology has been adequately studied histologically based on longitudinal transsections of femur through the epiphyseal disc in amongst others two 4-week toxicity studies in young adult rats and one 4-week toxicity studies in juvenile rats including delayed effects/recovery upon up to 8 weeks post-dosing. No drug-related adverse histopathological effects on growth plate morphology have been observed. This is in line with the only slight longitudinal growth reduction of rat femur and ulna being secondary to slight general body growth reduction in the juvenile rat. Would the Agency like to review histology slides or photographs and/or would the Agency prefer juvenile rat femur and ulna growth data expressed per body weight change as a means to demonstrate that there is a large safety margin before longitudinal growth is reduced by a specific effect on bone growth?

FDA Response:
Based on our review, the relationship between the reduction in the length of the femur and ulna and the body weight decrease in the 4-week juvenile rat study is not clear. It is recommended you submit your additional data analysis including rat femur and ulna growth data expressed per body weight change in order to support your conclusion that the effect on longitudinal growth was secondary to body weight reduction.

Submission of photomicrographs and morphometric analysis of the femoral growth plate from animals treated in the 4-week juvenile rat study may assist in understanding the growth effects of sugammadex and is encouraged.

9. Given the technical difficulty of sectioning undecalcified bone and the limitations in the resolution of micro-autoradiography as applied in report INT00029186 defining the exact binding site by this technique is not possible. However, binding to the anorganic extracellular matrix is most likely. This is based on structural analogy to other agents such as bisphosphonates, EDTA and tetracycline, as explained in section 5.1 of Position Paper: Retention and effects of Org 25969 in bone and teeth (R&D release report INT00047251) and by absence of binding to collagen containing structures such as cartilage. For the agents above it is known that incorporation occurs during mineralization of bone and the results of the microautoradiography study in rat bone are in line with this.

a. The photographs in the report of the micro-autoradiography may not be ideal for providing visual information regarding the binding site of sugammadex to bone. Therefore, would the Agency like to review slides or does the Agency consider the technique insufficient to reveal the location of binding?

b. Can the Agency further clarify which *"errors in description"* have been noted in the submitted materials that may have caused confusion in the review?

FDA Response:
The microautoradiography study provided relevant information on the location of sugammadex in long and flat bones in young adult rats. However, as you indicated, the data are not adequate to determine the exact binding site(s) of sugammadex. In addition, the value of the study was suboptimal due to small sample size, presence of label in control scapula from untreated rat (Fig.1), errors in figure legends (i.e. growth plate not identifiable in Figs. 1, 2, 5, 7, trabeculae not observed in Figs. 3, 5, 7) and inadequate quality of micrograph of femur growth plate area (Fig. 6). Submission of adequate low and high power micrographs particularly of the femoral metaphyseal area is requested to resolve this issue.

10. As sugammadex (Org 25969 and Org 48302) is not genotoxic, no continuous stimulation of the parathyroid gland will be present under the proposed conditions of use, its binding to bone is reversible, the estimated levels of human exposure is in the range 2.25, 4.5 or 18 µg/g bone (report INT00047251) and the accumulation factor is limited as there is also a phase of rather rapid release from bone (initial half-life in rat bone approx. 3 weeks), the Sponsor regards the risk for tumor formation negligible even for the pediatric population. Does the Agency have any specific considerations or observations regarding sugammadex triggering their concern for carcinogenic potential?

FDA Response:
The principal reasons for concern relate to the increased propensity for sugammadex deposition along with long retention (potentially years) expected in bones of pediatric patients. This, combined with the absence of definitive information on the binding site of sugammadex and long-term nonclinical studies is the foundation of the request for further information prior to an approval for use in pediatric patients. Demonstration of binding to

hydroxylapatite as well as submission of bone metabolism and histopathology data from the requested juvenile rat study with extended duration of follow-up would address this concern.

Other Studies (points #1, 2 and 4 action letter)
11. The action letter states: *"Additional studies to address the potential local effects in bone, such as in vitro bone resorption assay (45Ca release), assessment of bone turnover markers, hydroxyl apatite crystal growth and dissolution assay, and effect of in vitro bone decalcification on sugammadex retention."*

a. In an extensive package of nonclinical in vivo studies the actual result on bone and tooth physiology has been investigated in detail and a wide safety margin has been demonstrated for all relevant endpoints in bone and teeth. In addition, the Sponsor intends to conduct additional nonclinical studies with sugammadex to evaluate the effect on bone fracture repair and to evaluate the effect on bone in the juvenile rat using an intermittent dosing regimen and an extended follow-up period to further assess effects on bone. Could the Agency please clarify why and how the suggested additional studies to address the potential effects of bone recommended under 'Other studies' are considered important in the risk assessment based on an extensive package of nonclinical in vivo studies already available, which already demonstrate a wide safety margin?

b. Could the Agency please explain what is meant by *"effect of in vitro bone decalcification on sugammadex retention?"*

FDA Response:
The mechanism of action underlying the bone effects of sugammadex observed in nonclinical studies is not clear. It is possible that sugammadex binds to hydroxyapatite but no direct evidence for this hypothesis was provided. The Division believes that characterization of the binding of sugammadex to the bone mineral matrix constituents and its effects on bone cell activity would contribute to the understanding of its bone retention and help determine the relevance of the animal bone findings, respectively. Data can also be used to address long term bone toxicity concerns.

"Effect of in vitro bone decalcification on sugammadex retention" would mean an in vitro assay to determine the release of sugammadex from bone as a result of bone decalcification.

12. In the action letter, the Agency specifically requests to study the frequency and severity of cardiac arrhythmias and QTc prolongation occurring in patients receiving sugammadex versus those receiving other NMBA reversal agents and those not receiving reversal agents but who were administered an NMBA during their surgical procedure. The cardiac effects of sugammadex have been thoroughly investigated and reported in the NDA as follows:

• Two thorough QTc trials (19.4.109 and 19.4.105) have been conducted as per ICH E14 guideline. These trials not only studied the effect of therapeutic and supra-therapeutic doses of sugammadex alone on QTc, but also the rocuronium/sugammadex and vecuronium/sugammadex complex at the request of the Agency. Both thorough QTc trials were negative according to the ICH-E14 criteria.

• Patient ECG data have routinely been collected in Phase 2 studies (Trials 19.4.003 and 19.4.005) as well as in Trial 19.4.309 (cardiac) which provided further support for the absence of a relation between sugammadex and QTc prolongation in a patient setting.

• Pooling of the sugammadex data and a comparison to both placebo and neostigmine showed no clinically relevant effects of sugammadex on blood pressure, heart rate, pulse rate, respiratory rate or body temperature. Pooled electrocardiographic data were also rigorously analyzed for treatment-related abnormalities, and the results were consistent with conclusions of the two thorough QTc trials (19.4.109 and 19.4.105). The analyses of pooled ECG data show that sugammadex has limited effects on the electrocardiogram of subjects regardless of the NMBA administered (rocuronium, vecuronium, pancuronium, or no NMBA).

Furthermore, it is the Sponsors' understanding that expanded ECG safety evaluation during later stages of drug development is only required if the thorough QTc study is positive or if the thorough QTc study is negative but the available nonclinical data are strongly positive (ICH-E14). We believe based on the above data an expanded ECG safety evaluation is not warranted. Considering these extensive healthy volunteer and patient data demonstrating the beneficial cardiac safety pattern of sugammadex, which results or data from the sugammadex database support the Agency's request to investigate the frequency and severity of QTc prolongations and arrhythmias of sugammadex versus those receiving other NMBA reversal agents in a patient trial (and thereby deviating from the ICH guidance)?

FDA Response: While the data from the QTc studies indicated sugammadex does not prolong the QT interval, the clinical setting in which those studies took place was substantially different from the operating room setting in which the product will ultimately be used, i.e., subjects in the QTc studies were not undergoing surgical procedures. That difference appeared to have a substantial effect on the ECG based on the safety data generated in the clinical trials. Specifically, it is not clear why there was a three-fold greater incidence of QTc prolongation in sugammadex-treated subjects than in placebo-treated subjects that rose to the level of a serious adverse event (SAE), 3% versus 1%, respectively. In addition to QTc prolongation, other serious cardiac adverse events occurred more frequently in sugammadex-treated subjects than in either placebo- or neostigmine-treated subjects, despite your ECG morphology assessment with findings suggesting no substantial difference. These other serious cardiac adverse events included atrial fibrillation, cardiac arrest, cardiogenic shock, electro-mechanical disjunction, myocardial infarction and ventricular tachycardia. Although it was not possible to show cause and effect for these SAEs, the greater frequency with which they occurred in sugammadex-treated subjects than those in other treatment arms in randomized studies raised a safety concern. Therefore, further study was required, and the study should be powered to detect differences for these adverse events based on findings from the clinical trials submitted in the NDA.

It was noted that none of these cardiac adverse events occurred in a manner that appeared to be dose related and most occurred while subjects were being monitored as part of their anesthetic care, i.e., intraoperatively or in the Post Anesthesia Care Unit, where the monitoring and readily available treatments would favor a positive outcome. Therefore, the decision was made that, while these sugammadex-related effects required further evaluation, such a study could be conducted as a post-marketing commitment.

13. In the first sugammadex thorough QTc study (19.4.105), the Sponsor attempted to include an additional arm with a therapeutic dose of neostigmine (50 µg/kg) combined with 10 µg/kg glycopyrrolate. During the review of this thorough QTc protocol, the Agency questioned the need for adding this NMBA reversal agent arm. The combination of neostigmine/glycopyrrolate is commonly used as NMBA reversal agent, and based on a literature search this combination is associated with maximum mean QTc prolongations of approximately 30 ms and severe cardiac arrhythmias [1-3]. Therefore, can the Agency please explain their rationale for the current request to evaluate QTc prolongation (and cardiac arrhythmias) for other NMBA reversal agents and which specific agents are of interest to the Agency?

