CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022225Orig1s000

SUMMARY REVIEW

Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesia, Analgesia, and Addiction Products
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Summary Review for Regulatory Action

Date	December 15, 2015
From	Rigoberto Roca, M.D.
Subject	Deputy Division Director Summary Review
NDA/Supplement No.	022225
Applicant Name	Organon USA, Inc. / Merck & Co.
Date of Original Submission Receipt	October 31, 2007 Not Approvable letter issued July 31, 2008
Date of First Complete Response Submission Receipt	December 21, 2012 Complete Response letter issued September 20, 2013 (includes a 3-month clock extension)
Date of Second Complete Response Submission Receipt	October 22, 2014 Complete Response letter issued April 22, 2015
Date of Third Complete Response Submission Receipt	June 17, 2015
PDUFA Goal Date	December 17, 2015
Proprietary Name / Established (USAN) Name	Bridion / sugammadex sodium
Dosage Forms / Strength	Solution for intravenous injection / 100 mg/mL
Proposed Indication	Reversal of moderate or deep muscular blockade by rocuronium or vecuronium.
Recommended Action	Approval

Material Reviewed/Consulted OND Action Package, including reviews by:	
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Pharmacology Toxicology	Alex Xu, PhD; Jay Chang, PhD; Dan Mellon, PhD;
OPQ/ONDP	Julia Pinto, PhD
OCP/DCP II	Srikanth Nallani, PhD; Yun Xu, PhD
OCP/ Division of Pharmacometrics	Atul Bhattaram, PhD; Kevin Krudys, PhD
OSE/OMEPRM/DMEPA	James Schlick, MBA, RPh; Vicky Borders-Hemphill, PharmD
OSE/OMEPRM/DRISK	Leah Hart, PharmD; Kim Lehrfeld, PharmD; Claudia Manzo, PharmD
OPDP	Koung Lee; PharmD, Shenee Toombs, PharmD
OSI/DCCE/GCPAB	Cynthia Kleppinger, MD; Janice Pohlman, MD, MPH; Kassa Ayalew, MD, MPH
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DPMH	Carol Kasten, MD; Tamara Johnson, MD, MS; Lynne Yao, MD

DCCE = Division of Clinical Compliance Evaluation
DCP II = Division of Clinical Pharmacology II
DMEPA = Division of Medication Error Prevention and Analysis
DPARP = Division of Pulmonary, Allergy, and Rheumatology Products
DPMH = Division of Pediatrics and Maternal Health
DRISK = Division of Risk Management
GCPAB = Good Clinical Practice Assessment Branch
OCP = Office of Clinical Pharmacology
ODE II = Office of Drug Evaluation II
OMEPRM = Office of Medication Error Prevention and Risk Management
OND = Office of New Drugs
ONDP = Office of New Drug Products
OPQ = Office of Pharmaceutical Quality
OPDP = Office of Professional Drug Promotion
OSE = Office of Surveillance and Epidemiology
OSI = Office of Scientific Investigations

1. Introduction

The Applicant, Organon, Pharm, a subsidiary of Merck, Inc., has submitted a complete response to the Complete Response letter issued on April 22, 2015. This is the fourth review cycle for this application, from the time the Non-approval letter was issued on July 31, 2008.

This review will provide an overview of the regulatory and scientific facts of this application and issues that were identified during the course of the review of the submission. Aspects that will be touched upon include the regulatory history, the adequacy of the data to support the application, and the labeling requested by the Applicant. Due to the fact that there has been a limited amount of additional information submitted in support of this application since the Complete Response letter of April 22, 2015, this review will serve also serve as the primary clinical review, and the CDTL review.

A significant amount of this review will consist of content from my memo from the previous review cycle, dated April 21, 2015, which is appended to the end of this review.

2. Background

Sugammadex, also known as Org25969, is a new molecular entity of the γ-cyclodextrin class. It was designed, by selective addition of functional groups around the structure, to bind rocuronium and vecuronium. It consists of ring-like structure with a lipophilic core and a hydrophilic outer surface. The positively charged ammonium groups of rocuronium and vecuronium are attracted to the negatively charged sugar groups in the center, and then held in place by van der Waal's forces, hydrophobic and electrostatic interactions. The physical sequestration of the neuromuscular blocking agent from the neuromuscular junction will in effect reverse the paralysis. The initial submission of this application requested the following indication: for routine reversal of "shallow" and "profound neuromuscular blockade induced by rocuronium and vecuronium, and "immediate reversal" of neuromuscular blockade at 3 minutes after administration of rocuronium.

At this time, the Applicant has modified the indication to read as follows:

> [TRADENAME] is a selective relaxant binding agent indicated for the reversal of moderate or deep neuromuscular blockade induced by rocuronium or vecuronium.

In addition, the following language is being proposed for the Dosage and Administration section:

- Should be administered by trained healthcare providers.
- Administered as a single bolus injection.
- 4 mg/kg is recommended if recovery has reached 1-2 post-tetanic counts (PTC), train-of-four (TOF)-count 0 (deep blockade) following administration of rocuronium- or vecuronium-induced blockade.

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- 2 mg/kg is only recommended if spontaneous recovery has reached the reappearance of T2 (moderate blockade) following rocuronium- or vecuronium-induced blockade.
- 16 mg/kg is only recommended if there is an urgent or emergent need to reverse neuromuscular blockade following administration of rocuronium.

The regulatory history of this application is well-detailed in Dr. Simone's review of April 03, 2015, and will only be briefly summarized here.

- July 31, 2008 – the Agency issued a Not Approvable letter, citing two deficiencies:
  - Inadequate characterization of the hypersensitivity and anaphylactic reactions noted in the clinical trials, particularly with regard to the safety of repeat exposure to sugammadex.
  - Inadequate evaluation of the effects of sugammadex on coagulation.

- December 20, 2012 – the Applicant submitted a complete response to the July 31, 2008, Not Approvable letter, including the results of a clinical study, P06042, intended to evaluate the risk of hypersensitivity and anaphylactic reactions.

- September 20, 2013 – the Agency issued a Complete Response letter, because the routine inspection of the clinical sites involved in Study P06042 identified several protocol deviations that could impact the validity, reliability, and integrity of the data. Therefore, the deficiency related to the hypersensitivity and anaphylaxis reactions remained unresolved.

- November 21, 2013 – a meeting was held with the Applicant to discuss their plans to address the deficiency and, specifically, the key elements that should be incorporated into the new trial.

- October 22, 2014 – the Applicant submitted a complete response to the letter dated September 20, 2013, which included the results of Study P101, a study conducted to characterize the hypersensitivity and anaphylactic reactions because the results of Study P06042 were unreliable.

- June 19, 2015 – date of submission currently under review.

In this submission, the Applicant included a reanalysis of the results from Study P101, to evaluate the impact of the potential unblinding that occurred during the conduct of study, and which was identified during routine inspections conducted by the Division of Clinical Compliance Evaluation from the Office of Scientific Investigations. The assessment and conclusions by the review team are discussed further in Section 8 (Safety) of this review.

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3. Chemistry, Manufacturing, and Controls (CMC)

General Product Considerations
There was no new information submitted during this review cycle related to product quality.

Outstanding or Unresolved Issues
I concur with the conclusions reached by the product quality reviewers during the previous review cycles that there are no manufacturing issues that would preclude approval of this application.

4. Nonclinical Pharmacology/Toxicology

There had not been any nonclinical issues identified during the first three review cycles that would have precluded approval. The Applicant did not submit any new nonclinical data submitted during this review cycle.

However, the changes to the package insert that had been recommended during the first two cycles had not been communicated to the Applicant yet, so the review team focused on whether the recommendations were unchanged and the conversion sections of the insert to be in compliance with the Pregnancy and Lactation Labeling Rule (PLLR).

Outstanding or Unresolved Issues
There were no outstanding or unresolved pharmacology/toxicology issues that precluded approval during the first review cycle, and there are none during this review cycle.

5. Clinical Pharmacology/Biopharmaceutics

There were no clinical pharmacology issues that precluded approval during the three previous review cycles. The Applicant included in the previous review cycle's submission the study report of a study conducted to assess the pharmacokinetics of sugammadex in patients with renal impairment. The details of the study design are well-described in Dr. Nallani's review. The description of the study and his assessment of the results are reproduced below:

> This study (P105) was a 2-center, 2-part, open-label, single-dose (sugammadex 4 mg/kg) study evaluating the effect of chronic renal impairment on sugammadex PK in subjects with severe or moderate renal impairment compared to healthy matched control subjects. Part 1 (n=24) of this study included eight (8) subjects with severe (CLcr <30 mL/min), eight (8) subjects with moderate (CLcr 30 - <50 mL/min) renal impairment and eight (8) healthy control subjects (CLcr ≥80 mL/min). The spsonsor [sic] utilized previously established (and reviewed) bioanalytical methodology for assessing sugammadex plasma levels. The sponsor indicated that a preliminary review of the sugammadex concentration data from Part 1 of the study combined with dosing irregularities reported from the clinical research units indicated that in some subjects, doses may not have been administered directly into the vein, and likely infiltrated surrounding tissue. Substantial delays in Tmax (range: 1 to 4 hours) and an apparent absorption phase in the pharmacokinetic (concentration-time) profiles provided additional evidence of dosing issues. Given the apparent dosing irregularities in Part 1, the pharmacokinetic data from Part 1 are considered to be uninterpretable; therefore, the study was subsequently amended to include a Part 2 in order to achieve the original pharmacokinetic objectives of the study. Part 2 provided clarification on the dosing procedures in order to ensure that bolus IV administration was achieved

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(a direct stick method of administration through a fixed needle was used in Part 1) and the duration of pharmacokinetic collection was reduced to 10 days postdose in subjects with moderate and severe renal impairment with flexibility to extend the pharmacokinetic collection in subjects with severe renal impairment, if warranted. This reduction in collection time was based on Part 1 data indicating that, despite the dosing irregularities, none of the subjects with severe or moderate renal impairment had measurable sugammadex concentrations (all were < lower limit of quantitation [LLOQ]) on Day 7 (144 hours) and Day 4 (72 hours), respectively. In Part 2 (n=18) of this study, six (6) subjects with severe (CLcr <30 mL/min), six (6) subjects with moderate (CLcr 30 - < 50 mL/min) renal impairment and six (6) healthy control subjects (CLcr > 80 mL/min) received single doses of IV sugammadex (4 mg/kg). The total enrollment in this study was N=33. Eligible subjects from Part 1 could enroll in Part 2 (n=9 subjects participated in both parts).

