CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207865Orig1s000

CHEMISTRY REVIEW(S)

MEMORANDUM

DEPATMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTARTION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 6, 2015

FROM: Hamid R. Shafiei, Ph.D.
Review Chemist/ATL (ONDP/Division II/Branch V)

Moo-Jhong Rhee, Ph.D.
Branch Chief (ONDP/Division II/Branch V)

TO: Review #1 of NDA 207865 Emend for Oral Suspension

SUBJECT: Final OPQ Recommendation

In the Review # 1 of NDA 207865 Emend (aprepitant) for Oral Suspension, this NDA was not recommended for approval from the CMC perspective due to the following reasons:

1) CMC related label/labeling issues were ***not*** resolved.
2) Inadequate results from human factor studies (clinical)

1. The outcome of the human factor studies submitted in the NDA application during the first review cycle was found by the Office of New Drugs (OND) to be unacceptable due to dosing variability and errors committed by healthcare professionals and patient's caregivers.

   In the human factor studies, the healthcare professionals and patient's caregivers were instructed to follow the instruction for use (IFU) and measure 4.6mL of water and place it into the mixing cup (co-packaged) using the 5-mL oral dispenser (co-packaged), add the entire powder provided in the Emend pouch (b) (4) . The results of the studies showed serious confusion leading to inconsistencies in volume measurements and significant dosing errors. Based on the outcome of the human factor studies and further discussion, the OND and the applicant, reach consensus to conduct a new human factor study in which the dose preparation and dose dispensing is performed only by healthcare professional. It was agreed that if this human factor study is found successful, the way forward will be that the healthcare professionals will prepare the suspension for patient dosing, administer the first dose to the patients, and provide the caregivers with the prescribed dosage volume of the suspension in separate pre-filled oral dispensers for administration on day 2 and day 3. Based on the proposed study plan, the ATL asked

the applicant to conduct an in-use stability study to ensure the product remain stable for at least 3 days when stored in the oral dispenser as a suspension.

In amendment dated 10/29/2015, the applicant provided adequate in-use stability data demonstrating that the drug product is stable for more than 3 hours at room temperature (25°C / 60% RH) and for more than three days under the refrigeration condition (2°C – 8°C). Based on the review of the stability data, it was concluded that the product will be adequately stable to allow for healthcare professionals to prepare the suspension, dose the patient with on day 1, and provide the caregivers with prefilled oral dispensers for day 2 and day 3 dosing. The in-use stability data clearly supports permitting the caregivers to take the prefilled oral dispenser home within 3 hours and store them in the refrigerator for day 2 and day 3 dosing.

Although, the in-use stability data demonstrated that the drug product is adequately stable to support the proposed new IFU, the assay results for the lowest dosage volume of 0.6mL were measured within (b) (4)%. ONDP anticipated that this high assay results were due to the potential inherent error associated with delivering 0.6mL using a 5-mL oral dispenser. In a T-Con dated 11/12/2015, the applicant confirmed that the ONDP assumption was correct and the variability in the assay values was caused by the error in delivering a dosing volume 0.6mL using a 5-mL oral dispenser. The applicant explained that at in addition to measurement of an accurate dosage of 0.6mL using the graduation marks of the oral dispenser, at times the tip of the dispenser empties leading to slightly higher delivered dose.

Based on the doing error observed in the delivery of dosage volume of ≤0.6mL, the OND clinical team requested that the applicant also co-package a 1-mL oral dispenser to be used for delivering the dosage volumes of ≤1.0mL. To move forward with the addition of the 1-mL oral dispenser, the ATL asked that the applicant to conduct similar 3-day in-use stability study using the 1-mL dispenser and provided the results for assay and degradation product. In an amendment dated 12/02/2015. The applicant provided in-use stability data for 1-mL oral dispenser. The assay results illustrated a more accurate dose volume delivery for dosage volumes of ≤1.0mL using the 1-mL oral dispenser. No degradation products were detected during the in-use stability study. The summary of the in-use stability is provided in the table below.

The **summary of the in-use stability study for 1-mL and 5-ML oral dispenser**

Storage Conditions	Test	Syringe Size (mL)	Dosing Vol. (mL)	Time Point (Hour(s))						
				0	6	8	24	48	72	144
2-8°C	Assay (%LC)	5	0.6	(b) (4)						
			5.0							
	Deg/ Unknown		0.6							
			5.0							
	Assay (%LC)	1	0.5							
			1.0							
	Deg/ Unknown		0.5							
			1.0							
Room Temperature (8 hours), followed by 2-8°C	Assay (%LC)	5	0.6							
			5.0							
	Deg/ Unknown		0.6							
			5.0							
	PSD (mu)		0.6							
			5.0							
Room Temperature (6 hours), followed by 2-8°C	Assay (%LC)	1	0.5							
			1.0							
	Deg/ Unknown		0.5							
			1.0							
	pH	5	0.6							
			5.0							

NT: not tested
ND: none detected above LOQ (0.025%)

2. In the original NDA submission, the immediate (primary) drug product container closure label did not include drug product lot # and expiration. An IR was issued to the applicant to add the drug product lot # and expiration to the immediate container closure label and resubmit. The applicant has revised the immediate container label to include lot # and expiration and resubmitted. The new container label is provided in the figure below. The new immediate container label is considered satisfactory.

Immediate container (pouch) label

(b) (4)

Recommendation:

This NDA is now recommended for **approval** from the OPQ perspective with the product expiration dating period of 30 months.

