

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209381Orig1s000

NON-CLINICAL REVIEW(S)

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

**Addendum to
Pharmacology/Toxicology review of NDA 209381, Dated 11/29/2017**

Drug Product:	Plenvu® (PEG 3350, Sodium Ascorbate, Sodium Sulfate, Ascorbic Acid, Sodium Chloride, and Potassium Chloride) oral solution.
Indication:	Cleansing of the colon in preparation for colonoscopy
Applicant:	Norgine B.V., Amsterdam, Nederland
Review Division:	Division of Gastroenterology and Inborn Errors Product (DGIEP)
Reviewer:	Dinesh Gautam, Ph.D.
Supervisor/Team Leader:	Sushanta Chakder, Ph.D.
Project Manager:	Lawrence Allan

A nonclinical review of PLENVU® (PEG 3350, Sodium Ascorbate, Sodium Sulfate, Ascorbic Acid, Sodium Chloride, and Potassium Chloride) was finalized in DARRTs on November 29, 2017 (reference ID 4187530). In several places of the finalized pharmacology/toxicology review of the NDA, references were made to NDA 21881 for MOVIPREP, another bowel cleansing product, originally developed by Norgine, Ltd. In addition, an incorrect statement was made in the review that for nonclinical safety of PLENVU, the Applicant relied on the Agency's previous finding of safety of MOVIPREP. For nonclinical safety of PLENVU, the Applicant did not rely on the Agency's previous finding of safety of MOVIPREP. Full reports of all the nonclinical studies were submitted in NDA 209381, and the studies are summarized in the review.

The current Amendment to the NDA review, dated 11/29/2017 applies to following sections of the review.

Section 1.2 (Brief Discussion of Nonclinical Findings) of the review, dated 11/29/2017 should be replaced with the following.

1.2 Brief Discussion of Nonclinical Findings

PLENVU® (PEG 3350, Sodium Ascorbate, Sodium Sulfate, Ascorbic Acid, Sodium Chloride, and Potassium Chloride) is cathartic, indicated for bowel cleansing prior to colonoscopy. NDA 209381 is submitted under Section 505(b)(2). For nonclinical safety of PLENVU® was based on studies conducted with similar PEG related products containing PEG 3350, Sodium Ascorbate, Sodium Sulfate, Ascorbic Acid, Sodium Chloride, and Potassium Chloride, or PEG 3350, sodium chloride, potassium chloride and sodium bicarbonate. The Applicant submitted the reports of these studies in the NDA. The following studies with related PEG products were submitted: Pharmacology, 14- and 90-day repeat dose toxicology studies in rats and dogs, genotoxicity studies and reproductive toxicity studies. In addition, the Applicant relied on published literature for the safety of individual ingredients and flavor enhancers used in the PLENVU® formulation. The study reports are summarized below.

Oral toxicity studies of a similar PEG-containing product were conducted following repeated daily administration for 2 weeks in rats and dogs. Oral toxicity studies of 90-day duration were conducted with another product in rats and dogs. The toxicity profiles of these two products were almost similar. The results indicated that the kidney was the target organ of toxicity in rats based on the changes of the clinical chemistry and the kidney weight. In dogs, the major treatment related toxicity was decreased terminal body weight gain, emesis, diarrhea, and salivation.

In a fertility and early embryonic development study, the mating performance and fertility were not affected by the PEG product, and it was not teratogenic in rats and rabbits. In addition, no adverse effects of the PEG product on pre- and post-natal development in rats were observed.

The PEG product was not genotoxic in the Ames test, the mouse lymphoma cell (L5178Y TK^{+/+}) forward mutation assay, and the mouse micronucleus test.