Results and Conclusions: As a result of the dosing issues in Part 1, the final pharmacokinetic and subsequent statistical analyses were not conducted for Part 1 of the study. Based on data from Part 2, sugammadex exposure (AUC0-∞) was higher in subjects with moderate and severe renal impairment compared to healthy control subjects. Specifically, the GMR (90% CI) of AUC0-∞ in subjects with moderate and severe renal impairment compared to healthy subjects was 2.42 (1.84, 3.17) and 5.42 (4.12, 7.11), respectively. By comparison, the GMR (90% CI) of Cmax in subjects with moderate and severe renal impairment compared to healthy subjects was 0.92 (0.72, 1.18) and 0.94 (0.73, 1.21), respectively. Clearance progressively decreased and apparent halflife (t1/2) was progressively prolonged with increased levels of renal dysfunction.

Dr. Nallani's final assessment was that the findings from the analyses were similar to those from the previous review cycles, and could be incorporated into the label.

Outstanding or Unresolved Issues

There were no outstanding or unresolved clinical pharmacology issues that precluded approval during the previous review cycles, and there are none during this review cycle.

6. Clinical Microbiology

Sugammadex is not a therapeutic antimicrobial; therefore, clinical microbiology data were not required or submitted for this application.

7. Clinical/Statistical – Efficacy

There is no new information submitted during this review cycle to support the efficacy of sugammadex and, based on the reviews of the data submitted during the previous review cycles, none were needed. For a summary of the data that has been previously submitted in support of this application, the reader is referred to my review of April 21, 2015.

Outstanding or Unresolved Issues

I concur with the review team that there are no outstanding issues or concerns regarding the efficacy of sugammadex that would preclude approval.

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8. Safety

Study P101

The Applicant conducted Study P101, to address the deficiency identified in the Complete Response letter issued by the Agency on September 20, 2013. It was titled "A randomized, double-blind, placebo-controlled, parallel group study to evaluate the incidence of hypersensitivity after repeated single dose administration of sugammadex (MK- 8616) in healthy subjects." It had the following primary objective: to determine the number and percentage of subjects with adjudicated symptoms of hypersensitivity for each dose group of sugammadex and placebo. It also had several secondary objectives and exploratory objectives, as noted below.

Secondary Objectives:

- To determine the number and percentage of subjects with adjudicated anaphylaxis according to the definition of Sampson (Criterion 1) for each dose group of sugammadex and placebo.
- To investigate the change over time in frequency and severity of adjudicated hypersensitivity symptoms for each dose group of sugammadex and placebo.
- To evaluate the safety and tolerability of administration of repeated single doses of sugammadex in healthy subjects.

Exploratory Objectives:

- To measure levels of anti-sugammadex specific IgG and IgE antibodies in subjects with adjudicated symptoms of hypersensitivity and in a subset of subjects without adjudicated symptoms of hypersensitivity.
- To measure mast cell tryptase levels in subjects referred for adjudication of Potential Hypersensitivity.
- To collect samples for potential hypersensitivity research.

The design of the study is well-described in Dr. Simone's review, as well as in Dr. Erika Torjusen's consultative review (from the Division of Pulmonary, Allergy, and Rheumatology Products [DPARP]). Briefly, subjects were randomized to one of three treatments:

1. Treatment Arm A: Sugammadex 4 mg/kg single intravenous bolus injection in each of 3 periods
2. Treatment Arm B: Sugammadex 16 mg/kg single intravenous bolus injection in each of 3 periods
3. Treatment Arm C: Placebo single intravenous bolus injection in each of 3 periods

A schematic for the protocol is depicted below:

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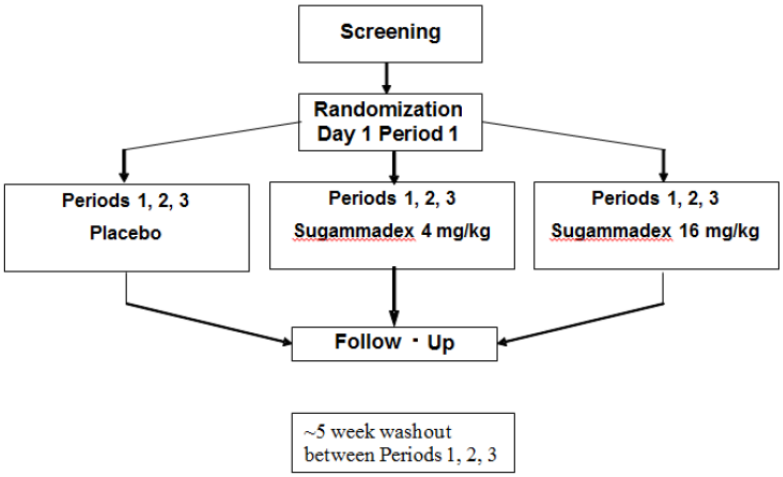

A total of 375 subjects were randomized and received at least one dose in the study. This was considered the All-Subjects-as Treated (ASaT) population. The subjects' disposition is summarized in the following table, reproduced from Dr. Torjusen's review.

Table 1: Patient Disposition - Study P101

	Placebo N=76	Sugammadex 4 mg/kg N=151	Sugammadex 16 mg/kg N=148
	n (%)		
Patients who completed the study	64 (84.2)	136 (90.1)	134 (90.5)
Patients who discontinued	12 (15.8)	15 (9.9)	14 (9.5)
Reasons for discontinuation			
Adverse Events	3 (3.9)	3 (2.0)	5 (3.4)
Lost to Follow Up	2 (2.6)	4 (2.6)	6 (4.1)
Physician Decision	1 (1.3)	0	0
Protocol Violation	1 (1.3)	4 (2.6)	0
Withdrawal by Subject	5 (6.6)	4 (2.6)	3 (2.0)
Hypersensitivity-Related†	1 (1.3)	1 (0.7)	5 (3.4)
Adverse Events	0	1 (0.7)	4 (2.7)
Lost to Follow Up	0	0	1 (0.7)
Withdrawal	1 (1.3)	0	0

† Subjects with suspected hypersensitivity reactions after one randomized dose
Source: Clinical Study Report P101 Module 5.3.5.4, Table 2, page 5, Clinical Study Report P101 Module 5.3.5.4, Section 16.2.1, p. 2-6

Dr. Torjusen noted in her review that adverse events were the most common reason for discontinuation among subjects in the 16 mg/kg group compared to the 4 mg/kg group. Furthermore, this relationship was even more pronounced among the patients experiencing a hypersensitivity adverse event, and there was the suggestion of a dose-response relationship.

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Dr. Torjusen's review provides more details regarding the adverse events and the specific symptoms that were reported by the subjects. In conclusion, Dr. Torjusen's review from the previous cycle noted the following:

> In this submission, the Applicant provided the results of a second dedicated hypersensitivity study, P101, a randomized, double-blind, placebo-controlled, parallel group study to evaluate the incidence of hypersensitivity after repeated single dose administration of sugammadex in healthy subjects.
>
> Using a predefined and mutually agreed-upon list of possible hypersensitivity signs/symptoms (see Appendix 2) and a targeted hypersensitivity assessment (see Appendix 3), the Applicant identified 137 cases of suspected hypersensitivity in 94 subjects, and 1 case of anaphylaxis. Using NIAID/FAAN criterion #1, DPARP agreed with the Applicant's single case identification of anaphylaxis. Study P101 consisted of 299 unique healthy volunteer subjects who received sugammadex. As a result, the frequency of anaphylaxis was 0.33% (1/299) in this study. It is of note that the case of anaphylaxis occurred on the first dose in the sugammadex 16 mg/kg group.
>
> Among the hypersensitivity cases that did not meet diagnostic criteria for anaphylaxis, the most common symptoms were nausea, pruritus, and urticaria. Several hypersensitivity symptoms, including erythema, eye disorders, nausea, sneezing, urticaria, and vomiting showed a dose-response, ore frequently occurring in the high-dose group when compared to the low-dose group and placebo. Hypersensitivity reactions were more frequently noted in the 16 mg/kg dose group, occurring ≤35 minutes of dosing, and with the first dose of sugammadex.
>
> Review of post-marketing reports, in the context of the data from controlled clinical trials, reveals the presence of a consistent constellation of symptoms including rash, erythema, urticaria, hypotension, and response to standard treatment for anaphylaxis/hypersensitivity reactions.
>
> Mechanistic data submitted do not elucidate a clear causal mechanism leading to anaphylaxis and hypersensitivity. While these in vitro data do not necessarily rule out an immunologic basis for the reactions, the totality of the available mechanistic and clinical data do not suggest that sensitization occurs upon repeat exposures or that the risk of hypersensitivity reactions increases with repeat exposure.
>
> DPARP concludes that sugammadex causes anaphylaxis and hypersensitivity events. This risk appears to increase with higher doses and does not appear to increase with repeated exposure. Whether this risk is greater than the risk for other drug products commonly used in the perioperative setting is difficult to determine. The incidence of anaphylaxis during general anesthesia reported in the literature covers a wide range, with estimates from 1:3500 to 1:25,000.[2,3] Given changes in medical and surgical practices over time, such as the decreased use of latex and utilization of new measures to prevent medical errors, obtaining an accurate estimate of the frequency of peri-operative anaphylaxis in the context of current standards of care is challenging. For this reason, there is no predetermined level of acceptable or unacceptable risk for anaphylaxis for new drug products. Ultimately, the risk-benefit assessment for sugammadex depends primarily on the efficacy and safety data specific to sugammadex and its expected use in a real-world setting.