Hamid Shafiei -S
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Date: 2015.12.06 11:25:36 -05'00'

Hamid R. Shafiei, Ph.D.
CMC Reviewer, Branch V, Division II, ONDP

Mark R. Seggel -S
Digitally signed by Mark R. Seggel -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Mark R. Seggel -S, 0.9.2342.19200300.100.1.1=1300071539
Date: 2015.12.06 14:47:50 -05'00'

Mark R. Seggel, Ph.D.
CMC Lead, Branch V, Division II, ONDP

for

Moo-Jhong Rhee, Ph.D.
Branch Chief, Branch V, Division II, ONDP

NDA 207865

EMEND™ (aprepitant) for Oral Suspension 125 mg

Merck Sharp & Dohme Corp.

Hamid R. Shafiei, Ph.D.

Review Chemist

Office of Pharmaceutical Quality
Office of New Drug Product Division II
Branch V

For Division of Gastroenterology and Inborn Errors Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 207865

2. REVIEW #: 1

3. REVIEW DATE: 07/20/2015

4. REVIEWER: Hamid R. Shafiei, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
8/16/2004 Pre-IND Meeting Minutes	04-Sep-2004
11/21/2005 EOP2 Meeting Minutes	21-Dec-2005
4/19/2007 Pre-NDA Reviewer Comments by Fax	25-Apr-2007

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	25-Jul-2014
Amendment (SDN-3)	26-Aug-2014
Amendment (SDN-4)	26-Aug-2014
Amendment (SDN-5)	03-Sep-2014
Amendment (SDN-6)	12-Sep-2014
Amendment (SDN-7)	15-Sep-2014
Amendment (SDN-8)	31-Oct-2014
Amendment (SDN-9)	25-Nov-2014
Amendment (SDN-10)	08-Jan-2015
Amendment (SDN-11)	06-Mar-2015
Amendment (SDN-12)	11-Mar-2015
Amendment (SDN-13)	12-Mar-2015
Amendment (SDN-14)	26-Mar-2015
Amendment (SDN-15)	09-Apr-2015
Amendment (SDN-16)	10-Apr-2015
Amendment (SDN-17)	20-May-2015
Amendment (SDN-18)	27-May-2015
Amendment (SDN-19)	28-May-2015

Amendment (SDN-20)	05-Jun-2015
Amendment (SDN-21)	08-Jun-2015
Amendment (SDN-22)	11-Jun-2015
Amendment (SDN-23)	29-Jun-2015
Amendment (SDN-24)	29-Jun-2015
Amendment (SDN-25)	30-Jun-2015
Amendment (SDN-26)	01-Jul-2015
Amendment (SDN-27)	01-Jul-2015
Amendment (SDN-28)	08-Jul-2015
Amendment (SDN-29)	10-Jul-2015

7. NAME & ADDRESS OF APPLICANT:

Name:	Merck Sharp & Dohme Corp.
Address:	126 E. Lincoln Ave. P.O. Box 2000, RY 33-200 Rahway, NJ 07065-0900
Representative:	Nicholas W. Andrew Director, Regulatory Affairs
Telephone:	(732) 594-5585
Email:	nicholas_andrew@merck.com

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: EMEND™
b) Non-Proprietary Name (USAN): Aprepitant
c) Code Name/# (ONDP only): N/A
d) Chem. Type/Submission Priority (ONDP only):
- Chem. Type: 3 (New Dosage Form)
- Submission Priority: P

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

10. PHARMACOL. CATEGORY: Antiemetic

11. DOSAGE FORM: powder for suspension

12. STRENGTH/POTENCY: 125 mg

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: __X__Rx ___OTC

Chemistry Review Data Sheet

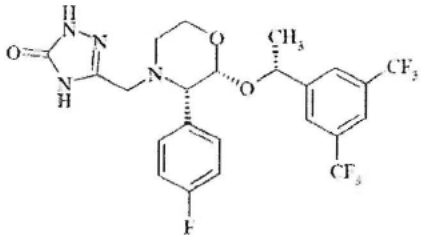
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X___Not a SPOTS product

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

Aprepitant: 5-[[(2*R*,3*S*)-2-[(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro-3H-1,2,4-triazol-3-one



Molecular Formula: $C_{23}H_{21}F_7N_4O_3$
Molecular Mass: 534.43
CAS No: 170729-80-3

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)		4		
	III				4		
	III				4		
	III				4		

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

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

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	50283	Aprepitant capsules and Aprepitant powder for suspension
NDA	21549	Emend (aprepitant) capsules, 40 mg, 80 mg, 125 mg

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
Office of Process and Facilities-Facilities Recommendation	Acceptable	07/14/2015	Vipul Dholakia
Pharm/Tox	N/A		
Biopharm	Adequate with postapproval commitment	07/16/2015	Tien Mien Chen
Methods Validation	N/A, according to the current IQP 5105		
Office of Drug Safety	Acceptable for "Emend" as the proprietary name	09/29/2014	Sherly Abraham
EA	Categorical exclusion granted	07/13/2015	James Laurenson
Microbiology	Acceptable	08/25/2014	Bryan S. Riley

Chemistry Review

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant of this NDA has provided sufficient information to assure the identity, strength, purity, and quality of the drug product.

The Office of Process and Facilities has made an overall "Acceptable" recommendation for the facilities involved in this NDA.

The claim for the Categorical Exclusion for the Environmental Assessment is granted.

