NDA 22225

WRITTEN REQUEST – AMENDMENT #3

Organon USA Inc.; a subsidiary of Merck & Co., Inc.
2000 Galloping Hill Road
Kenilworth, NJ 07033

Attention: Dori Glassner
Director, Global Regulatory Affairs

Dear Ms. Glassner:

Please refer to your correspondence dated July 17, 2019, requesting changes to FDA's October 28, 2016, Written Request for pediatric studies for Bridion (sugammadex) Injection.

We have reviewed your proposed changes and are amending the Written Request. All other terms stated in our Written Request issued on October 28, 2016, and as amended on May 24, 2017 and January 22, 2019, remain the same. (Text added is underlined. Text deleted is strikethrough.)

Study 1
Part A of this study must identify a dose to be used in Part B that will result in either a) exposures matching the adults or b) neuromuscular recovery times comparable to adults (as measured using time to a TOF ≥0.9).

Study 2
The dosing in this study will be based on the totality of PK and efficacy data obtained from Part A of Study 1.

In Study 2, and interim ~~safety and PK~~ analysis will be performed before:

- Proceeding to the next age cohort in Part A (refer to defined age cohorts in Section "Patients to be Studied" below).
- Proceeding to Part B of the study. First, PK and safety analyses will be performed. If the data suggests a change in PK for a given age cohort, then efficacy data may be considered. Once the interim ~~PK and safety~~ analyses have been performed for an age cohort in Part A, Part B of the study may begin to enroll that age cohort (i.e., prior to completion of all age cohorts in Part A) provided the dose remains unchanged. However, if any interim analysis (IA) suggests that a dose adjustment is required ~~change in PK for a given age cohort~~ then the data must be reported to and the dose for study in Part B for that age cohort agreed upon by the Agency prior to the initiation of Part B for ~~each~~ that age cohort and Part A of the

next adjacent younger age cohort.

Objectives for each study

- Study 1
  - Part A: To identify doses of sugammadex that will produce either a) similar exposure or b) comparable recovery times from NMB in the 2 to < 17 year old age group when compared to systemic exposure noted in adults following administration of the 2 mg/kg and 4 mg/kg doses.
- Study 2
  - Part A: To identify a dose of sugammadex for study in the birth to < 2 year old age group for Part B of Study 2. An interim safety and PK analysis will be performed before proceeding to the PK for the next age cohort (see age group in which studies will be performed in Section "Patients to be Studied" below). Should an IA PK assessment suggest a dose adjustment is needed to achieve exposures similar to the next adjacent older age cohort, efficacy data may be considered before modifying the dose.

Timeframe for submitting reports of the studies: Reports of the above studies must be submitted to the Agency on or before ~~October 27, 2019~~ August 31, 2023.

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated October 28, 2016, as amended by this letter and by previous amendments dated May 24, 2017, and January 22, 2019, must be submitted to the Agency on or before August 31, 2023, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a supplement to approved NDA 22225 with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter.

In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following:

- the type of response to the Written Request (i.e., complete or partial response);

- the status of the application (i.e., withdrawn after the supplement has been filed or pending);
- the action taken (i.e., approval, complete response); or
- the exclusivity determination (i.e., granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website.[1]

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

If you have any questions, call Allison Meyer, Sr. Regulatory Health Project Manager, at (301) 796-1258.

Sincerely,

{See appended electronic signature page}

Mary T. Thanh Hai, M.D.
Acting Director
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):
- Complete Copy of Written Request as Amended

[1] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm316937.htm

Written Request - Amendment #3

BACKGROUND:

These studies investigate the potential use of sugammadex in the treatment of reversal of neuromuscular blockade (NMB) induced by rocuronium and vecuronium in pediatric patients 0 to <17 years old.