The safety of the ascorbate/ascorbic acid levels in PLENVU® is supported by toxicology information from published literature. Sodium ascorbate is the sodium salt of ascorbic acid. In a 13-week repeat dose toxicity study with ascorbic acid, the NOAELs were reported to be 16900 and 21500 mg/kg/day for male and female mice, respectively, and 8100 and 9100 mg/kg/day for male and female rats, respectively. The NOAELs in rats and mice provide adequate safety margins for the proposed doses of ascorbic acid in PLENVU®. Ascorbic acid was negative in mutagenicity studies, and had no carcinogenic potential at doses up to 7200 mg/kg/day in mice and up to 3100 mg/kg/day in rats (National Toxicology Program technical report series no. 247, 1983). Thus, the available toxicology data support the safety of the ascorbic acid/sodium ascorbate level (927 mg/kg, based on a 60 kg body weight) in the drug product.

The two flavoring agents, Fruit punch flavor # (b) (4) and Mango flavor # (b) (4) used in the PLENVU® formulation, have not been previously used in FDA approved products. Based on the published nonclinical toxicology information of each component of these flavoring agents, there are no safety concerns for the flavoring agents at the proposed levels.

Thus, from a nonclinical standpoint, the safety of PLENVU® has been adequately addressed.

Page #4, review dated November 29, 2017, following footnote is not relevant. “² *Scientific Opinion on the re-evaluation of ascorbic acid (E 300), sodium ascorbate (E 301) and calcium ascorbate (E 302) as food additives. EFSA Panel on Food additives and Nutrient Sources added to Food (ANS). EFSA Journal 2015;13(5)4087.*”

Section 3, page # 18, the review dated November 29, 2017, states, “*The Applicant did not submit any nonclinical studies of NER1006 (PLENVU®) in the NDA. For nonclinical safety, the Applicant relied on their approved NDA for MOVIPREP® and published literatures.*”

The above statement should be replaced with “**The Applicant did not conduct any nonclinical studies of NER1006 (PLENVU®). However, in support of the nonclinical safety of PLENVU® (NER1006), full reports of the nonclinical studies conducted with similar products containing PEG 3350, Sodium Ascorbate, Sodium Sulfate, Ascorbic Acid, Sodium Chloride, and Potassium Chloride, or PEG 3350, sodium chloride, potassium chloride and sodium bicarbonate, in addition to studies from published literature were submitted in the current NDA.**”

Section 3.1, page # 18 of the review dated November 29, 2017, states, “*The Applicant relied on their approved NDA for MOVIPREP® for nonclinical safety of PLENVU®, and did not conduct any nonclinical studies in support of the NDA; however, published studies were submitted in support of the safety of some components of the drug product. Relevant published studies were reviewed.*”

This statement should be replaced with **“The Applicant did not conduct any nonclinical studies of NER1006 (PLENVU®). However, full reports of the nonclinical studies conducted with similar products containing PEG 3350, Sodium Ascorbate, Sodium Sulfate, Ascorbic Acid, Sodium Chloride, and Potassium Chloride, or PEG 3350, sodium chloride, potassium chloride and sodium bicarbonate, in addition to studies from published literature were submitted in the current NDA.”**

Section 3.3, page #18, of the review dated November 29, 2017, states, *“Pharmacology review of NDA 21-881 (MOVIPREP®, reviewed by Ke Zhang, Ph.D.) is referenced in this application”*.

Above statement should be replaced by **“No previous reviews are referenced”**.

Section 4, Page #18 of the review states, *“The applicant did not submit any pharmacology studies of (PLENVU®). For pharmacology studies, the Applicant relied on the nonclinical review of MOVIPREP® (NDA 21-881) reviewed by Dr. K. Zhang dated February 24, 2006. See nonclinical review of NDA 21-881 for additional information.”*

This statement should be replaced with, **“No pharmacology studies with PLENVU® were conducted”**.

Section 5, Pharmacokinetics/ADME/Toxicokinetics section, Page #19, of the review states, *“The applicant did not submit any pharmacokinetic studies with PLENVU®. The Applicant relied on their approved NDA (21-881) for pharmacokinetic studies reviewed by Dr. K. Zhang dated February 24, 2006.”*

This statement should be replaced with **“No pharmacokinetic studies with PLENVU® were conducted”**.