FDA Response: Based on the safety data provided in the NDA, sugammadex use resulted in a three-fold increase in the incidents of QTc prolongation, which rose to the level of a serious adverse event, compared to placebo. The reasons for such a difference are not known. In addition, as noted in the response to the question above, other serious cardiac adverse events occurred more frequently in sugammadex-treated subjects than in either placebo- or neostigmine-treated subjects. Here too, the reasons for such differences are unknown. Therefore, to adequately assess the role of the reversal agent and to provide a clinically relevant context for interpreting the findings, the recommendation was made that a study be conducted to evaluate the frequency and severity of cardiac arrhythmias and QTc prolongation occurring in patients receiving sugammadex versus those receiving other NMBA reversal agents and those not receiving reversal agents but who were administered an NMBA during their surgical procedure. Powering this study to detect differences for these adverse events based on the findings from the clinical trials submitted in the NDA will permit a determination of the role of the reversal agents, if any, in these cardiac events and of whether sugammadex differs significantly from other reversal agents in this regard. The Agency recognizes that neostigmine administered in combination with glycopyrrolate is the most commonly used NMBA reversal agent in the United States and appreciates the concern for the cardiac effects of these two agents; however, the results from the clinical trials for sugammadex, suggest that sugammadex poses a greater risk in this regard. Therefore, a study comparing the two reversal agents would not be unethical and would provide resolution to the extent of risk associated with each method of reversal. The use of a placebo- treatment arm would provide assay sensitivity.

14. At the time of the pre-IND meeting, the Division stated that *"A study specifically focused on patients with hepatic insufficiency is not required; however patients with hepatic impairment should not be excluded."* Therefore, we removed hepatic impairment from the exclusion criteria for most, if not all trials. Additionally, a hepatic study was not discussed or requested at the End of Phase 2 meeting. Please indicate what concern(s) prompted the request for a study in hepatically impaired patients.

FDA Response
Although hepatic impairment is not likely to affect PK of sugammadex as it is mainly eliminated in the kidney, hepatic impairment would affect PK of rocuronium or vecuronium. The reversal of rocuronium-or vecuronim-induced neuromuscular blockade (NMB) by sugammadex in hepatic impairment patients is anticipated to be longer than patients with normal hepatic function. (b) (4)

(b) (4) **The recovery times were derived based on the assumption that similar changes in the pharmacokinetics of sugammadex might be seen based on the findings of a study which evaluated the changes in pharmacokinetics of rocuronium in subjects with hepatic impairment. Because changes in the pharmacokinetics of sugammadex in patients with hepatic impairment are not expected, the assumptions of similar impact of hepatic impairment on the pharmacokinetics of sugammadex as observed for rocuronium might not be valid.** (b) (4) **, we would recommend that you conduct a PK-PD study in patients with hepatic impairment.**

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/s/

Allison Meyer
11/24/2008 02:25:25 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-225

Organon USA Inc.
56 Livingston Ave.
Roseland, NJ 07068

Attention: Dori L. Glassner
Director, Regulatory Affairs

Dear Ms. Glassner:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sugammadex sodium injection.

We also refer to your September 4, 2008, correspondence requesting a meeting to discuss the issues outlined in the Not Approvable letter dated July 31, 2008. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting.

The meeting is scheduled as follows:

Date: October 8, 2008
Time: 4:00 pm
Location: White Oak, Bldg. 22
10903 New Hampshire Avenue
Silver Spring, MD 20993

CDER participants: Curtis Rosebraugh, M.D., Ph.D.; Director, ODE II
Bob A. Rappaport, M.D.; Director, DAARP
Rigoberto Roca, M.D.; Deputy Director, DAARP
Leah Ripper; Associate Director of Regulatory Affairs, ODE II
Badrul A. Chowdhury, M.D.; Director, DPAP
Bindi Nikhar, M.D.; Team Leader, Anesthesia, DAARP
Arthur Simone, M.D., Ph.D.; Medical Officer, DAARP
Adam Wasserman, Ph.D.; Supervisor, Pharmacology/Toxicology, DAARP
Zengjun Xu, Ph.D., Pharmacology/Toxicology Reviewer, DAARP
Dionne Price, Ph.D.; Team Leader, Biometrics
Thomas J. Permutt, Ph.D.; Director, Biometrics
Suresh Doddapaneni, Ph.D.; Team Leader, Biopharmaceutics
Ali Al Hakim, Ph.D.; Branch Chief, ONDQA
Alan C. Schroeder, Ph.D.; CMC Reviewer
Allison Meyer; Regulatory Health Project Manager
Ayanna Augustus, Ph.D.; Regulatory Project Manager

Please have all your attendees bring photo identification and allow 15-30 minutes to complete security clearance. Please e-mail me any updates to your attendees at Allison.Meyer@fda.hhs.gov so that our security staff has sufficient advance time to prepare temporary visitor badges. Upon arrival at FDA, give the guards either of the following numbers to request an escort to the conference room: Allison Meyer, x 1258; the division secretary, x 2280.

Provide the background information for the meeting (three copies to the application and 17 desk copies to me) at least two weeks prior to the meeting. If the materials presented in the information package are inadequate to prepare for the meeting or if we do not receive the package by September 22, 2008, we may cancel or reschedule the meeting.

If you have any questions, call me at (301) 796-1258.

Sincerely,

{See appended electronic signature page}

Allison Meyer
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Ayanna Augustus
9/12/2008 12:21:39 PM

Fax

To: Sally Seymour, M.D.

301-796-9728

Fm: Dennis Ownby, M.D.

Confidential

August 1, 2008

Sally Seymour, M.D.
Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Room 3319
Silver Spring, MD 20993-0002

Dear Dr. Seymour:

I have reviewed the materials that accompanied you letter of July 16, 2008. These included:
1. Overview of chemical structure and mechanism of action of sugammadex sodium
2. Division of Pulmonary and Allergy consultation dated May 13, 2005
3. Division of Pulmonary and Allergy consultation dated June 16, 2008
4. The Applicants expert panel summary of April 17, 2008
5. Follow-up comments from the Applicant's expert panel of July 17, 2008
6. Discussion and summary of basophile assay results prepared by the Applicants consultant, (b) (4), May, 2008
7. Applicant's synopsis of skin test study identified as Study 19.4.110, November, 2007
8. Case narratives provided by the Applicant for three patients, numbers 106101008, 109101073, 115101008
9. Case report forms for all 12 suspected cases of anaphylaxis.

You had specifically asked my opinion as to whether any of the cases meet diagnostic criteria for anaphylaxis as outlined by the 2006 Joint NIAID/FAAN Second Symposium on Anaphylaxis (Sampson HA, et al. J Allergy Clin Immunol 2006;117:391-7).

As I interpret the criteria for diagnosis of anaphylaxis proposed in the Symposium, the cases related to sugammadex must meet the first set of criteria shown in Table I of the report. With the administration of sugammadex there was no reason to suspect that sugammadex was either a "likely" or "known" allergen for the subjects in these studies eliminating the second and third sets of criteria. Thus, the cases must show the "Acute onset of illness with involvement of the skin, mucosal tissues or both AND either respiratory compromise or reduce blood pressure. The symposia participants suggested that they expected that the first set of criteria would identify about 80% of cases.

In my opinion, case 106101008 is consistent with the Symposium criteria for anaphylaxis. Symptoms developed within minutes of the infusion. There was involvement of the skin. There was a decrease in blood pressure and an increase in heart rate. The symptom of nausea reported by the subject has been reported to be significantly associated with hypotension in anaphylaxis. (Brown SGA. J Allergy Clin Immunol 2004;114:371-376) Serum tryptase was elevated at 1 and 3 hours after the infusion and returned to baseline by 6 hours. There was also evidence of cutaneous sensitivity to

sugammadex from intradermal skin testing on two occasions making the presence of IgE antibodies specific for sugammadex or some byproduct of sugammadex likely. For me to accept that this subject had a nonallergic reaction to sugammdex would require very strong evidence that sugammadex can directly cause substantial release of mast cell mediators in some individuals.

Case 105101030 is reported to have had a rash on the forearms, flushing, difficulty breathing, documented tachycardia and a globus sensation. This case meets the criteria of rapid onset of skin symptoms. The critical issue is whether there was evidence of "respiratory compromise". It is not clear whether the criterion of respiratory compromise was met because of the inadequate description of the episode. If the patient described tightness of the chest, wheezing or was coughing and also complained of a sensation of swelling or tightness in the throat I would consider this a case of anaphylaxis. If the subject's chest and throat symptoms were less characteristic the case would not meet the criteria but would remain a concern. As a clinician I would strongly recommend that this person never be given this agent again unless it was essential to preserve life.

Case 105101028 meets the criteria of rapid onset of skin symptoms. It is not clear whether the decline in oxygen saturation from 100% to 96% resulted from breathing difficulties or some other reason such as the onset of tachycardia and bigeminy. I do not feel that this case can be accurately characterized because of the lack of information.

Cases 109101073, 115101008 and 105101001 appear to be adverse events related to sugammadex but are not highly characteristic of anaphylactic reactions in my opinion.

In the summary of the applicant's expert opinions there is a strong statement that none of the reactions described in these cases met the criteria of "life threatening" that is most commonly used to characterize anaphylaxis. I have been in many discussions with allergists where the question of whether a diagnosis of anaphylaxis hinges on the criteria of life threatening was discussed. Some practitioners would reserve the term anaphylaxis for systemic allergic reactions that were a major risk to life such as when a person requires mechanical ventilation for hours or days afterwards. They would call milder reactions, systemic allergic reactions, meaning that multiple organ systems were involved but person recovered without requiring major life support interventions. Others would call any systemic allergic reaction involving multiple organ systems anaphylaxis. This is seen in the Symposium report where they use the phrases, "potentially fatal" and "may cause death" rather than "life threatening". I can see why this is an important issue in a regulatory environment but in my opinion the distinction of "life threatening" is not pivotal. If a person has a reaction of sudden onset, that involves two or more organ systems, and there is reason to suspect from the symptoms, skin tests, antibody tests or assays of mediator release that IgE was involved in the pathophysiology of the reaction, I consider the person at high risk for anaphylaxis if reexposure occurs. I think that most experienced clinicians would agree with this assessment. I can not imagine that either Dr. Adkinson or Dr. Busse would agree to give either of the first two patients in this review another full intravenous dose of sugammadex without extraordinary precautions.