The Applicant included in this submission sensitivity analyses of the results from Study P101. The purpose of the analyses was to determine whether the presence of an unmasked data variable in the statistical platform had an impact on the interpretation of the results of the study. The analyses included evaluation of the number of hypersensitivity events reported before and after the unmasking occurred. The following is reproduced from Dr. Torjusen's review:

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The audit conducted during the routine inspection by the Office of Scientific Investigations (OSI) during the previous review cycle indicated protocol deviations and other findings that could impact the validity, reliability, and integrity of the data from Study P101.

As requested by the Agency in their Complete Response letter dated April 22, 2015, the Applicant performed sensitivity analyses for adjudicated hypersensitivity and adjudicated anaphylaxis based on a subset of subjects who did not have major protocol deviations as well as calendar time intervals for events related to the potential unblinding that occurred during the course of the trial.

The results from both sets of sensitivity analyses, those excluding subjects with protocol deviations, as well as the time interval-related summaries to account for the existence of an unmasked data variable in the statistical platform (CPI), supported the interpretations and conclusions of P101 data as reported by the Applicant.

Given that the number of doses administered during the calendar intervals analyzed over time, additional analysis of the total number of suspected hypersensitivity events over the total number of exposures by treatment group and interval was evaluated, as shown in Table 3.

Table 3. Total Number of Suspected Hypersensitivity Events Over Total Number of Exposures by Treatment Group and Interval– Study P101

# of events / # of exposures	**Placebo**	**Sugammadex 4 mg/kg**	**Sugammadex 16 mg/kg**
Interval 1 (Study Start to 3/10/2014)	9/96 (9.4%)	26/190 (13.7%)	33/190 (17.4%)
Interval 2 (3/11/2014 to 4/8/2014)	3/60 (5.0%)	13/120 (10.8%)	17/116 (14.7%)
Interval 3 (4/9/2014 to end of study)	5/53 (9.4%)	12/117 (10.3%)	19/114 (16.7%)
Total	17/209 (8.1%)	51/427 (11.9%)	69/420 (16.4%)
Source: Response to Clinical Information Request August 13, 2015			

As seen above, there was no meaningful change in the frequency of suspected hypersensitivity events after the potential unblinding. The results from both sets of sensitivity analyses, those excluding subjects with protocol deviations, as well as the time interval-related summaries to account for the existence of an unmasked data variable in the statistical platform (CPI), support the interpretations and conclusions of P101 data. In addition, results from the remaining inspections did not reveal any significant concerns regarding data integrity and study conduct. Accordingly, data from study P101were deemed valid for review.

During the discussion period of the advisory committee meeting, several members suggested that Applicant should conduct additional studies to determine which patients would be most at risk for hypersensitivity reactions or anaphylaxis. Dr. Torjusen addressed this suggestion in her review as follows:

The advisory committee suggested various post-marketing studies to identify the population(s) most at risk for experiencing anaphylactic and hypersensitivity events, to describe the outcomes in vulnerable subpopulations, and to further elucidate the underlying mechanism related to these events. While we acknowledge the committee's concerns, DPARP concludes that the Applicant has performed sufficient analyses and mechanistic studies to address the anaphylaxis and hypersensitivity safety signal. No individual patient or population risk factors were identified in this dedicated, repeat dose hypersensitivity study (P101). While it is true that Study P101 was conducted in a healthy volunteer population, this provides the most reliable information in an

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> unconfounded manner. While we cannot use these data to determine the exact risk estimates and outcomes in patient populations with varying levels of illness/comorbidities, the data we have can help to inform this risk. Anaphylaxis is by definition, a severe life threatening event; and therefore an appropriate assessment of the risks and benefits of sugammadex administration must be considered when treating patients with multiple comorbidities. While the underlying mechanism remains uncertain, requiring additional mechanistic studies in the context of numerous studies with predominantly negative results is of limited utility. Accordingly, DPARP does not recommend any additional post marketing studies to evaluate anaphylaxis and hypersensitivity at this time.

Additional Safety Data

As noted in Dr. Simone's review during the previous review cycle, the Applicant has conducted 24 additional clinical trials since the submission of the original application, increasing the size of the safety database to 6,050 subject exposures in 4,428 individuals. The Applicant indicates in the submission that sugammadex is currently approved in 75 countries, and marketed in more than 50 countries worldwide. The Applicant indicates in the current submission that, as of March 2015, there have been 12.1 million vials of sugammadex have been sold.

Since the previous review cycle, the only additional safety data submitted consisted of an update of the post-marketing experience. Review of that update does not alter the overall assessment of the safety database, which was summarized as follows in Dr. Simone's review of April 03, 2015:

> Regarding the updated safety database from the clinical development program, the analyses of common adverse events demonstrated that sugammadex had a safety profile that, in general, posed only minimal additional risk compared to placebo and a level of risk that appeared to be no worse than that of neostigmine. The most common adverse events were nausea, vomiting, and pain. Only dysgeusia, nausea, nasopharyngitis, and possibly headache, appeared to be sugammadex-dose related. Similarly, the analysis of SAEs reported in the clinical trials indicated that, overall, the safety profile for sugammadex was not substantially different than placebo or neostigmine, with the possible exception of cardiac rhythm related adverse events. These events included a range of conduction abnormalities most of which occurred within minutes following the administration of sugammadex and that resolved spontaneously. It is important to note that if these events are caused by sugammadex, it was only with the highest proposed dose, i.e., 16 mg/kg, that sugammadex appeared to differ substantially from placebo and neostigmine. Review of the postmarketing data produced similar findings; although, it was noted that many of the cardiovascular reactions occurred in the setting of hypersensitivity and anaphylactic reactions.
>
> The review of the updated safety database indicated that there were no subpopulations at greater risk from sugammadex or for whom the dose of sugammadex needed to be adjusted.
>
> Regarding the postmarketing adverse reaction database, the review of the data indicated that anaphylactic reactions were the most frequently reported adverse events followed by changes in heart rate and blood pressure. There was no indication of a new safety signal in the database.
>
> In summary, the safety profile for sugammadex has been adequately characterized to perform a benefit-risk analysis, provided the OSI inspections for Study P101 raise no concerns over data integrity. The overall safety of sugammadex did not differ substantially from placebo in the clinical trials, and sugammadex appears to pose no greater risk than neostigmine, with the exception of hypersensitivity and anaphylactic reactions that have been generally mild to moderate in severity, readily diagnosed with standard patient monitoring, and successfully treated, when intervention was needed.

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Outstanding or Unresolved Issues

I concur with the review team that there are no outstanding safety issues that would preclude approval.

9. Advisory Committee Meeting

This application was presented to the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) on November 6, 2015. The review team concluded during the first review cycle that the data supporting the efficacy of sugammadex was acceptable. However, there had been questions regarding the safety of sugammadex, as noted above, primarily with respect to the cardiac rhythm abnormalities, incidence of hypersensitivity reactions and anaphylaxis, and the implications of the effects that sugammadex had on commonly used assessment of coagulation bleeding parameters, concerns which had precluded approval of the application during the first review cycle.

The advisory committee meeting was convened in order to update the committee members on the additional safety data generated by the Applicant since the last presentation of the application to the committee, and to obtain the committee's input regarding the safety profile of the product. The questions posed to the committee were the following, with the tally of the votes being noted below each of the voting questions:

1. **VOTE:** Has the Applicant presented sufficient information to characterize the risk of hypersensitivity/anaphylaxis?

   Yes = 13 No = 1 Abstention = 0

2. **VOTE:** Has the Applicant presented sufficient information to characterize the risk of cardiac dysrhythmias?

   Yes = 14 No = 0 Abstention = 0

3. **DISCUSSION:** Are there issues not addressed in the supportive data that warrant the need for additional studies and, if so, should these studies be conducted before or after approval?

4. **VOTE:** Does the efficacy, safety and overall risk-benefit profile of sugammadex support the approval of this application?

   Yes = 14 No = 0 Abstention = 0

With respect to the discussion question posed to the Committee, they recommended that that additional information would be useful on certain subsets of the patient populations that might be prescribed sugammadex, such as the morbidly obese patients and patients with significant comorbid conditions. The Committee also indicated that better characterization of the patients who appeared to be non-responders would be important. The Committee noted that none of this information was required prior to approval of the application.