However, the labels/labeling issues have ***not*** been completely resolved as of this review.

Therefore, from the ONDP perspective, this NDA is ***not*** deemed ready for approval at this time in its present form per 21 CFR 314.125(b)(6), until the above issues are satisfactorily resolved (see the **List of Deficiencies** on page 86).

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

The applicant has agreed to develop appropriate acceptance criteria for the particle size distribution (PSD) (b) (4)
postapproval, update the drug product release and stability specification with a proposed acceptance criterion for D (b) (4) PSD (b) (4) submit the updated drug product specification to the FDA in a postapproval supplement within a year after the approval of this application.

II. Summary of Chemistry Assessments

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

(1) Drug Substance

The drug substance, aprepitant, is a selective high affinity human P neurokinin 1 (NK1) receptor antagonist. This drug substance in combination with other antiemetic agents including a 5-HT3 receptor antagonist and a corticosteroid has

been approved in 80 countries for the prevention of acute and delayed nausea and vomiting caused by the treatment of adult cancer patients with highly emetogenic and moderately emetogenic chemotherapy (CINV – HEC and CINV – MEC). Aprepitant capsules 80 mg and 125mg have been approved in the United States under NDA 21549 for the treatment CINV in adult patients and are marketed under the brand name Emend.

Aprepitant,

5-[[(2*R*,3*S*)-2-[(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro-3H-1,2,4-triazol-3-one

is an off-white to light yellow crystalline (b) (4) with molecular mass of 534.43 and molecular formula of $C_{23}H_{21}F_7N_4O_3$. This API is (b) (4) poor aqueous solubility and is classified as a BCS class (b) (4). The bioavailability of this API has been improved (b) (4) drug product.

The aprepitant drug substance intended for use as the active ingredient in the proposed drug product, Emend® (aprepitant) for Oral Suspension, 125mg (b) (4) API used in the currently approved Emend® capsules.

The proposed drug substance specification (b) (4) provided in the approved NDA 21549 for Emend® capsules. The proposed drug substance specification includes appropriate testing and acceptance criteria to assure that the drug substance produced from the proposed manufacturing process meet the targeted API quality attributes.

This application includes 126 months of supporting stability results from three batches of API manufactured at the previously approved manufacturing site (MSD International GmbH, Barceloneta, Puerto Rico) and 12 months of stability data from three batches of drug substance manufactured at the proposed commercial manufacturing site (b) (4). All stability data show no trends and/or significant changes in the API quality attributes. Furthermore, the stability profile of the drug substance batches manufactured at the proposed commercial manufacturing site is closely comparable to stability profiles of the batches manufactured at previously approved manufacturing site. The API stability data provided is considered satisfactory.

In conclusion, the applicant has provided sufficient information to assure, identity, strength, purity, quality, and stability of aprepitant intended for use as the active ingredient in the composition of the drug product, Emend® for Oral Suspension.

(2) Drug Product

The drug product Emend® (aprepitant) for Oral Suspension has been developed as an alternative formulation to currently approved Emend® capsules for dosing of pediatric patients who may not be able to swallow capsules. Emend® powder formulation [redacted] aprepitant drug substance approved for Emend capsules. However, powder for suspension is formulated using soluble excipients (except [redacted] ferric oxide [redacted]) so that upon suspension in an aqueous medium all excipient are dissolved producing a uniform suspension of [redacted] drug substance.

Emend® for Oral Suspension, is a pink to light pink [redacted] powder. It contains 125mg of [redacted] aprepitant as the active ingredient and hydroxypropyl cellulose [redacted], sodium lauryl sulfate, sucrose, lactose, anhydrous, red ferric oxide, sodium stearyl fumarate, [redacted]

This drug product is packaged into [redacted]. The to-be-marketed drug product packaging configuration is a cartoned kit consisting of the drug product [redacted], a mixing cup, a 5-mL oral dispenser, [redacted] approved by the agency. The proposed [redacted] The appropriateness of the proposed packaging is further supported by the results from long-term and accelerated stability studies. Therefore, the proposed packaging configuration is deemed satisfactory.

The drug product is tested and released according to a specification that is well-established based on pharmaceutical development, manufacturing capabilities, and the test results of historical batches of drug product produced to date. The proposed drug product specification is consistent with requirements in ICH Q3B guidelines.

This application also includes 18 months of long-term (30°C ± 2°C/75%RH ± 5%RH) and 6 month of accelerated (40°C ± 2°C/75%RH ± 5%RH) stability data in support of the proposed expiration dating period of 30 months. The storage condition for this drug product is specified as "Store at 20-25°C (68-77°F); excursions permitted between 15-30°C (between 59-86°F)". The proposed expiration dating period and storage condition is well supported by the stability data and are considered adequate.

In summary, this application has provided sufficient information to assure the identity, strength, purity, and quality, of Emend® for Oral suspension with an expiration period of 30 months.

Executive Summary Section

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	**Factors that can impact the CQA**	**Risk Ranking***	**Risk Mitigation approach in control strategy**	**Risk Evaluation**	**Lifecycle Considerations/ Comments****
Assay, stability	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	Particle size specifications for (b) (4)	L	(b) (4)
Physical stability (API)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L		L	
Content uniformity	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	Control of particle size for (b) (4) (b) (4) and API??? (b) (4)	L	Particle size distributions for (b) (4) (b) (4) are controlled.
Microbial-Limits	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L		L	
Dissolution	• Formulation • Raw materials • Process parameters • Scale/equipment • Site • Exclude major reformulations	M		L	API is a BCS class (b) (4) drug. Bioavailability of the drug product is achieved with the (b) (4) particles of the API, which is achieved by (b) (4) (b) (4) (b) (4) The process equipment and process parameters are critical for achieving consistent particle size distribution of the API. Since D (b) (4) PSD for the reconstituted drug product is added to the product release and stability specification, the risk is re-ranked as low.