Pediatric patients that undergo surgical procedures or are admitted to the Intensive Care Unit (ICU) sometimes require muscle relaxation in addition to anesthetic or sedation agents. Muscle relaxation is typically established with non-depolarizing neuromuscular blocking drugs like rocuronium or vecuronium. Prior to FDA approval of sugammadex in 2015, the only drugs available to reverse neuromuscular blockade were anti-cholinesterase drugs, of which neostigmine is most commonly utilized. Neostigmine produces cholinergic side effects (e.g., bradycardia) and, therefore, needs to be administered concurrently with an anticholinergic drug like glycopyrrolate or atropine. Neostigmine has been shown to adequately reverse neuromuscular blockade in patients who have spontaneous recovery of at least one twitch in a train-of-four, or a moderate level of NMB. Sugammadex offers a potential benefit over neostigmine, producing faster neuromuscular block reversal than neostigmine, as well as the ability to reverse deeper neuromuscular blockade than can be reversed with acetylcholinesterase inhibitors. Sugammadex, unlike neostigmine, does not inhibit acetylcholinesterase, therefore, cholinergic effects are not produced and co-administration of an anti-muscarinic agent (glycopyrrolate or atropine) is not needed. Because co-administration of anti-muscarinic agents is not necessary with sugammadex, the use of sugammadex might be associated with fewer adverse effects than the use of traditional reversal agents. Also, since sugammadex can reverse profound levels of neuromuscular blockade, its availability could render the use of succinylcholine unnecessary. Succinylcholine has potentially serious adverse effects and a boxed warning regarding the risk of cardiac arrest in pediatric patients.

Sugammadex forms a complex with the non-depolarizing neuromuscular blocking drugs rocuronium and vecuronium, thereby removing these agents from the neuromuscular junction and facilitating the return of muscle function. Given the mechanism of action of sugammadex, its efficacy profile is expected to hold true in pediatric patients from ≥ 2 years old to < 17 years old, and therefore full pediatric extrapolation can be utilized in these ages. Given the immaturity of multiple organ systems in patients < 2 years old including neonates, and in particular the neuromuscular system, the appropriate dose for efficacy, in addition to safety, must be established in the < 2 year old patient population. Therefore, efficacy in patients ages 0 to < 2 years old cannot be extrapolated and will be determined by the separate study outlined in the Written Request (WR).

Pharmacokinetic data, described below as Part A of Study 1, must be collected to accurately characterize the PK parameters in pediatric patients of 2 to 17 years of age. Pharmacokinetic data, described in Part A of Study 2, must be collected to accurately characterize the PK

parameters in pediatric patients 0 to <2 years of age. Part B of Studies 1 and 2 (described below), must employ doses identified from Part A of respective studies.

To obtain needed pediatric information on sugammadex, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the studies described below.

- *Nonclinical studies*:

Based on review of the available non-clinical toxicology, no additional animal studies are required at this time to support the clinical studies described in this Written Request.

- *Clinical studies:*

Study 1: This study will be a 2-part, randomized, assessor-blinded, multicenter study evaluating pharmacokinetics (PK) and safety of sugammadex used for reversal of neuromuscular blockade in pediatric patients 2 to < 17 years old.

Part A will be a randomized, multicenter study evaluating PK of sugammadex used for reversal of neuromuscular blockade in pediatric patients 2 to < 17 years old. Part A will evaluate initial doses of 2 mg/kg sugammadex for moderate block (spontaneous return of T2) and 4 mg/kg sugammadex for deep block (1-2 post-tetanic twitches).

Part B will be a randomized, assessor-blinded, active-controlled, multicenter study evaluating the safety of sugammadex for reversal of neuromuscular blockade induced by rocuronium and vecuronium in pediatric patients 2 to < 17 years old who have moderate (spontaneous return of T2 in a train-of-four) and deep block (at least 1 to 2 post-tetanic counts and no twitch responses to a train-of-four). The dosing for each depth of block in this study will be based on the results from Part A. In Part B, for patients with spontaneous recovery of T2, sugammadex will be compared to neostigmine.