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10. Pediatrics

The Applicant had previously conducted one trial which included pediatric patients (Trial 19.4.306). It was not conducted under an IND and included only foreign clinical sites (Germany, Finland, France, and the UK). The following description and summary of results are from the Applicant's submission:

> Summary of Pediatric Trial 19.4.306
> Trial 19.4.306 was designed as a dose-finding trial investigating 4 doses of sugammadex (0.5, 1.0., 2.0 and 4.0 mg/kg) and placebo for the reversal of rocuronium induced moderate NMB ("at the reappearance of T2") at different age groups of pediatric subjects. The trial also investigated a cohort of adult subjects. The full CSR for this trial was included in Module 5.3.4.2 of the original NDA for sugammadex. Table 1 summarizes the efficacy data by dose and age group and also presents an overview of the number of evaluated pediatric and adult subjects in Trial 19.4.306.

Table 1 Summary of the recovery times (min:sec) from start of administration of sugammadex to recovery of the T4/T1 ratio to 0.9 by dose and age group (PP group)

Age class	Statistic	Dose group				
		Placebo (N=12)	0.5 mg/kg Org 25969 (N=12)	1.0 mg/kg Org 25969 (N=13)	2.0 mg/kg Org 25969 (N=11)	4.0 mg/kg Org 25969 (N=11)
						(b) (4)

At present, the Applicant's proposed pediatric plan is to (b) (4) The Applicant intends to do a trial that will study sugammadex in all the pediatric age groups, in a staggered approach, for reversal of moderate and deep neuromuscular blockade induced by rocuronium or vecuronium.

The Applicant's plan was discussed at the Pediatric Review Committee (PeRC) meeting of March 4, 2015. The committee concurred that the application triggered the requirements under the Pediatric Research Act (PREA) of 2003, and that studies for all pediatric patients could be deferred because adult studies have been completed and the application appeared ready for

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approval. The committee did note that, if the application does get approved, the timeline for the completion of the studies should be advanced significantly.

The Applicant's proposed plan was presented to the PeRC on November 18, 2015. The committee concurred with the proposed pediatric development program.

11. Other Relevant Regulatory Issues

The Division of Good Manufacturing Practice Assessment (DGMPA) conducted inspections as part of the routine PDUFA pre-approval clinical investigation data validation in support of an NDA. In addition to the Applicant's central site, two clinical sites inspected: Michael R. Gartner, MD, in Lincoln, Nebraska, and Martha Hernandez-Illas, MD, in South Miami, Florida.

Dr. Kleppinger noted the following in her overall assessment of findings and recommendations:

> Dr. Gartner was issued a Form FDA-483, citing inspectional observations and the classification for this clinical site inspection is Voluntary Action Indicated (VAI). Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety and efficacy analyses. Reliability of data from this site is acceptable for use in support of the indication for this application.
>
> Dr. Hernandez-Illas was not issued a Form FDA 483; the classification of this clinical site inspection is NAI (No Action Indicated). Data from this site is considered reliable based on the available information.
>
> Merck was issued a Form FDA-483, citing inspectional observations and the recommended classification by the FDA ORA investigator for this Sponsor inspection is OAI (Official Action Indicated). As noted above, the potential unblinding of all subjects prior to database lock could impact the validity and reliability of the submitted data to determine the primary safety and efficacy analyses. Because of the potential unblinding of all subjects prior to database lock, it is recommended that the review team consider doing sensitivity analyses with a set of plausible possibilities, including analyses of the data for the time period before and after March 11, 2014. In addition, although no significant issues were noted at the two clinical sites inspected, it is recommended that the additional four clinical sites be inspected to evaluate adequacy of conduct of the study and determine whether there is any evidence of unblinding at site level.

During the current review cycle, the DGMPA conducted inspections of the four remaining clinical sites that participated in Study P101. The following table, adapted from Dr. Kleppinger's review, lists the sites inspected and the outcome of the inspection.

Clinical Site	Number of Subjects Randomized and Dosed	Inspection Date	Classification*
Luc M.A.B. Van Bortel Drug Research Unit Ghent Building K 4, 5th floor De Pintelaan 185 9000 Ghent, Belgium	40	06/08 – 06/11/2015	No Action Indicated (NAI)
Magdalena Petkova SGS Life Science Services	80	06/01– 06/05/2015	Voluntary Action Indicated (VAI)

Reference ID: 3860559

Clinical Pharmacology Unit Antwerpen Lange Beeldekensstraat 267B-2060 Antwerpen, Belgium			
Dennis Swearingen, M.D. Celerion, Inc. 2420 West Baseline Road Tempe, Arizona 85283	60	06/08 – 06/11/2015	No Action Indicated (NAI)
George J. Atiee, M.D. Worldwide Clinical Trials Early Phase Services, LLC 2455 Northeast Loop 410 San Antonio, TX 78217	62	05/18 – 5/22/2015	No Action Indicated (NAI)

*NAI = No deviation from regulations
VAI = Deviation(s) from regulations

Dr. Kleppinger's overall assessment recommendation in her review notes as follows:

> The inspection for this NDA resubmission consisted of all four remaining clinical sites of the six sites participating in Study P101: two domestic and two foreign clinical sites.
>
> Observations noted above for all four sites are based on the review of the Establishment Inspection Reports. One site, Dr. Petkova, was issued a Form FDA-483 citing inspectional observations and classification is Voluntary Action Indicated (VAI). Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety analyses. Reliability of data from this site is acceptable for use in support of the indication for this application.
>
> Drs. Van Bortel, Swearingen and Atiee were not issued a Form FDA 483; the classifications are all NAI (No Action Indicated). Data from these sites are considered reliable based on the available information.
>
> The study blind appeared to remain intact for the duration of the study at all four sites despite the potential unblinding of sponsor statisticians between March 11 and April 7, 2014. There was no evidence found that suggested any knowledge of the allocation of the subjects. In general, based on the inspections of the four clinical sites, the inspectional findings of these sites support validity of data as reported by the Sponsor under this NDA.

Outstanding or Unresolved Issues

The results of the inspection of the remaining clinical sites that were involved in Study P101 indicated that the data from the study were valid and could be relied upon to make a regulatory decision.

12. Labeling

The Office of Prescription Drug Products (OPDP), and the Division of Medication Error Prevention and Analysis (DMEPA) provided recommendations for modifications to the package insert, container labels, and carton labeling during the previous review cycles. As mentioned above, the review team also reviewed the package insert to assess what modifications were needed in order for it to be in compliance with the Pregnancy and Lactation Labeling Rule. This included a consultation with the Division of Pediatric and Maternal Health.

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Although the final wording in the package insert is still to be determined, the review team has identified the following aspects will need to be addressed:

- Indications and Usage section:
  The terms (b) (4) are relative terms and can mean different things to different people. The level of blockade, using descriptors observed during peripheral nerve stimulation would be more direct and objective.
- Dosage and Administration section:
  The clinical situations where the high dose (16 mg/kg) should be used will need to be clarified.
- Warnings and Precautions section:
  Several subsections within this section will need clarification.
- Clinical Trial Experience section:
  The adverse event experience observed in the clinical trials needs to be clarified.
- Postmarketing Experience section:
  The section currently includes cardiac disorders, but also needs to include other events observed, such as anaphylaxis and events where the product was reported as being ineffective.
- Overdosage section:
  The wording needs to be modified to ensure that (b) (4) in the Dosage and Administration Section.
- Controlled Clinical Studies section:
  Presentation of the efficacy data is to be presented in a manner that makes it clear that there were responders that had time periods were much delayed than the average value.

13. Decision/Action/Risk Benefit Assessment

Regulatory Action

Approval.

Risk:Benefit Assessment

The availability of a neuromuscular blocker reversal agent that achieves its desired result quicker than what is currently available would be a useful addition to the anesthesiologist's inventory of therapeutic agents. Such an agent would have the potential to allow the practitioner greater control over the degree and duration of neuromuscular blockade that would be necessary, because there would be greater flexibility on when the blockade would be reversed. The risks associated with the use of sugammadex, although not insignificant, are monitorable, and because the clinical location where sugammadex will be used is well-monitored, there is the expectation that there would be the opportunity to intervene and mitigate the risks of the event.

The Applicant has submitted adequate information to support the safety and efficacy of sugammadex when used as proposed by the Applicant.

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Recommendation for Postmarketing Risk Management Activities

I concur with the review team and the recommendations from the reviewers of the Division of Risk Management that risk mitigation measures beyond appropriate labeling is not needed for sugammadex.

Recommendation for other Postmarketing Study Requirements

This application is subject to the postmarketing requirements of the Pediatric Research Equity Act. As described in Section 10, the submission of pediatric data is currently deferred, and the Applicant intends to pursue a clinical trial to (b) (4) to the pediatric population.

In addition, I recommend that the following postmarketing requirements be imposed on the Applicant:

- A postmarketing requirement to evaluate the use of sugammadex in patients who are classified as ASA 3 and ASA 4.
- A postmarketing requirement to evaluate the use of sugammadex in patients who are morbidly obese.
- A postmarketing requirement to review data within their drug development program, as well as any postmarketing data that they have available, to better characterize patients who had a delayed response, or no response, to sugammadex.