Palatability	• Formulation • Excipient change • Process parameters • Scale/equipment • Site	L		L	Due to the presence of (b) (4) (b) (4) as two major components of the product, the risks related to the palatability of the drug product is considered low.

Reviewer assessment of the risk: *The potential risks to QTPP for Emend (aprepitant) for Oral Suspension were assessed in consideration of the proposed drug product manufacturing process, manufacturing equipment, in-process testing and control, control of critical steps, proposed drug product specification, and release and stability testing of the drug product. All risks were ranked as low with exception of the risk to the dissolution. The potential risk to the dissolution, a drug product quality attribute often used as the surrogate for bioavailability was ranked as medium. This ranking was assigned during initial quality assessment (IQA) because API used in this drug product is classified a BCS class (b) (4). To improve bioavailability, API (b) (4) use in the manufacture of the drug product. Therefore, the process equipment and process parameters used in the (b) (4) API are considered critical for achieving consistent particle size distribution (b) (4). After the review of the information provided, it was concluded that during the pharmaceutical and manufacturing development, the applicant had adequately monitored D (b) (4) of particle size distribution (PSD) of the API (b) (4). Additionally, the applicant has determined D (b) (4) PSD of the API in the oral suspension at time zero and 5 hours after reconstitution at initial stability time-point as well as all pivotal stability time-points for up to 18 months during the stability testing of the three formal stability batches of the drug product. Furthermore, the applicant has provided data-driven justification to show that D (b) (4) and D (b) (4) of the API PSD do not reveal any additional useful information for better control of the manufacturing process. The applicant also initially examined the PSD (b) (4) during process development in order to develop appropriate manufacturing process parameters. However, the applicant did not continue determination of PSD (b) (4) for the formal stability batches and beyond. Additionally neither the PSD of API in the oral suspension nor PSD (b) (4) were included in the commercial drug product specification. In a T-con on 07/10/2015 the agency requested the applicant to include testing and acceptance criteria for D (b) (4) for PSD of API in the reconstituted suspension as well as D (b) (4) for PSD (b) (4) in the drug product specification. In an amendment dated 07/10/201, the applicant provided an updated drug product specification that complied with the Agency's requests. Although the applicant agreed and added the testing for D (b) (4) for PSD (b) (4) to the release and stability specification, due to lack of sufficient data, the applicant has proposed setting the acceptance criterion for this attribute postapproval after sufficient data from commercial scale batches of drug product is collected.*

Based on the review of the information in this application, the updated specification, and the postapproval commitments, the risks to the dissolution is re-ranked as low.

B. Description of How the Drug Product Is Intended to Be Used

For adults and adolescents (aged 12 through 17 years), the recommended dose of EMEND® capsules is 125 mg orally on Day 1 and 80 mg orally on Days 2 and 3. For children (aged 6 months to less than 12 years), the recommended dose of EMEND® for Oral Suspension (b) (4).

C. Basis for Approval or Not-Approval Recommendation

Not-Approval per 21 CFR 314.125(b)(6):

The labels/labeling issues have not been completely resolved as of this Review.

III. Administrative

A. Reviewer's Signature

Hamid Shafiei -S

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Date: 2015.07.20 15:22:33 -04'00'

Hamid R. Shafiei, Ph.D.

B. Endorsement Block

Moojhong Rhee -S

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Moo-Jhong Rhee, Ph.D., Branch Chief, Branch V, Division II, ONDP

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(b) (4)

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

A. LABELING & PACKAGE INSERT

1. Package Insert

a) "Highlights" Section (21CFR 201.57(a))

EMEND (aprepitant) capsules, for oral use
EMEND (aprepitant) for oral suspension
Initial U.S. Approval: 2003

EMEND capsules: 40 mg; 80 mg; 125 mg (3)
EMEND for oral suspension: 125 mg (3)

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	EMEND (aprepitant)	Proprietary name and established name is provided. **Satisfactory**
Dosage form, route of administration	capsules, for oral for oral suspension	Dosage form, route of administration provided for capsules and for oral suspension. **Satisfactory**
Controlled drug substance symbol (if applicable)	Not applicable	Not applicable
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	capsules: 40 mg; 80 mg; 125 mg oral suspension: 125 mg	The dosage forms and strengths for capsules are described correctly. However, dosage form for oral suspension is not specified. **Satisfactory**

Conclusion: Adequate

(b) "Full Prescribing Information" Section

 # 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

EMEND capsules:

- 40 mg: white body and mustard yellow cap with "464" and "40 mg" printed radially in black ink on the body.
- 80 mg: white body and cap with "461" and "80 mg" printed radially in black ink on the body.
- 125 mg: white body and pink cap with "462" and "125 mg" printed radially in black ink on the body.

EMEND for oral suspension:

- 125 mg as a pink to light pink powder in a single-use pouch with 5 mL oral dosing dispenser and mixing cup.