Part A of this study must assess PK and identify a dose to be used in Part B. Results of Part A must be reported to and the dose agreed upon by the Agency prior to the initiation of Part B. Pharmacokinetics in the targeted pediatric population must be accurately evaluated and estimated in Part A of Study 1. Otherwise, additional PK samples may need to be collected in Part B of the study. Also, the study protocol must include stopping criteria for adverse events of interest (i.e., bradycardia and anaphylaxis). If greater than predicted cardiovascular adverse events (e.g., bradycardia) or unexpected severe adverse events in Study 1, Part A are observed, you will need to submit your safety data to the Agency for review prior to initiation of Study 2 enrollment. Finally, since the lower age sub-cohort (2 to < 6 years) is potentially at greater risk of adverse events, in particular bradycardia, you must ensure that at least N=2 for each level of block (moderate and deep) are between 2 to <3 years of age in Part A of the study.

Study 2: This study will be a 2-part, randomized, assessor-blinded, active-controlled,

multicenter study evaluating the PK, safety, and efficacy of sugammadex for reversal of neuromuscular blockade induced by rocuronium and vecuronium in pediatric patients ages 0 to < 2 years old. The dosing in this study will be based on the totality of PK and efficacy data obtained from Part A of Study 1.

Enrollment of Study 2 Part A may begin after completion of Study 1, Part A. As above, if greater than predicted cardiovascular adverse events (e.g., bradycardia) or unexpected severe adverse events in Study 1, Part A are observed, you will need to submit your safety data to the Agency for review prior to initiation of Study 2 enrollment.

Part A will be a single-arm, multicenter study evaluating PK of sugammadex for the reversal of neuromuscular blockade in pediatric patients 0 to < 2 years old. Panel 1 will evaluate the dose of sugammadex appropriate for moderate block (spontaneous return of T2 in a train-of-four) while Panel 2 will evaluate the dose appropriate for deep block (1 to 2 post-tetanic twitches).

Pharmacokinetics in the targeted pediatric population must be accurately evaluated and estimated in Panels 1 and 2. Otherwise, additional PK samples will need to be collected in Part B. The bioanalytical assay used to analyze PK samples must be agreed upon with the Agency.

Part B will be a randomized, assessor-blinded, active-controlled, multicenter study evaluating the efficacy and safety of sugammadex for reversal of neuromuscular blockade induced by rocuronium and vecuronium in pediatric patients age 0 to < 2 years old who have moderate block (spontaneous recovery of T2 in a train-of-four) and deep block (reached at least 1 to 2 post-tetanic counts and no twitch responses to a train-of-four). The active control (neostigmine) arm will evaluate patients with spontaneous recovery of T2 in a train-of-four, for comparison with the sugammadex cohort with spontaneous recovery of T2. This study must be designed to evaluate superiority to the active control arm for the primary efficacy endpoint for the cohorts with spontaneous recovery of T2.

In Study 2, an interim analysis will be performed before:

- Proceeding to the next age cohort in Part A (refer to defined age cohorts in Section "Patients to be Studied" below).
- Proceeding to Part B of the study. An interim analysis (IA) should be conducted before initiating the corresponding age cohort in Part B. However, if any IA suggests that a dose adjustment is required, the data must be reported and the dose to be utilized in Part B for the corresponding age cohort must be agreed upon by the Agency prior to the initiation of Part B for that age cohort.
- *Objective of each study:*
    - *Study 1:*
        - *Part A:* Part A of this study must assess PK and identify a dose to be used in Part B in patients 2 to < 17 years of age.

- *Part B:* To evaluate the safety and tolerability of sugammadex in pediatric patients 2 to < 17 years old. Descriptive efficacy findings should also be recorded. Efficacy findings, while not required to be statistically significant, should favor sugammadex.

- *Study 2:*

  - *Part A:* Part A of this study must assess PK and identify a dose to be used in Part B in in patients birth to < 2 year of age. An interim safety and PK analysis will be performed before proceeding to the PK for the next age cohort (see age group in which studies will be performed in Section "Patients to be Studied" below). However, if any IA suggests that a dose adjustment is required, the data must be reported and the dose to be utilized in Part B for the corresponding age cohort must be agreed upon by the Agency prior to the initiation of Part B for that age cohort.
  - *Part B:* To determine efficacy, safety, and tolerability of sugammadex in pediatric patients birth to < 2 years old.