The materials you furnished included a summary of the basophile histamine release testing done by (b) (4) The test conditions appear to have been appropriate and there was not clear evidence of IgE antibodies to sugammadex. My concerns about these results are: 1. histamine release is typically less sensitive than skin testing or direct intravenous challenge of an individual, 2. a relatively small number of individuals were tested, and 3. it is possible that sugammadex must be altered in some way in the body before it is capable of causing a reaction and the conditions for this alteration may not have been present in this assay system.

I would like to comment on one other issue that is part of this discussion. I would accept the applicant's assertion that anesthesiologists are well trained to support patients should they experience either anaphylaxis or some other type of severe reaction to this agent resulting in breathing difficulties or hypotension. My concern is the probability that with widespread use sugammadex will be associated with a major reaction in a person who is already physiologically unstable, either because of the type or extent of their surgery, their age or some preexisting condition and it will be the tipping point leading to death. I point to the article by Smith et al. (J Clin Invest 1980;66:1072-1080) demonstrating prolonged hypotension and hypoxia in individuals with anaphylaxis even though they were in an intensive care setting with anesthesiologists providing care at the onset of the anaphylactic episode.

I think that any physician considering the use of sugammadex would want to know whether this agent does produce IgE mediated sensitization or whether individuals with some other IgE sensitization have IgE antibodies which would cross react with sugammadex. (Such as reported with cetuximab, N Engl J Med 2008;358:1109-1117) In either case it would be advisable to screen individuals for sensitization before exposure to the agent. I also think it would be very important to have a reasonably accurate estimate of how often such reactions might be anticipated. I suspect that the use of the agent would be quite different is systemic allergic reactions occurred in 1 in 100 patients versus 1 in 1,000,000.

Thank you for the opportunity to be of assistance.

Sincerely,

Dennis R. Ownby, M.D.
Betty B. Wray Professor of Pediatrics and Medicine
Head, Section of Allergy and Clinical Immunology

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/s/

Allison Meyer
8/15/2008 01:45:03 PM
CSO
on behalf of Dennis Ownby, MD, Betty B Wray
Professor of Pediatrics & Medicine, Head, Section of
Allergy & Clinical Immunology

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-225 **DISCIPLINE REVIEW LETTER**

Organon USA Inc.
56 Livingston Avenue
Roseland, NJ 07068

Attention: June Bray
Vice President, Regulatory Affairs

Dear Ms. Bray:

Please refer to your October 30, 2007, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (b) (4) (Sugammadex Sodium) Injection 100 mg/mL.

We also refer to your submissions dated February 19 and May 16, 2008, which propose a new trade name (b) (4) for your product.

The Division of Medication Error Prevention (DMEDP) has completed the review of your submission and has the following comments. We request a prompt written response in order to continue our evaluation of your NDA.

Proprietary Name

The Division of Medication Error Prevention does not object to the use of the proprietary name, (b) (4) for this product. If any of the proposed product characteristics as stated in this review are altered prior to approval of the product, the Division of Medication Error Prevention rescinds this Risk Assessment finding, and recommends that the name be resubmitted for review.

Container Labels and Carton Labeling

1. Revise the presentation of the strength to follow the United States Pharmacopeia (USP) standard of total drug content followed by the concentration [e.g. 200 mg/2 mL (100 mg/mL)]. Total drug content should have greater prominence than strength.

2. The current presentation of the 2 mL and 5 mL labels are (b) (4) except for the vial size. Revise the labels and labeling so that they are clearly differentiated.

3. Change the font color or increase the prominence of the statement "Professional Sample - Not for Sale" to distinguish the professional sample from the retail product.

4. Per 21 CFR 201.10(g)(2), ensure that the established name is the same font size as the dosage form and at least ½ the size of the proprietary name. Have the prominence commensurate with the prominence of the proprietary name, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.

5. Increase the prominence of the storage precaution statement.

Insert Labeling

6. Revise the presentation of the strength to follow the USP standard of total drug content followed by the concentration [e.g. 200 mg/2 mL (100 mg/mL)]. Total drug content should have greater prominence than strength.

7. Do not use abbreviations (e.g. IV) or trailing zeros (e.g. 4.0 mg/kg) throughout the labels and labeling. FDA launched a campaign warning health care providers and consumers not to use error-prone abbreviations and trailing zeros. We strongly recommend that the abbreviations are written out in full and the trailing zeros are removed throughout the labels and labeling.

8. Remove the parenthesis for the dosing unit (mg/kg) in the table under Section 5.3.

9. Clarify the waiting time instructions for renal impaired patients, because the waiting time for normal renal function is "no waiting time."

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Allison Meyer, Regulatory Health Project Manager, at 301-796-1258.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Parinda Jani
6/18/2008 01:34:59 PM

From:	Walker, Diana
To:	Glassner, D. (Dori)
Subject:	NDA 22225 Clinical Information request 17jun13
Date:	Monday, June 17, 2013 4:31:30 PM
Importance:	High

Dear Dori,

I have received the following request from our clinical reviewer. Please respond to me via email as soon as possible followed by a submission to your NDA 022225. We request a response by Friday, June 21, 2013.

1. **Clarify the date that bradycardia was added to the Warnings and Precautions section and the Adverse Events section of the label?**
2. **Clarify which studies have had final study reports submitted to the agency but were not included in the most recent version of the ISS database.**
3. **Send a copy of all of the postmarketing reports/CIOMS forms that you have received to date.**

Please let me know if you need clarification of these questions.

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
06/18/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-225 **INFORMATION REQUEST LETTER**

Organon, Inc.
56 Livingston Avenue
Roseland, NJ 07068

Attention: Dori Glassner
Director, Regulatory Affairs

Dear Ms. Glassner:

Please refer to your October 30, 2007, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for sugammadex sodium.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. This pertains to your response to our comment #10 in your February 1, 2008, amendment. We recommend in addition that you make a post-approval agreement to evaluate real time stability of the (b) (4) using a validated method over 12 months to support the 12-month retest period, since only 6 months of data have been provided to the NDA using a non-validated HPLC method.

2. The following comment pertains to your response to our comment #8 in your March 10, 2008, amendment. Provide the SOP for visual inspection of Sugammadex Vials.

3. The following comment pertains to your response to our comment #14b in your March 10, 2008, amendment. Provide data to show that the method which you use to extract and determine (b) (4) is equivalent or better to the method described in (b) (4) and therefore, the maximum amount of (b) (4) permitted is the same or lower than the USP method

4. The following comment pertains to your response to our comment #15a in your March 10, 2008, amendment. It is premature to propose a reduced stability testing schedule for annual stability batches prior to the collection and our evaluation of the full stability data from the first three production scale batches. Restore the normal testing schedule in the stability protocol for the annual stability batches.

5. The following comment pertains to your response to our comment #19 in your March 10, 2008, amendment. Clarify that (b) (4) is included in the drug product specification for total degradation products, or justify not including it.

If you have any questions, call Allison J. Meyer, Regulatory Project Manager, at 301-796-1258.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Parinda Jani
5/20/2008 02:39:45 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

PDUFA GOAL DATE EXTENSION

NDA 22-225

Organon USA Inc.
56 Livingston Avenue
Roseland, NJ 07068

Attention: Dori Glassner
Director, Regulatory Affairs

Dear Ms. Glassner:

Please refer to your October 30, 2007, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for sugammadex sodium injection.

On February 28, 2008, we received your February 27, 2008, major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is July 30, 2008.

If you have questions, call me at (301) 796-1258.

Sincerely,

{See appended electronic signature page}

Allison Meyer
Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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 /s/
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Allison Meyer
3/14/2008 12:29:54 PM
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-225 **INFORMATION REQUEST LETTER**

Organon USA Inc.
56 Livingston Avenue
Roseland, NJ 07068

Attention: June Bray
Vice President, Regulatory Affairs

Dear Ms. Bray:

Please refer to your October 31, 2007, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Bridion™ (sugammadex sodium) Injection.

We are reviewing the Chemistry and Labeling sections of your NDA and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Address the following comments related to the labeling package insert:

   a) All headings and subheadings must be highlighted by bold type that prominently distinguishes the headings and subheadings from other labeling information. Therefore, for other labeling information, use bold type sparingly. Use another method for emphasis such as italics or underline (**Warning and Precautions 5.3; Drug Interactions 7.2).**

   b) Check that all the Full Prescribing Information headings and subheadings are named and numbered correctly as outlined under 21 CFR 201.56 (d)(1).

   c) List adverse reactions (in table format) identified in clinical trials that occurred at or above a specified rate appropriate to the safety database (Include event, number of patients, incidence, and comparators, if appropriate)[Clinical Trials Experience subsection].

2. With the description provided we are unable to reproduce the exact non-linear models applied to the degradant data (both primary (Oss) and supporting (Oss and Swords)). Provide for each and every non-linear model applied, the formula for the specific mathematical model employed, the method by which the power parameter was estimated, and the final model based on the data.

The following comments pertain to the drug substance:

3. Specify maximum hold times/conditions for the [redacted] (b) (4) in the synthesis of the drug substance, supported by stability data.

4. Provide master batch records/executed batch records for the drug substance.

5. In view of the stability behavior noted in batch AN, which has [redacted] (b) (4), as well as the data for more recent batches, we recommend that you tighten the limit for the [redacted] (b) (4) impurity in the drug substance.

The following comments pertain to the drug product.

6. Provide sampling plans for the drug product in-process and final product testing.

7. Clarify your [redacted] (b) (4). It appears that the theoretical yield should be close to [redacted] (b) (4) vials based on 2 mL/vial for a [redacted] (b) (4) batch, and based on 5 mL/vial for a [redacted] (b) (4) batch; however, the theoretical yields that you have provided are less than this: i.e., [redacted] (b) (4) vials for the [redacted] (b) (4) (2 mL/vial) batch and [redacted] (b) (4) vials for the [redacted] (b) (4) (5 mL/vial) batch.