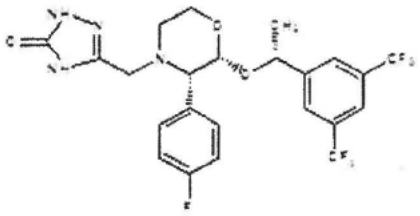
Chemistry Assessment Section

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Capsules and for Oral suspension	**Satisfactory**
Strengths: in metric system	capsules: 40 mg; 80 mg; 125 mg for oral suspension: 125 mg	**Satisfactory**
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Capsules: 40 mg: white body and mustard yellow cap with "464" and "40 mg" printed radially in black ink on the body. 80 mg: white body and cap with "461" and "80 mg" printed radially in black ink on the body. 125 mg: white body and pink cap with "462" and "125 mg" printed radially in black ink on the body. Oral suspension: 125 mg as a pink to light pink powder in a single-use pouch with 5 mL oral dosing dispenser and mixing cup	For labeling consistency, it is recommended to revise the reference to primary container from a pouch to sachet. **Satisfactory**

Conclusion: Adequate.

#11: Description (21CFR 201.57(c)(12))

EMEND (aprepitant) is a substance P/neurokinin 1 (NK1) receptor antagonist, an antiemetic agent, chemically described as 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro-3H-1,2,4-triazol-3-one. Its empirical formula is $C_{23}H_{21}F_7N_4O_3$, and its structural formula is:



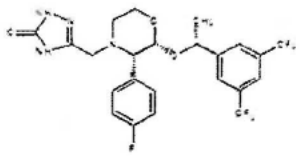
Aprepitant is a white to off-white crystalline solid, with a molecular weight of 534.43. It is practically insoluble in water. Aprepitant is sparingly soluble in ethanol and isopropyl acetate and slightly soluble in acetonitrile.

Each capsule of EMEND for oral administration contains either 40 mg, 80 mg, or 125 mg of aprepitant and the following inactive ingredients: sucrose, microcrystalline cellulose, hydroxypropyl cellulose and sodium lauryl sulfate. The capsule shell excipients are gelatin, titanium dioxide, and may contain sodium lauryl sulfate and silicon dioxide. The

40-mg capsule shell also contains yellow ferric oxide, and the 125 mg capsule also contains red ferric oxide and yellow ferric oxide.

Each pouch of EMEND for oral suspension 125 mg contains 125 mg of aprepitant and the following inactive ingredients: sucrose, lactose, hydroxypropyl cellulose, sodium lauryl sulfate, red iron oxide, and sodium stearyl fumarate.

Chemistry Assessment Section

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	EMEND (aprepitant)	Proprietary name and established name is described correctly. **Satisfactory**
Dosage form and route of administration	Capsule for oral administration For oral suspension	Dosage form and route of administration provided. **Satisfactory**
Active moiety expression of strength with equivalence statement for salt (if applicable)	For capsules: 40 mg, 80 mg, or 125 mg of aprepitant For pouch: 125 mg of aprepitant	**Satisfactory**
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Capsules inactive ingredients: sucrose, microcrystalline cellulose, hydroxypropyl cellulose and sodium lauryl sulfate. The capsule shell excipients are gelatin, titanium dioxide, and may contain sodium lauryl sulfate and silicon dioxide. The 40-mg capsule shell also contains yellow ferric oxide, and the 125 mg capsule also contains red ferric oxide and yellow ferric oxide. Oral suspension inactive ingredients: sucrose, lactose, hydroxypropyl cellulose, sodium lauryl sulfate, red iron oxide, and sodium stearyl fumarate.	Information for inactive ingredients are adequately provided. **Satisfactory**
Statement of being sterile (if applicable)	Not applicable	Not applicable
Pharmacological/ therapeutic class	Aprepitant is a substance P/neurokinin 1 (NK1) receptor antagonist, an antiemetic agent.	Adequately described. **Satisfactory**
Chemical name, structural formula, molecular weight	Chemical Name: 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro-3H-1,2,4-triazol-3-one. Molecular weight: 534.43 Structure:  Empirical formula: $C_{23}H_{21}F_7N_4O_3$	Chemical name, structural formula, molecular weight are appropriately provided. **Satisfactory**

If radioactive, statement of important nuclear characteristics.	Not applicable	Not applicable
Other important chemical or physical properties (such as pKa, solubility, or pH)	Aprepitant is sparingly soluble in ethanol and isopropyl acetate and slightly soluble in acetonitrile.	**Satisfactory**

Conclusion: Adequate.

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

No. 3855 — 125-mg capsules: Opaque, hard gelatin capsule with white body and pink cap with "462" and "125 mg" printed radially in black ink on the body. They are supplied as follows:
NDC 0006-0462-06 unit-dose package of 6.

No. 3854 — 80-mg capsules: White, opaque, hard gelatin capsule with "461" and "80 mg" printed radially in black ink on the body. They are supplied as follows:
NDC 0006-0461-02 unit-of-use BiPack of 2
NDC 0006-0461-06 unit-dose package of 6.

No. 3862 — Unit-of-use TriPack containing one 125-mg capsule and two 80-mg capsules.
NDC 0006-3862-03.

No. 6741 — 40-mg capsules: Opaque, hard gelatin capsule with white body and mustard yellow cap with "464" and "40 mg" printed radially in black ink on the body. They are supplied as follows:
NDC 0006-0464-10 unit-of-use package of 1
NDC 0006-0464-05 unit-dose package of 5.