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Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesia, Analgesia, and Addiction Products
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Summary Review for Regulatory Action

Date	April 21, 2015
From	Rigoberto Roca, M.D.
Subject	Deputy Division Director Summary Review
NDA/Supplement No.	022225/099
Applicant Name	Organon USA, Inc. / Merck & Co.
Date of Original Submission	October 31, 2007 Complete Response letter issued July 31, 2008
Date of First Complete Response Submission	December 21, 2012 Complete Response letter issued September 20, 2013 (includes a 3-month clock extension)
Date of Second Complete Response Submission	October 22, 2014
PDUFA Goal Date	April 22, 2015
Proprietary Name / Established (USAN) Name	Bridion / sugammadex sodium
Dosage Forms / Strength	Solution for intravenous injection / 100 mg/mL
Proposed Indication	Reversal of moderate or deep muscular blockade by rocuronium or vecuronium.
Recommended Action	Complete Response

Material Reviewed/Consulted OND Action Package, including reviews by:	
Medical Officer	Arthur Simone, MD, PhD
Pharmacology Toxicology	Alex Xu, PhD; Jay Chang, PhD; Dan Mellon, PhD;
OPQ/ONDP	Yong Hu, PhD; Julia Pinto, PhD
OPQ/DMA	Vinayak Pawar, PhD; Stephen Langille, PhD
OMPQ/DGMPA/NDMAB	Juandria Williams, PhD / Mahesh Ramanadham
OPQ/OBP/DBRR IV	Frederick Mills, PhD; Gerald Feldman, PhD
OCP/DCP II	Srikanth Nallani, PhD; Yun Xu, PhD
OCP/ Division of Pharmacometrics	Atul Bhattaram, PhD; Kevin Krudys, PhD
OSE/OMEPRM/DMEPA	James Schlick, MBA, RPh; Vicky Borders-Hemphill, PharmD
OSE/OPE/DPV II	Martin Pollock, PharmD; Sara Camilli, PharmD; Scott Proestel, MD
OSE/OMEPRM/DRISK	Leah Hart-Banks, PharmD; Kim Lehrfeld, PharmD; Reema Mehta, PharmD
OSI/DCCE/GCPAB	Cynthia Kleppinger, MD; Janice Pohlman, MD, MPH; Kassa Ayalew, MD, MPH
Project Management Staff	Diana Walker, PhD; Parinda Jani
OND/ODE II/ DPARP	Erika Torjusen, MD; Banu Karimi-Shah, MD; Badrul Chowdhury, MD, PhD
DPMH	Carol Kasten, MD

DBRR IV = Division of Biotechnology Review and Research IV
DCCE = Division of Clinical Compliance Evaluation
DCP II = Division of Clinical Pharmacology II
DGCPC = Division of Good Clinical Practice Compliance
DGMPA = Division of GMP Assessment
DMA = Division of Microbiology Assessment
DMEPA = Division of Medication Error Prevention and Analysis
DPARP = Division of Pulmonary, Allergy, and Rheumatology Products
DPMH = Division of Pediatrics and Maternal Health
DRISK = Division of Risk Management
DPV II = Division of Pharmacovigilance II
GCPAB = Good Clinical Practice Assessment Branch
NDMAB = New Drug Manufacturing Assessment Branch
OBP = Office of Biotechnology Products
OCP = Office of Clinical Pharmacology
ODE II = Office of Drug Evaluation II
OMEPRM = Office of Medication Error Prevention and Risk Management
OMP = Office of Medical Policy
OMPQ = Office of Manufacturing and Product Quality
ONDP = Office of New Drug Products
OPE = Office of Pharmacovigilance and Epidemiology
OPQ = Office of Pharmaceutical Quality
OPDP = Office of Professional Drug Promotion
OSE = Office of Surveillance and Epidemiology
OSI = Office of Scientific Investigations

1. Introduction

The Applicant, Organon, Pharm, a subsidiary of Merck, Inc., has submitted a complete response to the Complete Response letter issued on September 20, 2013. This is the third review cycle for this application, as it received a Non-approval letter on July 31, 2008.

This review will provide an overview of the regulatory and scientific facts of this application and issues that were identified during the course of the review of the submission. Aspects that will be touched upon include the regulatory history, the adequacy of the data to support the application, and the labeling requested by the Applicant.

2. Background

Sugammadex, also known as Org25969, is a new molecular entity of the γ-cyclodextrin class. It was designed, by selective addition of functional groups around the structure, to bind rocuronium and vecuronium. It consists of ring-like structure with a lipophilic core and a hydrophilic outer surface. The positively charged ammonium groups of rocuronium and vecuronium are attracted to the negatively charged sugar groups in the center, and then held in place by van der Waal's forces, hydrophobic and electrostatic interactions. The physical sequestration of the neuromuscular blocking agent from the neuromuscular junction will in effect reverse the paralysis. The initial submission of this application requested the following indication: for routine reversal of "shallow" and "profound neuromuscular blockade induced by rocuronium and vecuronium, and "immediate reversal" of neuromuscular blockade at 3 minutes after administration of rocuronium.

At this time, the Applicant has modified the indication to read as follows:

> [TRADENAME] is a selective relaxant binding agent indicated for the reversal of moderate or deep neuromuscular blockade induced by rocuronium or vecuronium.

In addition, the following language is being proposed for the Dosage and Administration section:

- Should be administered by trained healthcare providers.
- Administered as a single bolus injection.
- 4 mg/kg is recommended if recovery has reached 1-2 post-tetanic counts (PTC), train-of-four (TOF)-count 0 (deep blockade) following administration of rocuronium- or vecuronium-induced blockade.
- 2 mg/kg is only recommended if spontaneous recovery has reached the reappearance of T2 (moderate blockade) following rocuronium- or vecuronium-induced blockade.
- 16 mg/kg is only recommended if there is an urgent or emergent need to reverse neuromuscular blockade following administration of rocuronium.

The regulatory history of this application is well-detailed in Dr. Simone's review, and will only be briefly summarized here.

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- July 31, 2008 – the Agency issued a Not Approvable letter, citing two deficiencies:
  - Inadequate characterization of the hypersensitivity and anaphylactic reactions noted in the clinical trials, particularly with regard to the safety of repeat exposure to sugammadex.
  - Inadequate evaluation of the effects of sugammadex on coagulation.
- December 20, 2012 – the Applicant submitted a complete response to the letter, including the results of a clinical study, P06042, intended to evaluate the risk of hypersensitivity and anaphylactic reactions.
- September 20, 2013 – the Agency issued a Complete Response letter, because the routine inspection of the clinical sites involved in Study P06042 identified several protocol deviations that could impact the validity, reliability, and integrity of the data. Therefore, the deficiency related to the hypersensitivity and anaphylaxis reactions remained unresolved.
- November 21, 2013 – a meeting was held with the Applicant to discuss their plans to address the deficiency and, specifically, the key elements that should be incorporated into the new trial.
- October 22, 2014 – date of submission currently under review.

In this submission, the Applicant included the results from Study P101, a study conducted to characterize the hypersensitivity and anaphylactic reactions, because the results from Study P06042 had been deemed to be unreliable. The assessment and conclusions by the review team are discussed further in Section 8 (Safety) of this review.

3. Chemistry, Manufacturing, and Controls (CMC)

General Product Considerations

The drug substance (Org 25969), a modified γ-cyclodextrin, is an octasodium salt. The mode of action is based on the formation of 1:1 complex with rocuronium or vecuronium. The drug substance contains an impurity, (b) (4) is typically present at levels of (b) (4) in the representative drug substance batches. The drug substance is highly soluble in water; its hygroscopicity is managed by controlling manufacturing and storage conditions.

The drug product, a sterile parenteral solution for intravenous administration, is prepared by (b) (4), adjusting the pH to 7.5 with sodium hydroxide or hydrochloric acid, (b) (4) into 2 mL and 5 mL vials, and (b) (4) The target concentration of the active ingredients is 100 mg/mL (b) (4) The container closure system is a type I glass vial with a latex-free (b) (4) rubber closure and an aluminum flip off cap.

The product quality reviewer indicated in his review that critical process steps for the manufacture of the drug product include the following: (b) (4)

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(b) (4) The drug product is sensitive to light, especially under severe stress conditions. The Applicant proposes that the primary container be exposed to light no longer than 5 days, (b) (4) Dr. Hu's review indicated that the photostability data submitted in the application support the 5-day maximum limit on exposure to normal indoor lighting, (b) (4)

Specific Issues Identified in the Course of this Review Cycle

The assessments and conclusions of the review team for the two previous review cycles were that there were no product quality issues that precluded approval. In this submission, the Applicant changed the commercial manufacturing site for the drug product and modified certain aspects of the sterilization process.

The review team concluded that the Applicant provided adequate batch analysis data and additional stability data to support the proposed process change at the new site.

The product quality microbiology reviewer, Dr. Pawar, noted in his review that the product is manufactured by (b) (4) No deficiencies were noted with respect to the product quality microbiology requirements for a sterile product.

The facilities inspection did not identify and issues or concerns that would preclude approval.

Outstanding or Unresolved Issues

I concur with the conclusions reached by the product quality reviewers that there are no manufacturing issues that would preclude approval of this application.

4. Nonclinical Pharmacology/Toxicology

There had not been any nonclinical issues identified during the first two review cycles that would have precluded approval. The Applicant did not submit any new nonclinical data submitted during this review cycle.

However, the changes to the package insert that had been recommended during the first two cycles had not been communicated to the Applicant yet, so the review team focused on whether the recommendations were unchanged and the conversion sections of the insert to be in compliance with the Pregnancy and Lactation Labeling Rule (PLLR).

Outstanding or Unresolved Issues

There were no outstanding or unresolved pharmacology/toxicology issues that precluded approval during the first review cycle, and there are none during this review cycle.

5. Clinical Pharmacology/Biopharmaceutics

There were no clinical pharmacology issues that precluded approval during either of the two previous review cycles. The Applicant included in this submission the study report of a study conducted to assess the pharmacokinetics of sugammadex in patients with renal impairment.