- *Patients to be Studied:*

  - *Age group in which studies will be performed*:

    - Study 1 will evaluate patients from 2 to < 17 years old.
    - Study 2 will evaluate patients from birth to < 2 years old in cohorts by sequential approach as follows:
      - 6 months to < 2 years
      - 3 months to < 6 months
      - 28 days to < 3 months
      - Birth to 27 days

    Within each cohort, lower doses (e.g., 2 mg/kg) should be studied before higher doses (e.g., 4mg/kg) and interim safety analysis must be performed before proceeding to the next age cohort.
    - Study 2 may be initiated only upon completion and submission of safety data from Study 1 (Part A).
    - In each study, the number of patients must be approximately evenly distributed between genders and within each age cohort being studied.

  - *Number of patients to be studied:*

    - Study 1, Part A: The sample size must be sufficient to estimate the PK parameters (clearance and volume of distribution) by employing a scientifically justified PK approach. In addition, the study needs to be adequately powered to target a 95% CI within 60% and 140% of the point estimate for the geometric mean estimates of clearance and volume of distribution with 80% power for a drug in each age

group to be studied.

- Study 1, Part B: Study patients may include any patient that requires neuromuscular blocking agent (NMB) administration, including patients requiring NMB for elective/urgent/emergent surgical/interventional procedures and patients requiring NMB while undergoing treatment for a medical condition in the Intensive Care Unit.

  The following table represents the minimum number of patients to be studied in Study 1 in order to obtain adequate safety information:

Table 1

	Spontaneous Return of T2 (Moderate Block)	1-2 Post-tetanic Twitches (Deep Block)	Total
Part A: (PK)			
12 to < 17 years	4	4	8
6 to < 12 years	4	4	8
3 to < 6 years	4	4	8
2 to < 3 years	2	2	4
Part B (safety)			
12 to < 17 years	10	35	45
6 to < 12 years	10	45	55
2 to < 6 years	10	60	70
Totals	44	154	198

- As portrayed in the table above, there should be even distribution of patients across the entire 2 to < 17 year old range of ages in the 2 mg/kg cohort, with no more than 30% of patients from the 12 to < 17 year old age group. There should be a higher proportion of patients in the 2 to < 6 year old age group than in the older age groups for the 4 mg/kg. This will help determine whether the younger patients, who have rate-dependent cardiac output, have a disproportionally increased risk of bradycardia or increased severity of bradycardia associated with higher doses of sugammadex.
- Although the table above represents the minimum number for safety, the total sample size may be slightly higher to allow for practical allocation ratios.

- Study 2: Study patients may include any patient that requires neuromuscular blocking agent (NMB) administration, including patients requiring NMB for elective/urgent/emergent surgical/interventional procedures and patients requiring NMB while undergoing treatment for any medical condition in the Intensive Care Unit.
  - Part B of this study must be powered to detect a statistically

significant difference between study drug and control at the primary efficacy endpoint.

- In addition, due to safety concerns, particularly with the risk of bradycardia in patients < 2 years old, the following table represents the minimum number of patients to be studied in Study 2 in order to obtain adequate safety information:

Table 2

	Spontaneous Return of T2 (Moderate Block)	1-2 Post-tetanic Twitches (Deep Block)	Total
Part A: Panel 1 (PK)			
6 months - 2 years	3	N/A	3
3 months - < 6 months	3	N/A	3
28 days - < 3 months	3	N/A	3
0 – 27 days	3	N/A	3
Part A: Panel 2 (PK)			
6 months - 2 years	N/A	6	6
3 months - < 6 months	N/A	6	6
28 days - < 3 months	N/A	6	6
0 – 27 days	N/A	6	6
Part B (safety & efficacy)	25	30	55
Totals	37	54	91

- There should be even distribution of patients across the entire zero days to < 2 years range of ages, with each age cohort (as previously described) contributing at least 20% to the total study enrollment.
- Although the table above represents the minimum number for safety, the total sample size may be slightly higher to allow for practical allocation ratios.