No. 3066 — 125 mg for oral suspension: Pink to light pink powder, in a single-use-pouch, packaged as a kit with one 5 mL oral dosing dispenser and one mixing cup. It is supplied as follows:
NDC 0006-3066-03 – unit of use carton.

Storage and Handling

Capsules:

Store at 20-25°C (68-77°F) [see USP Controlled Room Temperature].

For Oral Suspension:

Store at 20-25°C (68-77°F); excursions permitted between 15-30°C (between 59-86°F).
Store in the original container. Do not open pouch until ready for use. (b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	Capsules: 40mg, 80 mg, and 125mg for Oral Suspension: 125mg	**Satisfactory**
Available units (e.g., bottles of 100 tablets)	Number units for each of the packaging configuration id adequately described (see the text provide above on page 76).	**Satisfactory**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	NDC number and product description are adequately provided (see the text provide above on page 76).	**Satisfactory**
Special handling (e.g., protect from light, do not freeze)	Not applicable	Not applicable
Storage conditions	Capsules: Store at 20-25°C (68-77°F) [see USP Controlled Room Temperature]. For Oral Suspension: Store at 20-25°C (68-77°F); excursions permitted between 15-30°C (between 59-86°F). Store in the original container. Do not open pouch until ready for use. (b) (4)	**Satisfactory**

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Distributed by: Merck Sharp & Dohme Corp., a subsidiary of **Merck & Co., Inc.,** Whitehouse Station, NJ 08889, USA	**Satisfactory**

Conclusion: Adequate.

2. Container Label

a) Immediate container

(b) (4)

Reviewer's Assessment:

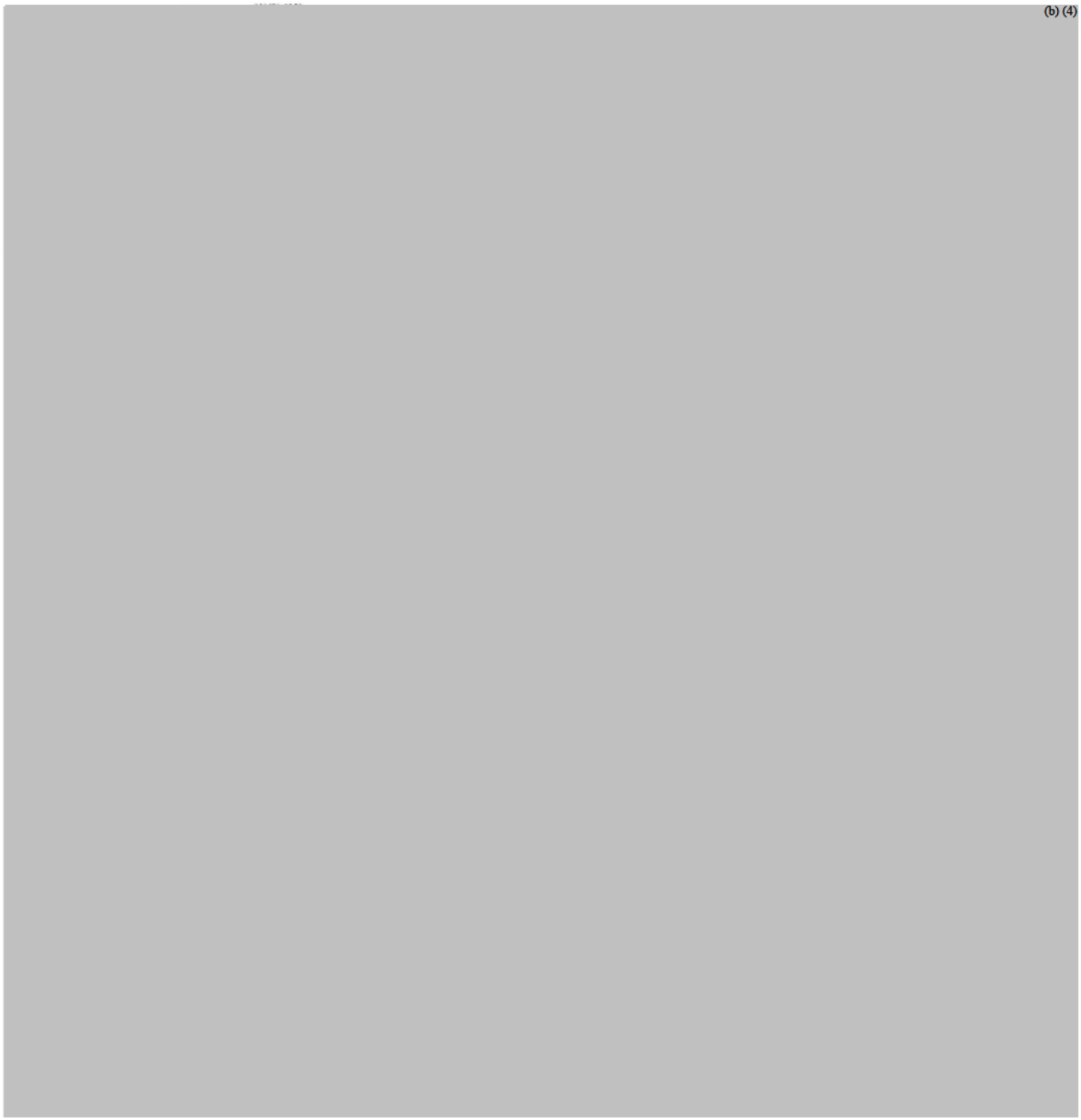
Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Proprietary name, established name are provided with appropriate font size and prominence that satisfies 21 CFR 201.10(g)(2).	**Satisfactory**
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	125mg	**Satisfactory**
Net contents (21 CFR 201.51(a))	125mg	**Satisfactory**
Lot number per 21 CFR 201.18	Not provided	**Unsatisfactory**
Expiration date per 21 CFR 201.17	Not provided	**Unsatisfactory**
"Rx only" statement per 21 CFR 201.100(b)(1)	"Rx only" is displayed.	**Satisfactory**
Storage (not required)	Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).	**Satisfactory**
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	NDC number provided	**Satisfactory**
Bar Code per 21 CFR 201.25(c)(2)**	Bar Code provided	**Satisfactory**
Name of manufacturer/distributor	Name of manufacturer/distributor is appropriately displayed.	**Satisfactory**
Others	Store in original container. Do not open pouch until ready for use. (b) (4)	**Satisfactory**