8. Clarify the acceptance criteria for the in-process control in drug product manufacture for visual inspection. Provide a justification for not providing master batch records for the drug product (e.g., indicate if no significant changes occurred between the executed batch records of the primary stability batches and the intended commercial batches).

9. Provide a sampling plan for release and stability testing of the drug substance and drug product.

10. Where compendial tests/standards are used that are not USP/NF tests/standards, demonstrate that they are equivalent or better to the current USP/NF tests/standards (if there are such tests/standards in USP/NF) and provide a copy of the non-USP/NF compendial tests/standards.

11. Provide a specific identifying number for each analytical method, with a means to distinguish different versions, e.g., by using a suffix number.

12. The following comment pertains to the method for "assay and identification of Org 25969 and Org 48302 and determination of degradation products by high performance liquid chromatography." Provide a labeled chromatogram to clarify the separation of all peaks in

the chromatogram for this method, including active ingredients, process impurities and degradation products.

13. We note that some of the batches in your release data just meet the minimum requirement for "extractables volume. Ensure that the overfill in manufacturing is sufficient for batches to consistently meet the acceptance criteria for this parameter.

14. The following comments pertain to your container closure system:

    a. Withdraw the proposals to use [redacted] (b) (4), or else provide drug product stability data and container closure data pertaining to these drug product components [redacted] (b) (4)

    b. Provide methods for testing for [redacted] (b) (4) of the glass vials or reference specific USP procedures. Indicate the equivalence of [redacted] (b) (4) expressed as [redacted] (b) (4)

    c. Clarify whether the proposed commercial manufacturing process will receive the rubber stoppers cleaned [redacted] (b) (4) [redacted] (b) (4) stoppers).

15. The following comments pertain to your stability protocol:

    a. Modify your post approval stability protocol for the first three production batches and for the annual stability batches, to include "code C" testing more frequently.

    b. Provide an agreement that you will complete the desired stability studies, submit the results periodically as specified by the Agency, and if approved, that you will withdraw from the market any lots found to fall outside the approved specifications for the drug product. If you have evidence that the deviation is a single occurrence that does not affect the safety and efficacy of the drug product, you should immediately discuss it with the reviewing division and provide justification for the continuing distribution of that lot.

16. Provide information pertaining to the analytical methods and their validations for quantitating leachables and metal chelation in stability samples of drug product.

17. Provide an overall clarification of the executed batch records and the many supplements from your Swords, Ireland facility to assist our review of your NDA. Indicate briefly what is provided in each section and how the separate parts of the batch records fit together to describe the entire manufacturing process. It appears that your "executed batch records" themselves from the Swords site do not seem to be as complete as those from the Oss site.

18. Provide an agreement to revisit the specifications for degradants in the drug product after you have gained more experience with the commercial manufacturing process.

19. Clarify whether the drug product specification for "total degradation products" (with an acceptance criterion of "< (b) (4) %" on stability) includes all of the drug substance related impurities that are controlled in the drug substance as well as the degradation products controlled in the drug product.

If you have any questions, call Allison J. Meyer, Regulatory Project Manager, at 301-796-1258.

Sincerely,

{See appended electronic signature page}

Bob Rappaport, M.D.
Director
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Rigoberto Roca
2/19/2008 05:56:54 PM
for Bob Rappaport, M.D.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-225

Organon USA Inc.
56 Livingston Avenue
Roseland, NJ 07068

Attention: June Bray
Vice President, Regulatory Affairs

Dear Ms. Bray:

Please refer to your new drug application (NDA) dated October 30, 2007, received October 31, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for BRIDION™ (sugammadex sodium) Injection.

We also refer to your submissions dated November 19 and 27, 2007.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is April 30, 2008.

We are reviewing your application according to the processes described in the *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products*. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by March 28, 2008.

During our filing review of your application, we have identified the following potential review issues:

1. Provide a 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.

2. The following comments pertain to your specifications for the proposed starting material, (b) (4).

   a. Identify the qualification process and criteria that you use to select a supplier.

   b. Provide justification with data to ensure that the proposed specifications and your qualification process will provide (b) (4) from multiple suppliers that is suitable for drug substance manufacture, including, for example, a consistent purity profile.

   c. Identify your suppliers and provide documentation to indicate that the gamma-cyclodextrin is made in cGMP compliant facilities.

   d. Specify what tests you perform on receipt of the (b) (4). If you rely on a certificate of analysis (COA) from your supplier, you are reminded that you need to periodically validate the information on the COA.

   e. Add an additional identification specification (i.e., infrared spectrum).

   f. Add appropriate specifications for the following attributes: color and clarity of solution, microbial limits, residue on ignition and reducing substances, to provide increased assurance of the quality of the starting material.

   g. Evaluate residual protein levels in (b) (4) from each of your intended sources, or alternatively, propose a specification to limit (b) (4).

   h. We recommend that you improve the method for assay, identification and related substances in (b) (4), so that it is more robust if small changes in composition of the mobile phase occur.

3. The following comments pertain to the manufacturing process and the control of intermediates for the drug substance.

   a. Provide summary data to justify the acceptable operating ranges for each (b) (4).

   b. Indicate what controls are employed to ensure completion of each (b) (4)

   c. Implement an assay specification for the (b) (4) and improve the specification for total organic impurities (to obtain a more accurate impurity profile) by developing a more specific impurities method which does not have such large differences in molar extinction coefficients for the (b) (4) and the potential impurities, and improve the robustness of the method.

4. The following comments pertain to drug substance impurities:

   a. Provide clarification of your reason for not evaluating organic impurities with [redacted] (b) (4)).

   b. Indicate whether any impurities have been detected which contain multiple [redacted] (b) (4) .

   c. This pertains to the drug substance specifications for specified unidentified organic impurities: indicate the identified and unknown impurities represented by each relative retention time (e.g., [redacted] (b) (4) impurity). This may be done in a footnote on the written specification.

   d. List identified impurities at levels above the identification threshold (such as [redacted] (b) (4) currently identified as [redacted] (b) (4) impurity) in the drug substance specifications as specified identified organic impurities.

5. The following comments pertain to the drug substance specifications:

   a. Develop specifications for the following parameters: color and clarity of solution, specific rotation, tests for yeasts and molds and absence of objectionable microorganisms (e.g., Salmonella species and Escherichia coli), and residue on ignition.

   b. Use USP test methods for water content, microbial limits, and bacterial endotoxins, unless you can demonstrate that the Ph. Eur. and JP methods are equivalent or better to the USP methods.

   c. Provide an agreement to revisit your impurity specifications after you have additional experience with the manufacture of the drug substance.

6. The following comments pertain to your analytical procedure: "Assay and Identification of Org 25969, Org 48302 and Determination of Impurities by High Performance Liquid Chromatography."

   a. Provide assurance that the proposed System Suitability Test requirements will ensure adequate resolution between peaks that are (or may be) close together. Examples of this include (but are not limited to) peaks corresponding to [redacted] (b) (4) and peaks corresponding to [redacted] (b) (4) and [redacted] (b) (4)

   b. Assign unique identifying numbers to your analytical procedures, with a provision for suffixes so that different versions of each method can be tracked.

c. Remove [redacted] (b) (4)," from HPLC columns designated in the methods, but you may list all validated columns.

d. Clarify in the method the preparation of [redacted] (b) (4)

7. The following comment pertains to your drug substance method for residual solvents by capillary headspace gas chromatography. Modify the method for residual solvents to include a system suitability test for resolution between [redacted] (b) (4).

8. The following comment pertains to your batch analyses for the drug substance batches.

   A number of batches of drug substance appear to be [redacted] (b) (4), when the assay (total Org 25969 and Org 48302, [redacted] (b) (4)) and total organic impurities are summed [e.g, assay plus total impurities = [redacted] (b) (4) (batch AP), [redacted] (b) (4)% (batch AQ), [redacted] (b) (4)% (batch L00027961)]. Explain the [redacted] (b) (4) observed.

9. The following comment pertains to your justification of the impurity specifications.

   Clarify why impurity [redacted] (b) (4) was not observed in the drug substance after batch AE, and why [redacted] (b) (4) was not observed in the drug substance prior to batch AE.

10. Provide maximum hold times for drug substance intermediates along with supportive stability data.

11. The only letters of authorization (LOAs) for supporting Drug Master Files (DMFs) found in the NDA are for DMFs [redacted] (b) (4) and [redacted] (b) (4). Provide all missing DMF LOAs.

12. Submit or identify the location in the submission for the following datasets to support PK/PD modeling and simulation analyses:

    a. All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been **excluded from the analysis** should be flagged and maintained in the datasets.

    b. Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

    c. A model development decision tree and/or table which gives an overview of modeling steps.

For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We acknowledge receipt of your request for a deferral of pediatric studies for this application for all pediatric patients including neonates, infants, children and adolescents.

If you have any questions, call Allison Meyer, Regulatory Project Manager, at (301) 796-1258.

Sincerely,

{See appended electronic signature page}

Bob Rappaport, MD
Director
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Bob Rappaport
12/27/2007 02:03:06 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-225

NDA ACKNOWLEDGMENT

Organon USA Inc.
56 Livingston Avenue
Roseland, NJ 07068

Attention: June Bray
Vice President, Regulatory Affairs

Dear Ms. Bray:

We have received your new drug application (NDA) submitted pursuant to section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Bridion™ (sugammadex sodium) 100 mg/mL injection

Date of Application: October 30, 2007

Date of Receipt: October 31, 2007

Our Reference Number: NDA 22-225

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 30, 2007 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must be in the Prescribing Information (physician labeling rule) format.

The NDA number provided above be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia and Rheumatology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http:www.fda.gov/cder/ddms/binders.htm.

If you have any questions, call me at (301) 796-1258.

Sincerely,

{See appended electronic signature page}

Allison Meyer
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Allison Meyer
11/14/2007 10:59:45 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 68,029

Organon
56 Livingston Avenue
Roseland, NJ 07068

Attention: Dori Glassner
Director, Regulatory Affairs

Dear Ms. Glassner:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Org 25969 Injection.

We also refer to the meeting between representatives of your firm and the FDA on October 30, 2006. The purpose of the meeting was to discuss your plans for submitting an NDA.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1258.