Representation of Ethnic and Racial Minorities: The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

- *Study endpoints:*

  - *Pharmacokinetic Endpoints:*
    Part A of Studies 1 and 2 must include precise estimates of clearance, and volume of distribution. Other PK parameters such as Cmax (in case of a slow infusion) and Area under the plasma concentration vs. time curve (AUC) should also be reported. The required blood sampling scheme to achieve precise PK parameters can be based on population PK approach. Part B of Studies 1 and 2 will collect confirmatory PK endpoints, if necessary.

- *Efficacy Endpoints:*
  - The primary efficacy endpoint for Part B of Study 1 will be the time to recovery to a TOF ratio of ≥0.9 and must be assessed by acceleromyography. Measures of compliance for Study 1 must include the use of a Neuromuscular Transmission Monitoring Data Adjudication Committee to assess neuromuscular monitoring data to confirm the acceptability of any deviations. Because full extrapolation of efficacy is acceptable, these endpoints will be measured as part of standard of care and will not be used to demonstrate efficacy.

  - The primary efficacy endpoint for Part B of Study 2 will be "time to extubation," defined as the interval from administration of reversal agent to removal of the endotracheal tube. Time to neuromuscular recovery, defined as the interval from administration of reversal agent to time to neuromuscular readiness for extubation, should also be measured as a secondary efficacy endpoint. Strict guidelines for determining readiness for extubation will need to be agreed upon at the time of final protocol submission. Study 2 must include an algorithm for measures of compliance to assess the acceptability of any deviations from these guidelines.

  - Secondary (exploratory) endpoints for both Study 1 and 2 should include incidence of non-responders.

- *Safety Endpoints:*
  - Safety outcomes must include physical exams, vital signs (blood pressure, heart rate, respiratory rate, and oxygen saturation), laboratory evaluations, and all adverse events. Adverse events of special interest will include hypersensitivity, anaphylaxis, and clinically-relevant bradycardia. Bradycardia must be clearly defined with strict heart rate parameters, length of time it persists, and clinical significance (i.e., resultant hypotension) for each age cohort within all studies.

  - The following adverse events must be actively monitored: bradycardia (see above). Furthermore, all episodes of heart rate decrease by >20% from baseline, regardless of duration and accompanying blood pressure, must be recorded. In addition, any events of recurrence of neuromuscular blockade must be monitored and recorded. All adverse events must be monitored until symptom resolution or until the condition stabilizes.

- The following adverse events must be captured when spontaneously reported: all adverse events must be captured for the duration of the study period.

  - A Data Monitoring Committee (DMC) must be included because findings of increased incidence of adverse events at an interim analysis,

particularly clinically significant bradycardia, may require termination of the study before its planned completion. See Guidance: Establishment and Operation of Clinical Trial Data Monitoring Committees http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126578.pdf

- *Known Drug Safety concerns and monitoring:*

  - Hypersensitivity and anaphylaxis has been found to occur in 0.3% of adult patients (cited in the current package insert)
  - Bradycardia incidence was 1% in adult patients receiving 2mg/kg and 4mg/kg doses, and 5% in adult patients receiving 16mg/kg doses (cited by the current package insert)
  - In clinical trials, a small number of patients experienced a delayed or minimal response to the administration of sugammadex (cited by the current package insert)
  - Recurrence of neuromuscular blockade may occur (cited by the current package insert):
    - Due to displacement of rocuronium or vecuronium from sugammadex by other drugs
    - When drugs which potentiate neuromuscular blockade are used in the post-operative phase
    - When lower than recommended doses of sugammadex are administered

- *Extraordinary results:* In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

- *Drug information:*

  - *dosage form*
    - 200 mg/2mL (100 mg/mL) in a single-dose vial for bolus injection
    - 500 mg/5mL (100 mg/mL) in a single-dose vial for bolus injection

  - *route of administration*
    - For intravenous use only

  Use an age-appropriate formulation in the studies described above. If an age-appropriate formulation is not currently available, you must develop and test an age- appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

In accordance with section 505A(e)(2), if

1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);
2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
3) you have not marketed the formulation within one year after the Agency publishes such notice,

the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be prepared by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for preparing an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using such a formulation, the following information must be provided for inclusion in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step preparation instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

- *Statistical information, including power of studies and statistical assessments:*

  - *Part A of Study 1:* Sample size for all studies must prospectively target a 95% confidence interval within 60% and 140% of the geometric mean estimates of clearance and volume of distribution for the drug in each pediatric subgroup with at least 80% power. Population PK modeling analysis based on sparse PK sampling, or other scientifically justified methods can be applied to achieve this precision standard [Wang Y. et al., Clarification on precision criteria to derive sample size when designing pediatric pharmacokinetic studies (J Clin Pharmacol. 2012 Oct; 52(10):1601-6)].