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The details of the study design are well-described in Dr. Nallani's review. The description of the study and his assessment of the results are reproduced below:

> This study (P105) was a 2-center, 2-part, open-label, single-dose (sugammadex 4 mg/kg) study evaluating the effect of chronic renal impairment on sugammadex PK in subjects with severe or moderate renal impairment compared to healthy matched control subjects. Part 1 (n=24) of this study included eight (8) subjects with severe (CLcr <30 mL/min), eight (8) subjects with moderate (CLcr 30 - <50 mL/min) renal impairment and eight (8) healthy control subjects (CLcr ≥80 mL/min). The spsonsor [sic] utilized previously established (and reviewed) bioanalytical methodology for assessing sugammadex plasma levels. The sponsor indicated that a preliminary review of the sugammadex concentration data from Part 1 of the study combined with dosing irregularities reported from the clinical research units indicated that in some subjects, doses may not have been administered directly into the vein, and likely infiltrated surrounding tissue. Substantial delays in Tmax (range: 1 to 4 hours) and an apparent absorption phase in the pharmacokinetic (concentration-time) profiles provided additional evidence of dosing issues. Given the apparent dosing irregularities in Part 1, the pharmacokinetic data from Part 1 are considered to be uninterpretable; therefore, the study was subsequently amended to include a Part 2 in order to achieve the original pharmacokinetic objectives of the study. Part 2 provided clarification on the dosing procedures in order to ensure that bolus IV administration was achieved (a direct stick method of administration through a fixed needle was used in Part 1) and the duration of pharmacokinetic collection was reduced to 10 days postdose in subjects with moderate and severe renal impairment with flexibility to extend the pharmacokinetic collection in subjects with severe renal impairment, if warranted. This reduction in collection time was based on Part 1 data indicating that, despite the dosing irregularities, none of the subjects with severe or moderate renal impairment had measurable sugammadex concentrations (all were < lower limit of quantitation [LLOQ]) on Day 7 (144 hours) and Day 4 (72 hours), respectively. In Part 2 (n=18) of this study, six (6) subjects with severe (CLcr <30 mL/min), six (6) subjects with moderate (CLcr 30 - < 50 mL/min) renal impairment and six (6) healthy control subjects (CLcr > 80 mL/min) received single doses of IV sugammadex (4 mg/kg). The total enrollment in this study was N=33. Eligible subjects from Part 1 could enroll in Part 2 (n=9 subjects participated in both parts).
>
> Results and Conclusions: As a result of the dosing issues in Part 1, the final pharmacokinetic and subsequent statistical analyses were not conducted for Part 1 of the study. Based on data from Part 2, sugammadex exposure (AUC0-∞) was higher in subjects with moderate and severe renal impairment compared to healthy control subjects. Specifically, the GMR (90% CI) of AUC0-∞ in subjects with moderate and severe renal impairment compared to healthy subjects was 2.42 (1.84, 3.17) and 5.42 (4.12, 7.11), respectively. By comparison, the GMR (90% CI) of Cmax in subjects with moderate and severe renal impairment compared to healthy subjects was 0.92 (0.72, 1.18) and 0.94 (0.73, 1.21), respectively. Clearance progressively decreased and apparent halflife (t1/2) was progressively prolonged with increased levels of renal dysfunction.

Dr. Nallani's final assessment was that the findings from the analyses were similar to those from the previous review cycles, and could be incorporated into the label.

Outstanding or Unresolved Issues

There were no outstanding or unresolved clinical pharmacology issues that precluded approval during the first review cycle, and there are none during this review cycle.

6. Clinical Microbiology

Sugammadex is not a therapeutic antimicrobial; therefore, clinical microbiology data were not required or submitted for this application.

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7. Clinical/Statistical – Efficacy

As noted by Dr. Simone, adequate data were submitted in the original application to support the efficacy of sugammadex in reversing neuromuscular blockade induced by rocuronium or vecuronium. The following table, reproduced from my review of July 18, 2008, summarizes certain key features of the pivotal studies that supported the efficacy of sugammadex.

	Study 301	**Study 302**	**Study 310**	**Study 303**
Location	Europe	United States	Europe	United States and Canada
Study period	November 2005 to March 2006	November 2005 to November 2006	November 2005 to May 2006	February 2006 to August 2006
Clinical scenario	"shallow" neuromuscular block, defined as the return of T_2 (the second twitch in a train-of-four stimulation)	"profound" neuromuscular block, defined as 1-2 post tetanic counts	"shallow" neuromuscular block, defined as the return of T_2	"Immediate" reversal (defined as 3 minutes following rocuronium administration)
Dose of sugammadex	2 mg/kg	4 mg/kg	2 mg/kg	16 mg/kg
Treatment groups	a. Rocuronium/Org25969 b. Rocuronium/neostigmine c. Vecuronium./Org25969 d. Vecuronium/neostigmine	a. Rocuronium/Org25969 b. Rocuronium/neostigmine c. Vecuronium./Org25969 d. Vecuronium/neostigmine	a. Rocuronium/ Org25969 b. Cis-atricurium/ neostigmine	a. Rocuronium/ Org25969 b. Succinylcholine/ no reversal agent
Number of patients	196 randomized	182 randomized	84 randomized	115 randomized
Primary efficacy endpoint	$T_4/T_1 = 0.9$	$T_4/T_1 = 0.9$	$T_4/T_1 = 0.9$	$T_1 = 0.1$

The efficacy results from the four studies are summarized in the following table, reproduced from my review of July 18, 2008.

Study #	**Scenario**	**Time (in minutes)**		**p-value**
		Sugammadex	**Comparator**	
301	Routine Shallow	1:29 (R) 2:48 (V)	18:30 16:48	<0.0001
302	Routine Profound	2:52 (R) 4:28 (V)	50:22 66:12	<0.0001
303	"Immediate"	4:22	7:04	<0.0001
310	Routine Shallow	2:02	8:46	<0.0001

The following paragraphs are reproduced from the Efficacy Summary in Dr. Simone's review.

Based on the clinical trials reported in the original NDA submission, sugammadex was found to

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be effective for reversing rocuronium- and vecuronium-induced neuromuscular blockade when administered under two clinical conditions:

1. With the spontaneous return of the second twitch (T2) of the abductor pollicus muscle, when a train-of-four (TOF) electrical stimulus is applied to the ulnar nerve.
2. With the presence of one to two post-tetanic contractions of the adductor pollicus longus muscle, when a TOF stimulus is applied following a tetanic electrical stimulus to the ulnar nerve.

Sugammadex was also found to be effective for reversing the neuromuscular blockade when it is given at three minutes following a rapid sequence induction (RSI) dose of rocuronium (1.2 mg/kg) rocuronium. This reversal occurs at the time when the maximal pharmacodynamic effect of rocuronium is expected.

For the first two clinical scenarios above, sugammadex provided a more rapid return of the ratio of the intensity of the fourth twitch (T4) in a TOF stimulus to that of the first twitch (T1) to 90% (T4/T1 = 0.9) compared to placebo or neostigmine, the anticholinesterase agent most commonly used in clinical practice for the reversal of nondepolarizing neuromuscular blocking agents (NMBAs).

For the third clinical scenario, sugammadex was compared to succinylcholine, a depolarizing NMBA for which there is no reversal agent. The primary efficacy endpoint studied in this scenario was the return of T1 in a TOF stimulus to 10% of its baseline value. Sugammadex reversed the neuromuscular blockade induced by rocuronium in less time than it took for the effects of succinylcholine to spontaneously resolve to the same point, 4.3 minutes versus 7.2 minutes on average, respectively. However, the clinical relevance of this level of recovery was not demonstrated in the clinical study and not otherwise provided by the Applicant.

The Applicant also evaluated the time to T4/T1 = 0.9 for the rocuronium/sugammadex treatment group as a secondary endpoint and the time for T1 to return to 90% of its baseline level following treatment with succinylcholine. These recovery points are likely to be more clinically relevant. For these endpoints, sugammadex induced recovery took an average of 5.4 minutes compared to the spontaneous succinylcholine recover which took an average of 10.9 minutes.

The Applicant indicated in the original NDA submission that the ability to reverse the highest labeled dose of rocuronium at the time of its maximum effect has the potential to reduce the morbidity and mortality that are associated with the inability to intubate or ventilate a paralyzed patient. However, they provided no evidence that such a claim is valid, and in the current submission, they have changed this use of sugammadex from "[i]f there is a clinical need for immediate reversal at 3 minutes following administration of rocuronium, a dose of 16.0 mg/kg BRIDION™ is recommended" to "16 mg/kg is only recommended if there is an urgent or emergent need to reverse neuromuscular blockade following administration of rocuronium." The revised use implies that the high dose of sugammadex (b) (4) when the need is urgent; however, there is no evidence (b) (4) The revised labeling (b) (4) Therefore, the label needs to be revised to reflect the conditions under which the three doses of sugammadex were found to be effective and (b) (4)

In the first resubmission, there was one new study that warrants special note especially as it relates to a study in the current submission. Study P05774 evaluated the T4/T1 values for subjects, at the time of extubation, after sugammadex was administered per proposed labeling at 1-2 PTCs and

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after neostigmine was administered per standard of care. Twitch monitoring was not used following administration of study drug to assess the level of recovery from neuromuscular blockade as part of overall evaluation of a patient's readiness to be extubated. The study showed that more subjects were extubated with T4/T1 < 0.9 when treated with neostigmine than with sugammadex. (b) (4)

(b) (4)

The current submission contains the final study report for clinical trial P07981 in which the Applicant evaluated the extent of residual paralysis that occurred in the Post-Anesthesia Care Unit (PACU) following treatment with either sugammadex or neostigmine. The results indicated that there was no residual paralysis, measured as T4/T1 ≥ 0.9, with sugammadex treatment; however, more than 50% of subjects had residual paralysis with neostigmine treatment. The trial also evaluated various time intervals relative to study drug administration, e.g., time to extubation, time to discharge from the operating room, and time to discharge from PACU, grip strength and pulmonary function testing were also performed on admission to PACU and when subjects were more awake. Despite the differences in residual paralysis, the only significant differences for the other endpoints were a 4 minute earlier time to extubation and discharge from the operating room for sugammadex-treated subjects. There was no difference for any other time interval assessed and no difference for either grip strength or any pulmonary function tests that were performed either on entry to the PACU or when the subjects were more fully awake. The trial and its findings are described in detail in Section 9.4. (b) (4)

In summary, the efficacy studies conducted over the entire development program support the finding that sugammadex is superior to neostigmine for reversing rocuronium and vecuronium when administered as proposed. The additional studies of the 16 mg/kg dose of sugammadex demonstrated that it is effective at reversing doses of rocuronium up to 1.2 mg/kg after 3 minutes. The studies showed that there was less residual paralysis following sugammadex treatment than neostigmine treatment; however, the residual paralysis was not associated with any differences in grip strengths, pulmonary function tests, or discharge from the PACU. The studies did not show the need for dose adjustments of sugammadex based on age, gender, race, renal impairment, or hepatic impairment.