Sincerely,

{See appended electronic signature page}

Allison Meyer
Regulatory Project Manager
Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

SPONSOR MEETING AGENDA

MEETING DATE: October 30, 2006

TIME: 3:30 pm

LOCATION: White Oak, Bldg. 22, Rm. 1311

APPLICATION: **IND 68,029**

PRODUCT: Org 25969

INDICATION: **Reversal of Neuromuscular Block**

SPONSOR: **Organon**

TYPE OF MEETING: Pre-NDA meeting

MEETING CHAIR: Sharon Hertz, MD; Deputy, Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)

MEETING RECORDER: Allison Meyer, Regulatory Project Manager

FDA Attendees	Title
Bob Rappaport, MD	Director
Sharon Hertz, MD	Deputy Director
Lex Schultheis, MD, PhD	Medical Officer
Adam Wasserman, PhD	Supervisor, Pharmacology/Toxicology
Ali Al Hakim, PhD	Pharmacuetical Assessment Lead
David Lee, PhD	Biopharmaceutics Reviewer
Dionne Price, PhD	Acting Team Leader, Statistics
Yongman Kim, PhD	Statistics Reviewer
Marty Pollock, PharmD	OSE, Safety Evaluator
Allison Meyer	Regulatory Project Manager
Organon	**Title**
Patrick Boen, MD	Medical
June Bray	Regulatory Affairs
Annie DePasquale	Regulatory Submissions
Diels van den Dobbelsteen, PhD	Toxicology and Drug Disposition
Dori Glassner	Regulatory Affairs
Gerald Quirk	Clinical Documentation
Henk Rietbergen	Biometrics
Sabina Rouf, PhD	Regulatory Affairs, CMC
Jean Smeets, PhD	Clinical Pharmacology and Kinetics
Tiffany Woo	Clinical Development
Alex Zwiers	Regulatory Affairs

Discussion: Following introductions, the discussion focused on the questions that were included in the September 27, 2006, meeting package. Prior to the meeting, the Sponsor was provided responses to the questions. The questions are presented below in *italicized* text, Agency responses, prepared prior to the meeting, are **bolded**. Discussion is presented in normal text.

CMC

Question 1: Does the Agency concur that the stability data from Organon (Ireland) Limited and N.V. Organon, Oss, The Netherlands is sufficient to support the proposed shelf-life of (b) (4) months at room temperature if supported by statistical evaluation of stability data?

FDA Response:
CMC information regarding details and comparison of the manufacturing processes performed at the above two sites which produced the stability batches should be provided in the NDA. These data will be reviewed and evaluated with respect to the proposed expiry dating of (b) (4) months.

Submit the stability data in SAS transport format program that includes all stability indicating attributes.

Question 2: Does the Agency concur that the (b) (4) of Org 25969 Solution for Injection is an (b) (4)?

FDA Response: The information provided supports the assertion that the (b) (4) Because you have referenced (b) (4) documentation we want to clarify that (b) (4) is not an option until a suitable period of successful operation of the proposed cycle has been accomplished. The release specifications should include a sterility test.

Discussion: The Sponsor explained that they did not intend to do (b) (4) testing, however, a (b) (4) within USP standards is being utilized. The Division stated that the USP cannot be the only reference, validation of the sterilization cycle is also necessary. The Sponsor will provide validation of the (b) (4) cycle.

Question 3: Does the Agency concur with the proposed Table of Contents for the Drug Substance part of Module 3 for Org 25969?

FDA Response:
Yes

Question 4: ...Organon, therefore, proposes to submit one EBR for each presentation of primary stability batch manufactured at N.V. Organon and Organon (Ireland) Limited in the NDA (four EBRs in total) and no EBR for the Phase 3 clinical batches. Does the Agency concur with Organon's proposal?

FDA Response:
The proposal is acceptable provided that:

- **The manufacturing processes from the above two sites are comparable and identical.**
- **The primary stability batches are representative of the Phase 3 clinical batches**
- **The primary and Phase 3 batches are produced under a similar manufacturing process**
- **All batches are manufactured at comparable scale**

Question 5: ...For Org 25969 Method Validation Package, Organon proposes to provide this information for only non-compendial methods used for release testing of drug substance and drug product batches from which samples will be submitted for method validation. For compendial methods, references to the relevant chapters of the pharmacopoeias will be provided. Does the Agency concur with Organon's proposal?

FDA Response:
The proposal is acceptable provided that full details of the non-compendial methods will be provided in the NDA (i.e. experimental details of each method and its corresponding validation). For compendial methods, appropriate references (method name and relevant chapter) should be provided in the NDA. A complete validation package for the endotoxin testing method per <USP85> and limits selected should be included in the application.

Additional CMC comments for the NDA:

- **For the drug substance, related impurities must be monitored and reported when above (b) (4)%, identified when possible when above (b) (4)%, and qualified when consistently above (b) (4)%. Impurities exceeding (b) (4)% in the drug substance should be supported by safety studies.**

- **For the drug product, process impurities need not be quantitated in the drug product, but their levels should be listed and designated as having been quantitated at the drug substance stage. However, degradants must be monitored and reported when above (b) (4)%, identified when possible when above (b) (4)%, and qualified when consistently above (b) (4)%.**

- **The limits for impurities and degradation products in the drug substance and drug product should conform to ICH Q3A "Impurities in New Drug Substances," dated February11, 2003) and Q3B "Impurities in New Drug Products" dated November 14, 2003) guidelines.**

- **It is recommended that the test methods and acceptance criteria be based on ICHQ6A guideline " Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances"**

- **Submit a well documented pharmaceutical development report as per ICHQ8 guideline**

- **Provide a statement that all sites involved in manufacturing, testing and packaging of the drug substance and the drug product are ready for inspection**

- **Provide complete names, addresses, CFN numbers and contact persons for the above sites**

Discussion: The Sponsor noted that base on a previous agreement, impurities determined to be (b) (4) were allowed to have a higher qualification threshold than recommended in ICH guidelines. The Division confirmed that the agreement stated that impurities which were (b) (4) as defined in previous discussions could have a specified limit of (b) (4)%. The Division noted that all other impurities not meeting the prespecified definition would be held to standard ICH limits for reporting, identification, and qualification.

Pharmacology/Toxicology

Question 6: Does the Agency concur with this proposal for qualification of new (b) (4) *s found in subsequent batches after NDA approval?*

FDA Response:
This extended single-dose toxicity studies in combination with a single Ames test is acceptable for (b) (4) **without structural alerts for genotoxicity; however, the Sponsor should utilize all bacterial strains unless justification can be provided that the two strains suggested are most appropriate.** (b) (4) **with structural alerts will require a full evaluation in two in vitro genotoxicity tests.**

Question 7: …Given the ADME profile of Org 25969, Organon proposes not to perform any Cytochrome P450 inhibition study and drug metabolizing enzyme induction studies. Does the Agency concur?

FDA Response:
Yes

Question 8: Reference is made to our submission dated May 26, 2005 (serial no. 025) at which time we submitted the justification for the higher NOEL in the rabbit embryo-fetal development study. Does the Agency concur with the justification?

FDA Response:
We concur with this justification.

Clinical/Statistical

Question 9: Does the Agency agree that appropriate and adequate efficacy studies have been conducted to support the review of the NDA?

FDA Response: The pivotal studies appear to be adequately designed to support efficacy. The complete thorough QT study report should be included with the NDA submission.

Question 10: Does the Agency agree that the proposed presentation of efficacy data in CTD Module 2.7.3 is appropriate to support the review of the NDA?

FDA Response:
In general, your proposed presentation of efficacy data appears to be adequate.

Data from studies of Org 25969 administration at 1-2PTCs and studies where Org 25969 was given 15 minutes after a neuromuscular blocking agent should be analyzed independently. Your analysis of data pooled from both types of studies may also be presented in addition to separated analyses of the individual studies.

Studies where Org 25969 was given to immediately reverse a maximum neuromuscular blockade will not be considered as an evaluation of "Emergency Reversal" because the studies were not conducted under emergency conditions.

Discussion: The Sponsor recognized that they did not study "emergency patients," and will refer to these patients as having had "immediate reversal" for purposes of discussion in the NDA application. The Sponsor would like to include the study in the clinical studies section of the package insert, but was not proposing terminology for the label at this time. The Division agreed that it was premature to discuss specific wording for the package insert.

The Sponsor referred to page 57 and 59 of the briefing book, referencing a trial for pediatric and adult patients. The pediatric data from this study will not be included for efficacy, however, it will be summarized for safety in the NDA. The Division indicated that this was acceptable.

Question 11: Does the Agency agree that appropriate and adequate safety evaluations have been conducted in the studies to support the review of the NDA?

FDA Response: It appears to be acceptable. The final determination is made during the filing review.

Question 12: Does the Agency agree with the safety data presentation in CTD Module 2.7.4 and the ISS located in Module 5.3.5.3?

FDA Response:
In general, the proposed presentation of safety data appears to be acceptable.

An analysis of all cases of recurarization should be presented. An early concern regarding Org 25969 was the potential that the free drug could also bind concomitant medications. Evidence that concomitantly administered medication required dose adjustment in clinical trials should be presented and separately analyzed.

Discussion: The Sponsor stated that Phase 3 records of recurarization with exogenous compounds are available. There are a handful of case narratives associated with CRFs that identify recurarization as an adverse event. The Sponsor planned to pool safety information for Phase 2 and 3 studies where Org 25969 was used in conjunction with a neuromuscular blocking agent, and analyze safety for Phase 1 separately because Phase 1 studies evaluated administration of Org 25969 alone. The Division recommended presenting safety data using several approaches, particularly for the AE profiles. For example, it would be useful to understand whether an adverse event was associated with Org 25969 given by itself and/or when given concomitantly with a neuromuscular blocking agent. The largest "N" could then be used for each type of adverse event to provide the most informative data for the label.

Question 13: Organon plans to include subject narratives for SAE's and deaths that occur. Does the Agency agree with our proposal regarding the presentation of subject narratives?