  - *Part B of Study 1:* The study should enroll enough patients to address the safety concerns (see **Error! Reference source not found.**~~Table 1~~). Descriptive data

must be provided for safety endpoints. The analysis must also include a descriptive summary of the efficacy results by age group.

- *Part A of Study 2*: Sample size for all studies must prospectively target a 95% confidence interval within 60% and 140% of the geometric mean estimates of clearance and volume of distribution for the drug in each pediatric subgroup with at least 80% power. Population PK modeling analysis based on sparse PK sampling, or other scientifically justified methods can be applied to achieve this precision standard [Wang Y. et al., Clarification on precision criteria to derive sample size when designing pediatric pharmacokinetic studies (J Clin Pharmacol. 2012 Oct; 52(10):1601-6)].

- *Part B of Study 2:* The primary null hypothesis is that sugammadex is equal to neostigmine with respect to the primary endpoint, time to extubation in patients recovering from moderate (spontaneous recovery of T2 in a train-of-four) neuromuscular blockade. The alternative hypothesis is that sugammadex and neostigmine are different with respect to the primary efficacy endpoint. The primary analysis population must be all patients who are randomized and receive at least one dose of study drug. Patients that fail to reach the primary endpoint, time to extubation, should be censored in your primary analysis and you should carefully document why this endpoint was not reached for each patient.

  In addition to the minimal number of patients needed for safety information (see **Error! Reference source not found.** ~~Table 2~~), this study must be powered to detect a treatment difference in the primary endpoint with at least 80% power and an overall two-sided Type I error at 5%.

For Part B of both Study 1 and 2, with respect to the primary efficacy analysis, the protocol should describe the estimand of primary interest. Since the estimand of interest is the treatment effect in all patients randomized regardless of adherence, you should include provisions to limit missing data through study design and education of investigators and patients, and pre-specify analysis methods to account for missing data for the primary and key secondary efficacy analyses. We recommend designs that encourage continued collection of efficacy data even after study treatment discontinuation, and these post-treatment data should be included in the primary analysis.

- The protocol and statistical analysis plan must be submitted and agreed upon with the Division prior to the initiation of pediatric studies.

- *Labeling that may result from the studies*: You must submit proposed pediatric labeling to incorporate the findings of the studies. Under section 505A(j) of the Act, regardless of whether the studies demonstrate that sugammadex is safe and effective, or whether such study results are inconclusive in the studied pediatric populations or subpopulations, the labeling must include information about the results of the studies. Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers

at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the studies.

- *Format and types of reports to be submitted*: You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the studies should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

  Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance.

  Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf and referenced in the FDA Guidance for Industry, Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications at http://www.fda.gov/Cder/guidance/7087rev.htm.

  Timeframe for submitting reports of the studies: Reports of the above studies must be submitted to the Agency on or before August 31, 2023. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

  Response to Written Request: Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the

Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the studies. If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

Furthermore, if you agree to conduct the studies, but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. In addition, send a copy of the cover letter of your submission via fax (240-276-9327) or messenger, to the Director, Office of Generic Drugs, CDER, FDA, Document Control Room, Metro Park North VII, 7620 Standish Place, Rockville, MD 20855-2773.

In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following:

- the type of response to the Written Request (i.e., complete or partial response);
- the status of the application (i.e., withdrawn after the supplement has been filed or pending);
- the action taken (i.e., approval, complete response); or
- the exclusivity determination (i.e., granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found at www.ClinicalTrials.gov.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARY T THANH HAI
11/23/2019 06:51:54 AM