Outstanding or Unresolved Issues

I concur with Dr. Simone that there are no outstanding issues or concerns regarding the efficacy of sugammadex that would preclude approval.

8. Safety

Study P101

The Applicant conducted Study P101, to address the deficiency identified in the Complete Response letter issued by the Agency on September 20, 2013. It was titled "A randomized, double-blind, placebo-controlled, parallel group study to evaluate the incidence of hypersensitivity after repeated single dose administration of sugammadex (MK- 8616) in healthy subjects." It had the following primary objective: to determine the number and percentage of

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subjects with adjudicated symptoms of hypersensitivity for each dose group of sugammadex and placebo. It also had several secondary objectives and exploratory objectives, as noted below.

Secondary Objectives:

- To determine the number and percentage of subjects with adjudicated anaphylaxis according to the definition of Sampson (Criterion 1) for each dose group of sugammadex and placebo.
- To investigate the change over time in frequency and severity of adjudicated hypersensitivity symptoms for each dose group of sugammadex and placebo.
- To evaluate the safety and tolerability of administration of repeated single doses of sugammadex in healthy subjects.

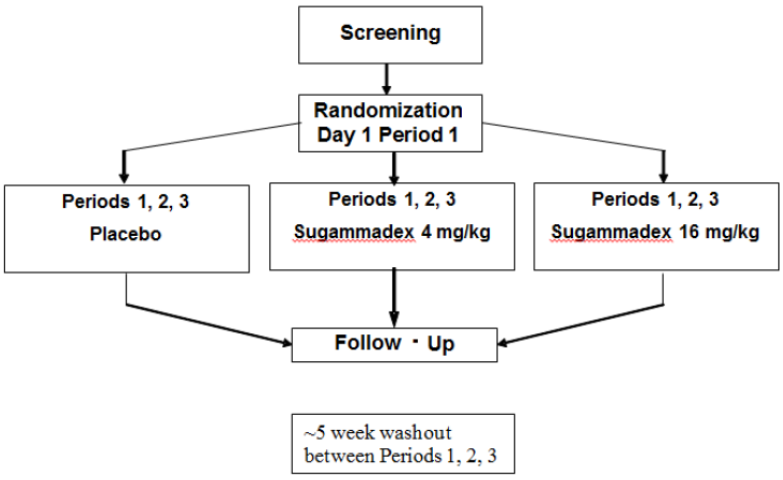
Exploratory Objectives:

- To measure levels of anti-sugammadex specific IgG and IgE antibodies in subjects with adjudicated symptoms of hypersensitivity and in a subset of subjects without adjudicated symptoms of hypersensitivity.
- To measure mast cell tryptase levels in subjects referred for adjudication of Potential Hypersensitivity.
- To collect samples for potential hypersensitivity research.

The design of the study is well-described in Dr. Simone's review, as well as in Dr. Erika Torjusen's consultative review (from the Division of Pulmonary, Allergy, and Rheumatology Products [DPARP]). Briefly, subjects were randomized to one of three treatments:

1. Treatment Arm A: Sugammadex 4 mg/kg single intravenous bolus injection in each of 3 periods
2. Treatment Arm B: Sugammadex 16 mg/kg single intravenous bolus injection in each of 3 periods
3. Treatment Arm C: Placebo single intravenous bolus injection in each of 3 periods

A schematic for the protocol is depicted below:



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A total of 375 subjects were randomized and received at least one dose in the study. This was considered the All-Subjects-as Treated (ASaT) population. The subjects' disposition is summarized in the following table, reproduced from Dr. Torjusen's review.

Table 1: Patient Disposition - Study P101

	Placebo N=76	**Sugammadex 4 mg/kg N=151**	**Sugammadex 16 mg/kg N=148**
	n (%)		
Patients who completed the study	64 (84.2)	136 (90.1)	134 (90.5)
Patients who discontinued	12 (15.8)	15 (9.9)	14 (9.5)
Reasons for discontinuation			
Adverse Events	3 (3.9)	3 (2.0)	5 (3.4)
Lost to Follow Up	2 (2.6)	4 (2.6)	6 (4.1)
Physician Decision	1 (1.3)	0	0
Protocol Violation	1 (1.3)	4 (2.6)	0
Withdrawal by Subject	5 (6.6)	4 (2.6)	3 (2.0)
Hypersensitivity-Related†	1 (1.3)	1 (0.7)	5 (3.4)
Adverse Events	0	1 (0.7)	4 (2.7)
Lost to Follow Up	0	0	1 (0.7)
Withdrawal	1 (1.3)	0	0

† Subjects with suspected hypersensitivity reactions after one randomized dose
Source: Clinical Study Report P101 Module 5.3.5.4, Table 2, page 5, Clinical Study Report P101 Module 5.3.5.4, Section 16.2.1, p. 2-6

Dr. Torjusen noted in her review that adverse events were the most common reason for discontinuation among subjects in the 16 mg/kg group compared to the 4 mg/kg group. Furthermore, this relationship was even more pronounced among the patients experiencing a hypersensitivity adverse event, and there was the suggestion of a dose-response relationship.

Dr. Torjusen's review provides more details regarding the adverse events and the specific symptoms that were reported by the subjects. In conclusion, Dr. Torjusen's review noted the following:

> In this submission, the Applicant provided the results of a second dedicated hypersensitivity study, P101, a randomized, double-blind, placebo-controlled, parallel group study to evaluate the incidence of hypersensitivity after repeated single dose administration of sugammadex in healthy subjects.
>
> Using a predefined and mutually agreed-upon list of possible hypersensitivity signs/symptoms (see Appendix 2) and a targeted hypersensitivity assessment (see Appendix 3), the Applicant identified 137 cases of suspected hypersensitivity in 94 subjects, and 1 case of anaphylaxis. Using NIAID/FAAN criterion #1, DPARP agreed with the Applicant's single case identification of anaphylaxis. Study P101 consisted of 299 unique healthy volunteer subjects who received sugammadex. As a result, the frequency of anaphylaxis was 0.33% (1/299) in this study. It is of note that the case of anaphylaxis occurred on the first dose in the sugammadex 16 mg/kg group.

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> Among the hypersensitivity cases that did not meet diagnostic criteria for anaphylaxis, the most common symptoms were nausea, pruritus, and urticaria. Several hypersensitivity symptoms, including erythema, eye disorders, nausea, sneezing, urticaria, and vomiting showed a dose-response, ore frequently occurring in the high-dose group when compared to the low-dose group and placebo. Hypersensitivity reactions were more frequently noted in the 16 mg/kg dose group, occurring ≤35 minutes of dosing, and with the first dose of sugammadex.
>
> Review of post-marketing reports, in the context of the data from controlled clinical trials, reveals the presence of a consistent constellation of symptoms including rash, erythema, urticaria, hypotension, and response to standard treatment for anaphylaxis/hypersensitivity reactions.
>
> Mechanistic data submitted do not elucidate a clear causal mechanism leading to anaphylaxis and hypersensitivity. While these in vitro data do not necessarily rule out an immunologic basis for the reactions, the totality of the available mechanistic and clinical data do not suggest that sensitization occurs upon repeat exposures or that the risk of hypersensitivity reactions increases with repeat exposure.
>
> DPARP concludes that sugammadex causes anaphylaxis and hypersensitivity events. This risk appears to increase with higher doses and does not appear to increase with repeated exposure. Whether this risk is greater than the risk for other drug products commonly used in the perioperative setting is difficult to determine. The incidence of anaphylaxis during general anesthesia reported in the literature covers a wide range, with estimates from 1:3500 to 1:25,000.2,3 Given changes in medical and surgical practices over time, such as the decreased use of latex and utilization of new measures to prevent medical errors, obtaining an accurate estimate of the frequency of peri-operative anaphylaxis in the context of current standards of care is challenging. For this reason, there is no predetermined level of acceptable or unacceptable risk for anaphylaxis for new drug products. Ultimately, the risk-benefit assessment for sugammadex depends primarily on the efficacy and safety data specific to sugammadex and its expected use in a real-world setting.

Additional Safety Data

As noted in Dr. Simone's review, the Applicant has conducted 24 additional clinical trials since the submission of the original application, increasing the size of the safety database to 6,050 subject exposures in 4,428 individuals. The Applicant indicates in the submission that sugammadex is currently approved in 75 countries, and marketed in more than 50 countries worldwide.