FDA Response:
Submit narratives for patients who were discontinued because of an adverse event. Narratives of cases of recurarization and of changes in concomitant drug dosing in the perioperative period will also be requested. Narratives of adverse events related to ventilation or perioperative decrements in renal function will also help to expedite the review.

Question 14: Does the Agency agree to defer the pediatric studies for all ages until 3 years after NDA approval?

FDA Response: It may be possible to defer pediatric studies. Provide a rationale for your proposed request to defer for 3 years.

Discussion: The Division stated that the rationale should be provided with the NDA.

Question 15: Does the Agency agree with Organon's proposal regarding the format of an electronic submission:

FDA Response: Your proposed format appears to be acceptable.

Question 16: Organon is proposing to provide electronic data sets for Phase 1, 2, and 3 studies in accordance with the January 1999 Guidance for Industry titled "Providing Regulatory Submissions in Electronic Format – NDAs." Does the Agency agree with Organon's proposal?

FDA Response: The 1999 eNDA Guidance has been withdrawn. After 12/31/2007 all electronic NDA submissions must be in eCTD format. See "Providing Regulatory Submissions in electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications" 4/19/06 and "Study Data Specifications" updated 7/7/2006 at http://www.fda.gov/cder/regulatory/ersr/ectd.htm. In the meantime, legacy (non-eCTD) electronic submissions will be accepted.

Question 17: Based on the information presented in this pre-NDA meeting package, does the Agency agree that the proposed NDA submission is adequate for review to support an indication of reversal of neuromuscular block induced by rocuronium or vecuronium?

FDA Response: It appears to be acceptable. The final determination is made during the filing review.

……..

Additional FDA Comments:

1. Your integrated safety dataset must include the following:

    a. a unique patient identifier
    b. the Study number
    c. the treatment assignment
    d. the gender, chronological age (not date of birth), race and any other relevant demographic characteristics
    e. dosing at time of the reported adverse event
    f. dosing prior to adverse event (if dosing was changed)
    g. the duration of each adverse event (or start and stop dates)
    h. the total time exposure to the study drug at time of the adverse event
    i. the outcome of event
    j. a flag indicating whether or not the event occurred within 30 days of discontinuation of active treatment (either due to premature study drug discontinuation or protocol-specified end of active treatment due to end of study or crossover to placebo)
    k. a marker for serious adverse events
    l. the verbatim term and the preferred term
    m. all concomitant medications
    n. dates, formatted as dates rather than text

Discussion: The Sponsor stated, in reference to (d), that the Phase 3 studies will follow the 2005 guidance for demographics, while the Phase 1 and 2 studies will follow the earlier guidance. The Division agreed.

The Sponsor stated, in reference to (j), that the reports will indicate a 7-day timeline, rather than 30 days. The Division agreed.

2. Ensure that coding of variables is consistently applied across all datasets. For example, a dataset code for placebo should be identical for all study data tables rather than "PBO" for one study and "0 mg" in another study.

3. All datasets must contain the following variables/fields (using consistent format and coding):

    a. Unique patient identifier
    b. Study number
    c. Treatment assignment
    d. Demographic characteristics (age, race, gender)

4. Similar datasets must be consistent in the use of variable names and coding for all trials. For example, in efficacy datasets, a variable such as the demonstrated presence of head lift for > 5 seconds should not be listed as "DIDITOK" in one trial and "HEADSUP" in another trial.

5. All datasets must be in SAS Transport format.

Discussion: The Sponsor stated that they will also provide XLM files for ECG data. The Division agreed.

6. If MedRA is used for coding adverse events, all hierarchal levels of coding should be included, as well as the verbatim term:

    a. System organ class (SOC)
    b. High level group terms (HLGT)
    c. Higher level terms (HLT)
    d. Preferred terms (PT)
    e. Lowest level terms (LLT)

7. In addition to CRFs for all deaths and SAEs, provide CRFs for all patients who discontinued from all studies, including those who discontinue because of:

    a. Adverse events
    b. Investigator decision
    c. Sponsor request
    d. Withdrew Consent

e. Other: For patients listed as discontinued due to 'other' reasons, the verbatim reason for discontinuation (as written in the CRF) should be included in the dataset.

Discussion: The Sponsor stated that there are a low number of narratives for these events in the CRFs. The Division stated that they should be ordered by category and identified in the table of contents.

8. A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities should be provided. Also, a listing should be provided of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the "investigations" SOC or in an SOC pertaining to the specific abnormality. For example, all AEs coded as "hyperglycemia" (SOC metabolic) and "low blood glucose" (SOC investigations) should be tabulated. Analyses of the frequency of specific abnormalities across treatment groups are not sufficient without ready identification of each patient with such abnormalities by their unique patient identifier.

9. Analyses of laboratory values should include assessments of changes from baseline to worst value, not simply the last value.

Discussion: The Sponsor stated that this will be done in the ISS, not in each study report. The Division agreed.

10. Provide a comprehensive index of the submission to include all headings as well as an index of all the literature references included in the submission.

Discussion: The Sponsor stated that the index will be submitted in accordance with the eCTD guidance. References will be listed in Module 2 only as summary documents. The full references will be provided upon request.

Action Items:

The Sponsor will:

1. Provide information to support the validation of sterility testing.
2. Provide justification of the higher identification/qualification limits of impurities.
3. List patient IDs for 5 categories in the CRFs.
4. Submit XLM files for ECG data.
5. Provide justification of pediatric deferral in the NDA submission.
6. Pool safety data in the NDA submission.
7. Submit tradename for review.

Minutes recorded by:
Allison Meyer, Regulatory Project Manager

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/s/

Allison Meyer

12/1/2006 02:56:51 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 68,029

Organon USA, Inc.
375 Mt. Pleasant Avenue
West Orange, NJ 07052

Attention: Dori Glassner
Director, Global Regulatory Affairs

Dear Ms. Glassner:

Please refer to the meeting between representatives of your firm and FDA on May 3, 2005. The purpose of the meeting was to discuss the results of the Phase 2 program for Org 25969 and the upcoming development program for Phase 3.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7426.

Sincerely,

{See appended electronic signature page}

Allison Meyer
Regulatory Project Manager
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

Industry Meeting Minutes

Date/Time: May 3, 2005/ 11:00 am
Location: Parklawn, Conference Room C
Application: **IND 68,029**
Sponsor: Organon USA, Inc.
Drug/Dosage Form/Doses: Org 25969
Indication: Reversal of neuromuscular block induced by rocuronium or vecuronium
Type of Meeting: Type B
Meeting Chair: Rigoberto Roca M.D., Deputy Director
Minutes Recorder: Allison Meyer, Regulatory Project Manager

Sponsor Attendees	**Title**
Patrick Boen, M.D.	Medical Affairs
Diels van den Dobbelsteen, Ph.D.	Toxicology and Drug Disposition
Peter Glass, M.D.	Consultant Anesthesiologist
Dori Glassner	Regulatory Affairs
Bart Ploeger, Ph.D.	Consultant
Meera Rangarajan, Ph.D.	CMC
Henk Rietbergen, Ph.D.	Biometrics
Jean Smeets, Ph.D.	Clinical Pharmacology and Kinetics
Sabina Rouf, Ph.D.	Regulatory Affairs, CMC
Jan Vader, Ph.D.	Process Chemistry
Tiffany Woo	Clinical Development
Alex Zwiers	Regulatory Affairs
FDA Attendees	**Title**
Bob A. Rappaport, M.D.	Division Director, DACCADP
Rigoberto Roca, M.D.	Deputy Director
Arthur Simone, M.D., Ph.D.	Acting Team Leader, Anesthetics
Lex Schultheis, M.D., Ph.D.	Medical Reviewer
David Eric Lees, M.D.	Medical Reviewer
Ravi Harapanhalli, Ph.D.	Team Leader, Chemistry
Dan Mellon, Ph.D.	Team Leader, Pharmacology/Toxicology
Dionne Price, Ph.D.	Statistician
Suliman Al-Fayoumi, Ph.D.	Biopharmaceutics Reviewer
Shannon Benedetto, Pharm.D., MBA	Regulatory Review Officer, DDMAC
Elaine Hu, R.Ph.	Group Leader, DDMAC
Debi Tran, Pharm.D.	Regulatory Reviewer, DDMAC
Allison Meyer	Regulatory Project Manager

BACKGROUND: Phase 2 development is nearing completion in the United States and Europe, therefore, Organon plans to begin Phase 3 in the United States and Europe during 2nd quarter 2005. Accordingly, at this time Organon would like to discuss proceeding with the Phase 3 clinical development in the United States and Europe.

DISCUSSION: Following introductions and opening remarks, the discussion focused on the Sponsor's questions that were included in the March 31, 2005, meeting package. The Sponsor's questions are presented below in *italicized* text and in the order in which they were addressed at the meeting. Agency responses, prepared prior to the meeting and presented on slides, are **bolded**. Discussion is presented in normal text.

Note: Answers to the questions were provided to the Sponsor prior to the meeting. Only the questions needing clarification were discussed.

Question 1a: Does the Agency agree with the proposed specification setting for the drug substance?

FDA RESPONSE

- **The proposed specification setting strategy based on statistical analysis, process development, analytical capabilities, and toxicological qualifications seems appropriate.**
- **The proposed acceptance criteria for the impurities are considered tentative in nature and will be evaluated at the NDA.**
- **A major unidentified impurity at** (b) (4) **is currently proposed at NMT** (b) (4) **% and is considered an overestimation because of** (b) (4) **. Structural identity and response factor determinations are expected for this impurity at the NDA.**
- (b) (4)
  - **Structural identity and similarity with the drug substance**
  - **Revised acceptance criteria based on the determination of the true response factor**
  - **Analysis of all batches considered representative of the proposed commercial manufacturing process**
- (b) (4)
- **It is therefore recommended that this issue be resolved as soon as possible, preferably at the pre-NDA meeting.**

Discussion: There was no further discussion on this question.

Question 1b: (b) (4) *herefore, Organon has developed a proposal on how to present this approach in the CMC section of the NDA as well as in the package insert. Does the Agency concur with this proposal?*

FDA RESPONSE

- **The approach seems reasonable. However, its regulatory implications will be assessed at the NDA.**
- **The acceptance criteria for Org 25969 and Org 48302 will be assessed and finalized during the NDA review.**
- (b) (4) .