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.
**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion: The lot number and expiration date should be added to the immediate container label.

b) Carton

(b) (4)



Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	Proprietary name, established name are provided with appropriate font size and prominence that satisfies FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2).	**Satisfactory**
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	The following strengths are provided or (b) (4) (b) (4) are consistent with requirements in 21CFR 201.10(d)(1); 21.CFR 201.100(b)(4). 125mg	**Satisfactory**
Net contents (21 CFR 201.51(a))	Single dose kit. Each single dose kit contains 1 pouch of Emend, 1 mixing cup, 1 dispenser	**Satisfactory**
Lot number per 21 CFR 201.18	Appropriately displayed.	**Satisfactory**
Expiration date per 21 CFR 201.17	Appropriately displayed.	**Satisfactory**
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(b)(5)(iii)]	Not applicable	Not applicable
Sterility Information (if applicable)	Not applicable	Not applicable
"Rx only" statement per 21 CFR 201.100(b)(1)	Appropriately displayed.	**Satisfactory**
Storage Conditions	Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).	**Satisfactory**
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Appropriately displayed.	**Satisfactory**
Bar Code per 21 CFR 201.25(c)(2)**	Appropriately displayed.	**Satisfactory**
Name of manufacturer/distributor	Manufactured for and distributed by: (b) (4)	**Satisfactory**
"See package insert for dosage information" (21 CFR 201.55)	Appropriately displayed.	**Satisfactory**
"Keep out of reach of children" (optional for Rx, required for OTC)	Appropriately displayed.	**Satisfactory**

Route of Administration (not required for oral, 21 CFR 201.100(b)(3))	Route of administration is provided as oral	**Satisfactory**

Conclusion: Adequate.

B. ENVIRONMENTAL ASSESSMENT OR CLAIM OF CATEGORICAL EXCLUSION

A categorical exclusion from the preparation of an environmental assessment (EA) was requested under 21 CFR 25.31(b). The basis of this exclusion is the fact that the estimated concentration of the active ingredient at the point of entry into the aquatic environment will be less than 1 ppb from all products using this material as the active ingredient. The requested for the categorical exclusion was reviewed by the CMC Environmental Assessment Reviewer, Dr. James Laurenson. Dr. Laurenson completed his review of the application found the claim for the categorical exclusion acceptable (see the attached email from DR. Laurenson dated 07/13/2015). Therefore, the categorical exclusion from the environmental assessment analysis is granted.

III. List Of Deficiencies

A. Drug Substance: None
B. Drug Product: None
C. Process/Facility: None
D. Biopharmaceutics: None
E. Microbiology : None
F. Label/Labeling:

Immediate container: Add lot number and expiration date to the immediate container label.

IV. Attachment – Environmental Assessment

Shafiei, Hamid

From: Laurenson, James
Sent: Monday, July 13, 2015 5:28 PM
To: Shafiei, Hamid
Subject: RE: NDA 207865 (aprepitant)

BEST AVAILABLE COPY

Here's my review.
Jim

The claim for a categorical exclusion from an environmental assessment noted that the expected introduction concentration (EIC) of aprepitant would be below 1 part per billion (ppb), and that the EIC calculation included all forms and strengths of the drug substance. Given the potential for thyroid and other endocrine-related effects, as noted in nonclinical data, FDA considered whether developmental or reproductive effects could occur in the aquatic environment at concentrations below 1 ppb, based on information in FDA's recent draft guidance on this subject, Environmental Assessment: Questions and Answers Regarding Drugs With Estrogenic, Androgenic, or Thyroid Activity (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM444658.pdf). Furthermore, the initial claim for a categorical exclusion did not provide a statement of no extraordinary circumstances, as required per 21 CFR 25.15(a). Therefore, FDA requested the following from the applicant: (1) supporting data for the categorical exclusion and (2) a statement regarding extraordinary circumstances.

The applicant responded that the thyroid effects in rats were considered rodent-specific, secondary to liver enzyme induction. The testicular and uterine effects were noted as non-specific, reversible, and related to changes in body weight. The mechanism of action (i.e., substance P/neurokinin 1 (NK1) receptor antagonism) was noted as not indicative of any *a priori* concerns for reproduction or development. In addition, the EIC was estimated to be (b) (4) ppb, which is (b) (4) % of the categorical exclusion benchmark of 1 ppb, indicating a high margin of safety.

The applicant also responded that to the best of their knowledge, no extraordinary circumstances exist in regards to this action.