Section 6.5, Repeat-Dose Toxicity section, Page #26, of the review states, *“The applicant did not submit any repeat dose toxicity studies of PLENVU®. The Applicant cross referenced their NDA (21-881; MOVIPREP®) for repeat dose toxicity studies and reviewed by Dr. K. Zhang dated February 24, 2006.”*

The above statement should be replaced with, **“The applicant did not submit any repeat dose toxicity studies of PLENVU. However, the Applicant submitted reports of the nonclinical studies conducted with similar products containing PEG 3350, Sodium Ascorbate, Sodium Sulfate, Ascorbic Acid, Sodium Chloride, and Potassium Chloride, or PEG 3350, sodium chloride, potassium chloride and sodium bicarbonate, in addition to published literature”**.

Section 7, Genetic Toxicology section, Page #30, of the original review states, *“No genetic toxicology studies of PLENVU® were submitted by the Applicant in this NDA. For genetic toxicology studies, the Applicant cross-referenced their previous NDA (21-881) and reviewed by Dr. K. Zhang dated February 24, 2006. See nonclinical review of NDA 21-881 for additional information.”*

This statement should be replaced with **“No genetic toxicology studies of PLENVU® were submitted in the NDA. However, genetic toxicology studies with a similar PEG product and published genetic toxicology studies of some components of PLENVU® were included in the submission.”**

Section 9, Page #32 of the review dated November 29, 2017, states, *“No reproductive and developmental toxicology studies were submitted by the applicant. The applicant cross referenced NDA 21-881 for reproductive and developmental toxicology, and reviewed by Dr. K. Zhang February 24, 2006. See nonclinical review of NDA (21-881) for additional information.”*

This statement should be replaced with, **“No reproductive and developmental toxicology studies of PLENVU® were submitted by the applicant. However, the Applicant submitted reports of the studies conducted with similar PEG-related products”.**

Section 11, page #32, Integrated Summary and Safety evaluation section of the review states, *“In this 505 (b)(2) NDA, the Applicant did not submit any nonclinical studies, and for nonclinical safety, the Applicant relied on the Agency’s previous finding of safety of MOVIPREP®. In addition, the Applicant relied on published literature to support the safety of some components of the product. The nonclinical safety of MOVIPREP® was established under NDA 21-881 and are summarized briefly in this review.”*

Above statement should be replaced with **“The Applicant did not submit any nonclinical studies with PLENVU® in the current NDA. To support nonclinical safety, studies conducted with similar PEG related products (PEG 3350, Sodium Ascorbate, Sodium Sulfate, Ascorbic Acid, Sodium Chloride, and Potassium Chloride) or (PEG 3350, sodium chloride, potassium chloride and sodium bicarbonate), were submitted. In addition, relevant published literatures were used to support the safety of individual components of PLENVU®”.**

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

/s/

DINESH C GAUTAM
04/19/2018

SUSHANTA K CHAKDER
04/19/2018

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 209-381
Supporting document/s: 0009
Applicant's letter date: April 13, 2017
CDER stamp date: April 13, 2017
Product: Plenvu[®] (PEG 3350, Sodium Ascorbate, Sodium Sulfate, Ascorbic Acid, Sodium Chloride, and Potassium Chloride) oral solution.
Indication: Cleansing of the colon in preparation for colonoscopy
Applicant: Norgine B.V., Amsterdam, Nederland
Review Division: Division of Gastroenterology and Inborn Errors Product (DGIEP)
Reviewer: Dinesh Gautam, Ph.D.
Supervisor/Team Leader: Sushanta Chakder, Ph.D.
Division Director: Donna Griebel, M.D.
Project Manager: Lawrence Allan

Disclaimer

Except as specifically identified, all data and information discussed below are necessary for approval of NDA 209-381, and are owned by Norgine B.V., or are data for which Norgine B.V. has obtained a written right of reference. Any information or data necessary for approval of NDA 209-381 that Norgine B.V. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Norgine B.V. does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 209-381.