Discussion: (b) (4)

The Sponsor confirmed that they are detecting only a single impurity containing a (b) (4) . Further, the Sponsor confirmed that all of the impurities they have identified to date contain a (b) (4) .

Additional CMC Comments for the NDA

- **Fully validated analytical methods**
- **A well documented pharmaceutical development report includes a description of how raw material controls and synthetic process optimization led to a reduction in the formation of impurities and by-products.**
- **Fully validated analytical methods**
- **A well documented pharmaceutical development report includes a description of how raw material controls and synthetic process optimization led to a reduction in the formation of impurities and by-products.**

Discussion: There was no further discussion on this slide.

Pharmacology/Toxicology Comment

- **The qualified level of Org 48302 in the Embryo-fetal development study in the rabbit (30 mg) is below the maximal human exposure to the compound at the upper**

end of its specification (73 mg in a 65 kg individual). This study should be repeated unless an adequate justification can be provided.

Discussion: The Sponsor referenced pages 247-248 of the meeting package, stating that the NOAEL at 65 mg/kg/day in the embryo rabbit study qualified at 30 mg; however, the rat study has an even higher qualification. The Sponsor considered 65 mg a conservative estimate. In terms of the toxicity noted, the 65 mg/kg/day dose resulted in fetal body weight reduced by 14%; however, this factor is considered to be attributed to the larger number of pups in the litters of some dams. Specifically, they noted that there was reduced fetal body weight in dams with a litter of 12 or more pups. The incidence of such litters was higher in the high-dose group, occurring in 58% of litters.

The Division requested that the Sponsor provide their rationale for the use of the higher NOAEL value along with supporting documentation from the literature for review. The Division will examine the submission and let the Sponsor know if we concur with the proposed evaluation.

Question 2: What is the response to the PK/PD model submission dated July 15, 2004 and August 25, 2004?

FDA RESPONSE

- **The overall design of the PK/PD model submitted appears acceptable though the selection of the first decision point in your overall interaction strategy, the KA value cut-off of the interacting drug, may be set too high.**
  - **Based on the in vitro drug interaction study involving Org 25969, naloxone and remifentanil submitted (Serial #003, Appendix 5) Org 25969 at a relevant concentration produces a decrease in the free remifentanil and free naloxone concentrations in the isolated mouse vas deferens model and shifts the naloxone curve indicating a reduced effect of naloxone. This interaction occurs at a KA = 0.05 (remifentanil) and KA=0.018 (naloxone) which are at or below your proposed cut-off value.**

Discussion: The Sponsor asked for a more detailed response to this question. Dr. Mellon indicated that the Division is concerned with the proposal to establish the K_A value associated with remifentanil as the cut-off point below which there would be no need for further evaluation of potential drug interactions. Specifically, the data demonstrating an apparent Org 25969 interaction with naloxone, which has a lower K_A value then remifentanil, argues that there are potential interactions with drugs that would be excluded from further evaluation based on the K_A value proposed as the cut off point. As the PK/PD model is important to establishing the profile of Org 25969, it will need to be supported by additional data.

Question 3: Organon concludes that the effect of foamy cytoplasma of umbrella cells/hypertrophy of urothelium of urinary bladder as observed in repeated dose toxicity studies in the rat is of little if any relevance for man based on the wide safety windown and the apparent higher sensitivity of rodents to this effect. Organon proposes to not perform any further preclinical work to study this effect. Does the Agency concur with this proposal?

FDA RESPONSE

- **Yes**

Discussion: There was no further discussion on this question.

Question 4: Organon concludes that the slight retention of Org 25969 in bone is without biological consequences and further toxicological investigations and therefore not performed. To study the fate of the retained radiolabeled Org 25969, Organon proposes (b) (4) *. Does the agency concur with this proposal?*

FDA RESPONSE

- **No**
- **You should determine the duration until complete removal of radiolabeled Org 25969 from both femur bone and joint as well as a selection of other similar sites.**
- **An appropriate non-rodent mammal will need to be examined for bone deposition and retention. This model should be selected to mimic the bone quality, structure and turnover observed in humans as closely as possible.**
- **Testing should be performed that will identify the cellular binding sites for Org 25969 within bone and fully characterize its effect on dynamic mechanisms responsible for bone growth, modeling and remodeling.**
- **Juvenile animal studies will need to be conducted prior to the conduct of any pediatric studies with Org 25969.**

Discussion: The Sponsor noted that they have already begun to further characterize the potential significance of the apparent bone deposition and will examine additional bones and joints via drug deposition studies. The Sponsor expressed concern that the use of micro-radiography will not provide adequate resolution to identify the molecules that the radiolabel was binding to, and asked if the Division could suggest another method of analysis. Dr. Mellon noted that he did not have a method in mind, however, should internal discussions raise a possible method, the Division would inform the Sponsor. The Sponsor hypothesized that the molecule may bind to carboxylic acid groups, and there is a high chance of it binding to calcium as well. The Sponsor stated they would like to study this in the rat model since that is where they have noted the accumulation and inquired if the Division thought that would be acceptable. The Division noted that in terms of long-term effects on bone quality, the rat may not be the best model to mimic the potential stresses on the joints. The Sponsor should examine and provide data from other potential models, and if they feel that the rat is the most appropriate model, they should submit the justification to the Division for evaluation.

The Sponsor noted that bone quality was studied in a 4-week toxicology study. Following discussions with their consultants on this issue, the Sponsor concluded that process staining was an adequately sensitive marker, and thus, did not conduct biomechanical studies. The Sponsor stated that they do not believe that the findings indicate clinically significant alterations and noted that there were no signals noted in the embryofetal development studies. However, the Sponsor could evaluate bone quality assessments in the juvenile animal study.

The Division requested data to show specifically where and to what Org 25969 is binding in the body and to clarify if it also accumulates in other joints. The Division indicated that it is important to show complete reversal of the apparent accumulation in both the joint and bone. The Division suggested that the Sponsor continue to work on the mechanism studies as they may clarify the most appropriate path forward for development of the drug product.

Question 5: The human ADME characteristics of Org 25969 are well understood from available preclinical and clinical studies. Therefore, Organon believes that a dedicated excretion balance/metabolism study with radiolabeled drug in humans is not warranted and is proposing not to conduct such a study as part of the clinical development program for Org 25959. Does the Agency concur?

FDA RESPONSE

- **You should conduct a mass balance study as available data does not appear to account for the total disposition of Org 25696 in humans.**

Discussion: The Sponsor stated their intention is to perform a urinary excretion study rather than a radiolabeled mass balance study. If significant levels are found, mass balance studies would not be done. The Sponsor asked if a 90% urinary excretion level will be satisfactory. Metabolism is unlikely to play an important role in the elimination of Org 25969 as metabolism and mass balance studies have already been performed in the rat and dog, and they show that less than 1% is metabolized.

The Division stated that 90% seems reasonable, but the data will have to be analyzed. Understanding where the compound is excreted is necessary for the benefit versus risk analysis. The data on the extent of drug elimination in the urine needs to be provided. The drug-drug interaction model seems reasonably predictive, however it needs further validation. The data for validation could be generated in the pivotal trials.

Dr. Mellon suggested that the Sponsor may find that data from a human mass balance study could prove valuable for interpreting the preclinical data suggesting deposition in bone.

Question 6: Does the Agency agree with our proposal to use a one-sided significance level of 0.025 in the pivotal trials?

FDA RESPONSE

Yes, the proposal is acceptable.

- **The statistical justification provided for the transformation of the response variable is valid; however, you should also give consideration to the effect of the transformation on the clinical interpretation of the results.**

- **You should specify a plan to handle missing data.**

Discussion: There was no further discussion on this question.

Question 7: Does the Agency consider the clinical development program sufficient to support the intended indication and dosing recommendations?

FDA RESPONSE:

The general plan to focus study recovery from T2 and from 1-2 PTC is reasonable. Your pivotal trials should encompass the range of clinical comorbidity (ASA 1-4) and demographics expected to be encountered in practice when reversal of NMB is indicated. Focused studies of special populations such as the elderly or patients with renal insufficiency are useful, but should not result in exclusions for the pivotal trials.

Discussion: There was no further discussion on this question.

Comments on Studies 19.4.301 and 302

- **While your preliminary work did not demonstrate a difference in the time to reverse neuromuscular blockade used with sevoflurane compared to propofol, the data are limited. The anesthetic regimens should be comparable between treatment groups.**

- **Reversal of deep neuromuscular blockade with neostigmine is not standard clinical practice and may result in delayed recurarization. The rationale for using neostigmine as a comparator reversal agent from deep neuromuscular blockade 1-2 PTC should be clarified.**

Discussion: The Sponsor stated their intention to remove the option to use propofol from the protocol. A new revision to the development plan incorporates a pilot study of attempted reversal from deep neuromuscular blockade using neostigmine while patients are extensively monitored. This pilot study is expected to demonstrate that reversal of deep neuromuscular blockade with neostigmine is ineffective and will be helpful in determining an appropriate comparator for the planned pivotal trial 19.4.302.

Study 19.4.303

- **The 3 minute latency between administration of rocuronium and Org 25969 may be longer than necessary to demonstrate emergency reversal of rocuronium. The reasoning for the time delay before treatment should be supported.**

Discussion: The Sponsor indicated that reversal of rocuronium is most difficult 3 minutes after administration because muscle weakness is at its maximum. Attempted reversal of rocuronium at less than 3 minutes is expected to be less problematic. Their goal is to evaluate the ability of Org 25969 to reverse neuromuscular blockade in the worse case scenario.

Question 8: Organon plans to utilize the same dose of Org 25969 for both rocuronium-induced block and vecuronium-induced block in the two pivotal trials (19.4.301 and 19.4.302). Organon

is proposing that the results of these studies will also be used to support the use of as well as dosing recommendations for Org 25969 for reversal of vecuronium-induced block in the special populations. Does the Agency agree with our proposal?