FDA has reviewed the information provided by the applicant and has concluded that the categorical exclusion request, supplemented by information submitted to support the request and aid in determining whether extraordinary circumstances exist, is adequate. FDA concludes that no additional environmental information is warranted for this application, and that the claim of categorical exclusion is accepted.

From: Laurenson, James
Sent: Wednesday, June 17, 2015 1:49 PM
To: Shafiei, Hamid
Subject: RE: NDA 207865 (aprepitant)

Hamid, as I noted on the phone, I'm fine w/their response. Do you know if there's a sharepoint draft review template set up for this so I can add my review to it?
Jim

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From: Jennings, Kerri-Ann
Sent: Friday, June 05, 2015 11:12 AM
To: Laurenson, James; Chen, Tien Mien
Cc: Ghosh, Tapash; Shafiei, Hamid; Rhee, Moo Jhong
Subject: FW: NDA 207865 (aprepitant)

Hello Albert and Jim.

Attached please find the response to your Information Requests.

Thank you.

Kerri

From: Andrew, Nicholas W. [mailto:nicholas_andrew@merck.com]
Sent: Friday, June 05, 2015 10:44 AM
To: Jennings, Kerri-Ann
Subject: RE: NDA 207865 (aprepitant)

Kerri-Ann,

Please find enclosed our response to the FDA IR. This was formally submitted to FDA today.

Please let me know if I can provide any additional information at this time.

Cheers

Nick

Nick Andrew
Merck & Co., Inc.
Director, Worldwide Regulatory Affairs
P.O. Box 2000 - RY 34-B253
Rahway, NJ 07065
nicholas_andrew@merck.com
(732)-594-5585 - voice
(732)-594-4980 - fax

From: Andrew, Nicholas W.
Sent: Wednesday, June 03, 2015 6:28 PM
To: 'Jennings, Kerri-Ann'
Subject: RE: NDA 207865 (aprepitant)

Kerri-Ann,
Just a quick note to let you know that we are on track to submit a response to your informational request on Friday. As requested, I will email a courtesy copy to you when we formally submit.

Cheers,

Nick

From: Andrew, Nicholas W.
Sent: Friday, May 29, 2015 3:57 PM

To: 'Jennings, Kerri-Ann'
Subject: RE: NDA 207865 (aprepitant)

Hi Ms. Jennings,
I can confirm receipt of this email. I will review the request with my team and let you know if we have any concerns with the timing and whether any clarification is needed.

Cheers,

Nick

Nick Andrew
Merck & Co., Inc.
Director, Worldwide Regulatory Affairs
P.O. Box 2000 - RY 34-B293
Rahway, NJ 07065
nicholas_andrew@merck.com
(732)-594-5585 - voice
(732)-594-4980 - fax

From: Jennings, Kerri-Ann [mailto:Kerri-Ann.Jennings@fda.hhs.gov]
Sent: Friday, May 29, 2015 3:24 PM
To: Andrew, Nicholas W.
Subject: NDA 207865 (aprepitant)

Hello Mr. Andrew,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for aprepitant, NDA 207865.

We are reviewing the Quality sections of the application and have the following comments and information requests. We request a written response by COB. June 5, 2015, in order to continue our evaluation of your NDA.

Environmental Analysis
In your environmental analysis, you note that the Expected Introduction Concentration (EIC) of aprepitant will be below 1 part per billion (ppb), and that the EIC calculation includes all forms and strengths of the drug substance. Given the potential for thyroid and other endocrine-related effects, as noted in nonclinical data, there might be implications for developmental or reproductive effects in the aquatic environment at concentrations below 1 ppb. (See FDA's recent draft guidance on this subject at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM444658.pdf.) Furthermore, your claim for a categorical exclusion did not provide a statement of no extraordinary circumstances, as required per 21 CFR 25.15(a). Therefore, please provide supporting data for your categorical exclusion request, including a statement about extraordinary circumstances. If the statement of no extraordinary circumstances cannot be supported, an Environment Assessment (EA) will be required. Contact the Agency (Regulatory Health Project Manager) for additional information.

Biopharmaceutics
In your September 12, 2014 response to previous Biopharmaceutics information request, you stated that you selected the surfactant, (b)(4)% Tween 80 based on the equilibrium solubility of aprepitant at ambient temperature (Table 2, p2). However, the dissolution testing was conducted at 37°C. The dissolution results (Figures 1 and 2, p.3 and 4) showed that (b)(4)% is more than you needed/selected. Therefore, it is expected that at 37°C, the surfactant needed is probably (b)(4)% (according to Figure 2, upper right-hand panel). You

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also provided dissolution profile of Emend for oral suspension (Figure 3), but the scale for the X and/or Y axis is not specified.

Resubmit Figure 3 with appropriate legend and scale specified. Also, clarify the results presented (Tables 1 and 2, Figures 1 to 3) as to which was obtained from aprepitant (b) (4) particles and which was by (b) (4) particles.

Finally, provide a complete dissolution development report using (b) (4) % of surfactant for dissolution testing at 37°C and your justification of your proposed dissolution method and dissolution acceptance criterion.

Let me know if you are unable to meet the requested response date or if you have further questions.

Please email me a courtesy copy of your responses and submit an official amendment to the NDA, 207865.

Confirm receipt of this email.

Thank you.

Regards,

Kerri-Ann E. Jennings, MS, BSN, RN
LCDR, United States Public Health Service
Regulatory Business Process Manager
FDA/CDER/OPQ/OPRO
Phone (301) 796-2919