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Executive Summary

6.2 1.1 Recommendations

1.1.1 Approvability

No nonclinical approvability issues have been identified.

1.1.2 Additional Non Clinical Recommendations

None

1.1.3 Labeling

The draft labeling of Plenvu[®] oral solution generally conforms to the format specified under 21CFR 201.57(c)(9)(i) through (c)(9)(iii) Requirements for PLLR (Pregnancy and Lactation Labeling Rule) Prescription Drug Labeling. No changes are recommended.

(b) (4)

8.1 Pregnancy

Sponsor's version:

Risk Summary

(b) (4)

Evaluation: No changes are recommended in this section.

(b) (4)

6.3 1.2 Brief Discussion of Nonclinical Findings

PLENVU® (PEG 3350, Sodium Ascorbate, Sodium Sulfate, Ascorbic Acid, Sodium Chloride, and Potassium Chloride) is indicated for bowel cleansing prior to colonoscopy. The current NDA is submitted under Section 505(b)(2). The Applicant did not submit any new nonclinical studies of PLENVU® in the NDA. For nonclinical safety, the Applicant relied on the MOVIPREP® oral suspension (PEG 3350, Sodium Ascorbate, Sodium Sulfate, Ascorbic Acid, Sodium Chloride, and Potassium Chloride), which was approved in 2006 (NDA 21-881). The Applicant also relied on published literature for the safety of the individual ingredients and flavor enhancers of PLENVU®. The comparative composition of PLENVU (NER1006) and MOVIPREP is shown in the Table below. NER1006 has lower PEG 3350 and sodium sulfate and higher sodium ascorbate levels compared to MOVIPREP. The safety of the ascorbate/ascorbic acid levels in PLENVU is supported by toxicology information from published literature. Sodium ascorbate is the sodium salt of ascorbic acid. In a 13-week repeat dose toxicity study with ascorbic acid, the NOAELs were reported to be 16900 and 21500 mg/kg/day for male and female mice, respectively, and 8100 and 9100 mg/kg/day for male and female rats, respectively. The NOAELs in rats and mice provide adequate safety margins for the proposed doses of ascorbic acid. Ascorbic acid was negative in mutagenicity studies, and had no carcinogenic potential at doses up to 7200 mg/kg/day in mice (NTP 1983)¹ and up to 2000 mg/kg/day in rats (EFSA Journal 2015;13(5)4087)². Thus, the available toxicology data support the safety of the ascorbic acid/sodium ascorbate level (927 mg/kg, based on a 60 kg body weight) in the drug product.

¹ Carcinogenesis bioassay of L-ascorbic acid (vitamin c) (Cas no. 50-81-7) in F344/n rats and B6C3F1 mice (feed study). National Toxicology Program technical report series no. 247, 1983.

² Scientific Opinion on the re-evaluation of ascorbic acid (E 300), sodium ascorbate (E 301) and calcium ascorbate (E 302) as food additives. EFSA Panel on Food additives and Nutrient Sources added to Food (ANS). EFSA Journal 2015;13(5)4087

	NER1006		MOVIPREP [®]		MOVICOL [®]		
Active Ingredient	Total Oral Administration		Total Oral Administration		Oral Dose (g/pouch)	Oral Dose ² (mg/kg/day)	Oral Dose ³ (mg/kg/day)
	g/person	mg/kg ¹	g/person	mg/kg ¹			
PEG 3350	140.00	2000	200	2850	13.125	563	1501
Sodium sulphate (b) (4)	9.00	129	15	214	-	-	-
Sodium ascorbate	48.11	687	11.8	169	-	-	-
Ascorbic acid	7.54	108	9.4	134	-	-	-
Sodium chloride	5.20	74	5.38	77	0.3507	15	40
Potassium chloride	2.20	31	2.03	29	0.0466	2	5
Sodium bicarbonate	-	-	-	-	0.1785	8	21

¹ bodyweight adjustment for a 70 kg person.