FDA RESPONSE:

Extrapolation is not possible for groups where dosing has not been approved such as the use of vecuronium in pediatric patients under the age of 7 weeks. It may be possible to extrapolate dosing in adult populations with renal disease and in the elderly age group.

Discussion: There was no further discussion on this question.

Question 9: Organon would like to readdress the issue with the Agency to obtain concurrence on the use of AMG throughout the Phase 3 program for measurement of our efficacy parameters.

FDA RESPONSE:

While the use of AMG may be scientifically justifiable, it is not a technique commonly used in the United States. It will be difficult to base (b) (4) guidance for Org 25969 entirely on results of an assessment tool that is not used frequently in the typical clinical setting.

Discussion: The Sponsor indicated that, in study 194311, they plan to collect elapsed-time data beginning with the administration of Org 25969 and ending with the reversal of neuromuscular blockade. An open-label study is planned with objective monitoring. The Sponsor asked if, for example, 95% of patients were reversed in 4 minutes and 99% of patients were reversed in 7 minutes, could these data be used to guide clinical use of their product. The Sponsor stated that their impression was that anesthesiologists use both the elapsed time from drug administration and the patient response to twitch monitoring to estimate residual neuromuscular blockade in the clinical setting.

The Division stated that the relationship of elapsed time following administration of ORG 25969 to reversal of neuromuscular blockade using highly sensitive equipment, such as AMG, is likely to be useful, but efficacy should also be assessed using monitoring that is readily available in the clinical settings for which the drug is intended. The Division stated that AMG is not widely used in the United States and, therefore, an alternative measure of muscle function should be used as a comparator, even though AMG-generated data might be used as primary endpoints. The findings from AMG analysis may be adequately supported by commonly used clinical markers of recovery of muscle strength, such as head lift for 5 seconds.

Question 10: Organon proposes to exclude the tests of clinical signs of recovery from the Phase 3 program since collection of this data will not aid in correlating TOF readings to clinical observations nor would the recording of clinical signs lead to meaningful recommendations for the attending physician. Does the Agency concur?

FDA RESPONSE:

Clinical signs of reversal and residual weakness should be incorporated into Phase 3 protocols as secondary endpoints because data relating a variety of clinical indicators to reversal is likely to be useful in clinical practice.

Discussion: The Sponsor acknowledged that AMG is not widely used in the U.S. They also noted that it is difficult to demonstrate recovery from neuromuscular blockade using clinical criteria when patients are emerging from general anesthesia because of changing or depressed levels of consciousness. They plan to include an assessment of consciousness that will be applied prior to a clinical evaluation of recovery from neuromuscular blockade in their protocols.

The Division indicated that while clinical evaluation of recovery from neuromuscular blockade may at times be hampered by the residual effects of anesthetics on patients' level of consciousness, it is, nonetheless, routinely performed as an essential assessment prior to extubation. Org 25969 will need to be evaluated for safety and efficacy under the actual conditions of use. The benefit-risk analysis required for drug approval will rely most heavily on data derived from actual conditions of use studies.

Question 11: It is proposed that the post-operative monitoring period be conducted according to normal clinical practice that is conducted at the participating sites for the Phase 3 trials. It is also proposed to eliminate the assessment of clinical signs (see previous question). Does the Agency concur?

FDA RESPONSE:

- **It is unclear whether displacement of rocuronium or vecuronium from Org 25969 can be precipitated by administration of concomitant medication and result in unexpected weakness.**

- **We will need evidence that patients who have otherwise recovered from anesthesia are not at risk if they receive drugs with a high binding affinity for Org 25969 in an unmonitored setting.**

- **In addition, it may be useful to stipulate a minimum duration for post-anesthesia monitoring in your clinical trials to facilitate data analysis.**

Discussion: The Division expressed concern that drugs given peri-operatively may precipitate weakness by displacing of rocuronium from Org 25969, (e.g., steroids given prophylactically to patients for reactive airway disease), or to blunt inflammatory effects of surgery.

The Sponsor stated that they expect to be able to quantitatively predict the degree of displacement of rocuronium and vecuronium from ORG 25969 following treatment with steroids and other critical drugs used in the perioperative setting using their PK/PD model and that the results will be made available to the agency.

Question 12: Organon proposes to eliminate the extensive ECG monitoring in the future Phase 3 studies. Does the Agency concur?

FDA RESPONSE:

Preliminary trials have reported QT and QTc prolongation associated with Org 25969. It will be necessary to closely monitor patients in Phase 3 trials unless a thorough QT study demonstrates that treatment with Org 25969 does not cause QT prolongation.

Discussion: The Division stated that until Org 25969 is thoroughly assessed, as per the Guidance, for QTc prolongation, all patients will require continuous ECG monitoring with appropriately timed supplemental 12-lead ECG monitoring. The timing for conducting the thorough QTc prolongation study is left to the Sponsor's discretion, but the requirement of patient monitoring in the interim generally dictates that the QTc study be completed before the Phase 3 protocols are initiated.

Question 13: Does the Agency agree that the definition of "Serious trial procedure-related events" can be used in the clinical development program for Org 25969 including the IND clinical trials?

FDA RESPONSE:

We need clarification whether the exclusions you proposed are intended to define specific instances or are examples of a range of circumstances that might be excluded from expedited SAE reporting.

Discussion: The Sponsor stated that this will be specific to each protocol.

Question 14: Does the Agency concur with the selection of doses for our Phase 3 trials?

FDA RESPONSE:

Your preliminary data indicates that the time to reverse 1-1.2 mg/kg rocuronium decreased by 1-2.5 minutes for a 16 mg/kg dose of Org 25969 compared with a 8 or 12 mg/kg dose. Doses of Org 25969 below 16 mg/kg may warrant study for immediate reversal of NMB if adverse events are related to the dose of Org 25969.

Discussion: There was no further discussion on this question.

Question 15: Does the Agency agree to defer the pediatric study in neonates until after approval?

FDA RESPONSE:

We recommend deferral of studies in pediatric patients below the age of renal maturity (2 years).

Discussion: The Sponsor stated that a study in pediatric patients has already started in Europe. At the time of the NDA, there will be data on patients under 2 years old. (b) (4)

(b) (4)

The Agency would generally require evidence of safety and efficacy in adults and older pediatric patients before considering studies using the drug in children under two years of age.

A pediatric written request may be possible. The Division will likely consult the Division of Pediatrics regarding this matter.

The Sponsor may submit reports from the European study to the Division for ongoing review. All available data must be reported with an NDA, but only data from studies that meet Agency standards for ethical scientific conduct can be considered in support of a finding of efficacy.

Question 16:Organon believes that collecting laboratory values after 2-4 weeks in this study (in combination with the available preclinical and clinical safety information) would be sufficient to address the Agency's concern about delayed toxicity. Does the Agency concur?

FDA RESPONSE:

We are concerned that your timing of biomarker collection to monitor renal function may miss signs of acute renal injury. Laboratory testing 1 to 3 days following exposure to Org 25969 may be needed unless you can present a compelling rationale that indicates that your proposed monitoring will have a very high level of sensitivity to detect early signs of transient renal injury.

Discussion: The Sponsor stated that there will be additional tests at the post-operative visit, 24 hours following exposure to Org 25969. The Sponsor will present evidence to confirm that their testing plan is sufficiently sensitive to capture events of acute renal injury that may result from toxicity associated with Org 25969.

The Division stated that they will look forward to reviewing the data supporting the sensitivity of the proposed renal function tests.

Question 17: Does the Agency agree with Organon's plan to incorporate health economic assessments (QoR-40 and RASQ) as part of the development program for Org 25969?

FDA RESPONSE:

- **It is acceptable to incorporate health economic assessments in clinical development trials.**
- **Organon's plan to include the QoR-40 domain scores for some of the Phase III trials is acceptable.**
- **Organon's plan to collect data using the RASQ from anesthesiologists and trial nurses in Phase III trials is acceptable.**
- **We would not agree that the outcomes measured by these questionnaires represents health economic information.**

Discussion: There was no further discussion on this question.

Question 18: Does the Agency agree (b) (4)

FDA RESPONSE:

- **It is not possible to evaluate** (b) (4)
- **We recommend that Organon provide background information on the conceptual framework, instrument development, and validation of the QoR-40 and RASQ within and outside of the clinical development program.**
- **The protocols that included the QoR-40 did not address treatment comparisons or how analysis plans will address the impact of multiple comparisons.**
- **Data from the RASQ would be exploratory only, since Organon does not plan to include the RASQ in the phase III protocols or submit data from the RASQ in the database or analysis for the Phase III trials.**
- (b) (4)

Discussion: There was no further discussion on this question.

Question 19: Organon would like to obtain the Agency's initial thoughts on the suitability of Org 25969 for "priority review."

FDA RESPONSE:

To qualify for priority review, Org 25969 must offer a significant improvement in the rescue treatment from a "cannot ventilate - cannot intubate" situation following induction of anesthesia. It will be necessary to demonstrate that Org 25969 offers significant improvement in the full context of current airway management paradigms and the use of anesthetic agents.

- **(http://www.asahq.org/publicationsAndServices/Difficult%20Airway.pdf)**

Discussion: There was no further discussion on this question.

ACTION ITEMS:

The Sponsor will:

1. Further characterize the PK/PD model in terms of the proposed cut-off point for remifentanil.
2. Submit their rationale with supporting documentation that Org 48302 is adequately qualified in terms of the reproductive toxicology study and submit the justification for NOAEL as 200 mg not 65 mg.
3. Explore the mechanism of bone deposition and clarify the specific site of binding leading to deposition in bone and joint tissue. In addition, propose and justify the most appropriate model to characterize the potential clinical significance of this finding.
4. Extend the monitoring for bone deposition in the preclinical models beyond 7 days, in order to demonstrate complete reversal of the deposition.
5. Resubmit Protocols #301 and #302, removing propofol use, and add clinical assessments of return of normal neuromuscular function before extubation, discharge from the operating room, and discharge from the PACU.
6. (b) (4)
7. Provide the impurity CMC data in the NDA.

The Division will review and comment on the submitted QTc prolongation protocol.

Minutes prepared by:
Allison Meyer

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Allison Meyer
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