Dr. Simone's conclusions regarding the safety database were as follows:

> Regarding the updated safety database from the clinical development program, the analyses of common adverse events demonstrated that sugammadex had a safety profile that, in general, posed only minimal additional risk compared to placebo and a level of risk that appeared to be no worse than that of neostigmine. The most common adverse events were nausea, vomiting, and pain. Only dysgeusia, nausea, nasopharyngitis, and possibly headache, appeared to be sugammadex-dose related. Similarly, the analysis of SAEs reported in the clinical trials indicated that, overall, the safety profile for sugammadex was not substantially different than placebo or neostigmine, with the possible exception of cardiac rhythm related adverse events. These events included a range of conduction abnormalities most of which occurred within minutes following the administration of sugammadex and that resolved spontaneously. It is important to note that if these events are caused by sugammadex, it was only with the highest proposed dose, i.e., 16 mg/kg, that sugammadex appeared to differ substantially from placebo and neostigmine. Review of the postmarketing data produced similar findings; although, it was noted that many of the cardiovascular reactions occurred in the setting of hypersensitivity and anaphylactic reactions.

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> The review of the updated safety database indicated that there were no subpopulations at greater risk from sugammadex or for whom the dose of sugammadex needed to be adjusted.
>
> Regarding the postmarketing adverse reaction database, the review of the data indicated that anaphylactic reactions were the most frequently reported adverse events followed by changes in heart rate and blood pressure. There was no indication of a new safety signal in the database.
>
> In summary, the safety profile for sugammadex has been adequately characterized to perform a benefit-risk analysis, provided the OSI inspections for Study P101 raise no concerns over data integrity. The overall safety of sugammadex did not differ substantially from placebo in the clinical trials, and sugammadex appears to pose no greater risk than neostigmine, with the exception of hypersensitivity and anaphylactic reactions that have been generally mild to moderate in severity, readily diagnosed with standard patient monitoring, and successfully treated, when intervention was needed.

Outstanding or Unresolved Issues

I concur with the review team that there are no outstanding safety issues that would preclude approval.

9. Advisory Committee Meeting

An advisory committee meeting that was scheduled for March 18, 2014 was canceled pending resolution of concerns about potential data integrity issues. These concerns are further described below in Section 11 of this review.

10. Pediatrics

The Applicant had previously conducted one trial which included pediatric patients (Trial 19.4.306). It was not conducted under an IND and included only foreign clinical sites (Germany, Finland, France, and the UK). The following description and summary of results are from the Applicant's submission:

> Summary of Pediatric Trial 19.4.306
> Trial 19.4.306 was designed as a dose-finding trial investigating 4 doses of sugammadex (0.5, 1.0., 2.0 and 4.0 mg/kg) and placebo for the reversal of rocuronium induced moderate NMB ("at the reappearance of T2") at different age groups of pediatric subjects. The trial also investigated a cohort of adult subjects. The full CSR for this trial was included in Module 5.3.4.2 of the original NDA for sugammadex. Table 1 summarizes the efficacy data by dose and age group and also presents an overview of the number of evaluated pediatric and adult subjects in Trial 19.4.306.

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Table 1 Summary of the recovery times (min:sec) from start of administration of sugammadex to recovery of the T4/T1 ratio to 0.9 by dose and age group (PP group)

Age class	Statistic	Dose group				
		Placebo (N=12)	0.5 mg/kg Org 25969 (N=12)	1.0 mg/kg Org 25969 (N=13)	2.0 mg/kg Org 25969 (N=11)	4.0 mg/kg Org 25969 (N=11)
[redacted]						

(b) (4)

At present, the Applicant's proposed pediatric plan is to [redacted] (b) (4). The Applicant intends to do a trial that will study sugammadex in all the pediatric age groups, in a staggered approach, for reversal of moderate and deep neuromuscular blockade induced by rocuronium or vecuronium.

The Applicant's plan was discussed at the Pediatric Review Committee (PeRC) meeting of March 4, 2015. The committee concurred that the application triggered the requirements under the Pediatric Research Act (PREA) of 2003, and that studies for all pediatric patients could be deferred because adult studies have been completed and the application appeared ready for approval. The committee did note that, if the application does get approved, the timeline for the completion of the studies should be advanced significantly.

11. Other Relevant Regulatory Issues

The Division of Good Manufacturing Practice Assessment (DGMPA) conducted inspections as part of the routine PDUFA pre-approval clinical investigation data validation in support of an NDA. In addition to the Applicant's central site, two clinical sites inspected.

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Dr. Kleppinger noted the following in her overall assessment of findings and recommendations:

> Dr. Gartner was issued a Form FDA-483, citing inspectional observations and the classification for this clinical site inspection is Voluntary Action Indicated (VAI). Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety and efficacy analyses. Reliability of data from this site is acceptable for use in support of the indication for this application.
>
> Dr. Hernandez-Illas was not issued a Form FDA 483; the classification of this clinical site inspection is NAI (No Action Indicated). Data from this site is considered reliable based on the available information.
>
> Merck was issued a Form FDA-483, citing inspectional observations and the recommended classification by the FDA ORA investigator for this Sponsor inspection is OAI (Official Action Indicated). As noted above, the potential unblinding of all subjects prior to database lock could impact the validity and reliability of the submitted data to determine the primary safety and efficacy analyses. Because of the potential unblinding of all subjects prior to database lock, it is recommended that the review team consider doing sensitivity analyses with a set of plausible possibilities, including analyses of the data for the time period before and after March 11, 2014. In addition, although no significant issues were noted at the two clinical sites inspected, it is recommended that the additional four clinical sites be inspected to evaluate adequacy of conduct of the study and determine whether there is any evidence of unblinding at site level.

The findings from the inspections were discussed with the Applicant at a face-to-face meeting held on March 4, 2015. The Applicant submitted a briefing package and made a presentation at the meeting, describing the protocol violations, the genesis for the evaluations, the actions that they took upon becoming aware of the violations and their assessment of the potential impact the violations had on the results of the study. The Applicant indicated at the meeting that sensitivity analyses had not yet been conducted to assess the impact of the affected data on the overall results of the study.

Internal discussions were held after the meeting between the review division, and representatives from ODE II and OND. The outcome of the discussions was that, even though the observed protocol violations had a low probability of having a significant impact on the results of Study P101, the sequence of events that resulted in the protocol violations made it necessary to inspect the remaining clinical sites. Because these inspections could not be conducted prior to the already-scheduled advisory committee, the meeting had to be canceled.

Outstanding or Unresolved Issues

The issue of the risk of hypersensitivity and anaphylaxis, particularly after repeated exposure, appears to have been adequately addressed by the results from Study P101. However, due to the concerns identified by the routine inspections, it is not clear whether the results from this study

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are valid or reliable. It will be necessary to inspect the remaining clinical sites before a final conclusion can be made regarding Study P101.

12. Labeling

The review team continued internal discussions regarding the package insert, in anticipation of sharing the modifications with the Applicant during the next review cycle. The Division of Medication Error Prevention and Analysis (DMEPA) provided recommendations for modifications to the package insert, container labels, and carton labeling during the previous review cycles.

Although the final wording in the package insert is still to be determined, the review team has identified the following aspects will need to be addressed:

- Indications and Usage section:
  The terms [redacted] (b) (4) are relative terms and can mean different things to different people. The level of blockade, using descriptors observed during peripheral nerve stimulation would be more direct and objective.
- Dosage and Administration section:
  The clinical situations where the high dose (16 mg/kg) should be used will need to be clarified.
- Warnings and Precautions section:
  Several subsections within this section will need clarification.
- Clinical Trial Experience section:
  The adverse event experience observed in the clinical trials needs to be clarified.
- Postmarketing Experience section:
  The section currently includes cardiac disorders, but also needs to include other events observed, such as anaphylaxis and events where the product was reported as being ineffective.
- Overdosage section:
  The wording needs to be modified [redacted] (b) (4) what is noted in the Dosage and Administration Section.
- Controlled Clinical Studies section:
  [redacted] (b) (4)

As mentioned above, the review team also reviewed the package insert to assess what modifications were needed in order for it to be in compliance with the Pregnancy and Lactation Labeling Rule. This included a consultation with the Division of Pediatric and Maternal Health.

The Office of Prescription Drug Products (OPDP) deferred any review the label until the next review cycle.

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13. Decision/Action/Risk Benefit Assessment

Regulatory Action

Complete Response.

Risk:Benefit Assessment

The Applicant has submitted adequate information to support the safety and efficacy of sugammadex when used as proposed by the Applicant. However, the observations from the routine inspections indicated several protocol violations that raised questions about the integrity and reliability of the data generated from Study P101, the key study intended to address the remaining deficiency. Although review of the violations at one of the two clinical sites inspected and the unblinding of subjects prior to database lock at the Applicant's central site had a low probability of having a significant impact on the results of the study, inspection of the remaining clinical sites was deemed to be necessary in order to establish whether there were other protocol violations that would further impact the validity and integrity of the data. Since these inspections could not logistically be carried out prior the already-scheduled advisory committee meeting, the meeting was canceled. Subsequently, my recommendation is that this application be given a Complete Response at this time.

Recommendation for Postmarketing Risk Management Activities

None.

Recommendation for other Postmarketing Study Requirements

This application is subject to the postmarketing requirements of the Pediatric Research Equity Act. As described in Section 10, the submission of pediatric data is currently deferred, and the Applicant intends to pursue a clinical trial to (b) (4) o the pediatric population.

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/s/

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12/15/2015