² following administration of 3 pouches/day for constipation to a 70 kg person

³ following administration of 8 pouches/day for fecal impaction to a 70 kg person

2 Drug Information

2.1 Drug: PLENVU[®] oral solution.

PLENVU[®] oral solution contains polyethylene glycol (PEG 3350), sodium sulfate, sodium chloride, potassium chloride, sodium ascorbate with ascorbic acid (b) (4), sucralose, aspartame, mango flavor and fruit punch flavor.

2.1.1 CAS Registry Number

Polyethylene glycol (PEG 3350): 25322-68-3
 Sodium sulfate: 7757-82-6
 Sodium chloride: 7647-14-5
 Potassium chloride: 7447-40-7
 Sodium ascorbate: 134-03-2
 Ascorbic acid: 50-81-7

2.1.3 Code Name

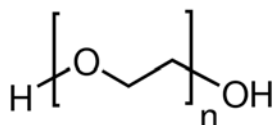
NER1006

2.1.5 Molecular Formula/Molecular Weight

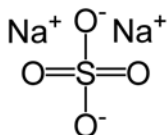
Polyethylene glycol (PEG 3350): H-(OCH₂CH₂)_n-OH/3350
 Sodium sulfate: Na₂SO₄/142.04
 Sodium chloride: NaCl/58.44
 Potassium chloride: KCl/74.55
 Sodium ascorbate: C₆H₇NaO₆/198.11
 Ascorbic acid: C₆H₈O₆/176.12

2.1.6 Structure

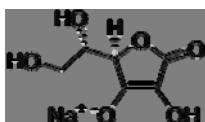
Polyethylene glycol (PEG 3350):



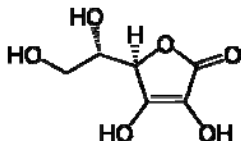
Sodium sulfate:



Sodium ascorbate:



Ascorbic acid:



2.1.7 Pharmacologic class

Bowel cleansing agent.

2.2 Relevant IND/s, NDA/s, and DMF/s

NDA: 21-881: MOVIPREP[®] oral solution: Norgine LTD, UK; bowel cleansing agent.

2.3 Clinical Formulation

2.3.1 Drug Formulation

The drug product is supplied as a split oral dosing formulation containing two doses of powders for reconstitution. The first dose contains polyethylene glycol (PEG) 3350 and sodium sulfate, and the second dose contains a high amount of sodium ascorbate with ascorbic acid combined with a lower amount of PEG 3350. Both doses contain electrolytes, (b) (4) and flavoring agents. The doses are each reconstituted with 500 mL (approx. 16 fl. oz.) water and administered in a split-dosing regimen either where one solution is given in the evening and the other in the morning prior to the clinical procedure, or where the two solutions are both given on the same day but about (b) (4) 2 hours apart. The composition of the drug product is shown in the Applicant's Table below.

Name of Ingredients	Concentration after Reconstitution (g/500 mL)			Total Concentration after Reconstitution (g/L)
	First Dose*	Second Dose**	Second Dose**	Combined Daily Dose
		Pouch A	Pouch B	
Active Ingredients				
PEG 3350	100.00	40.00	Not present	140.00
Sodium sulfate (b) (4)	9.00	Not present	Not present	9.00
Sodium chloride	2.00	3.20	Not present	5.20
Potassium chloride	1.00	1.20	Not present	2.20
Sodium ascorbate	Not present	Not present	48.11	48.11
Ascorbic acid	Not present	Not present	7.54	7.54
Excipients				
Aspartame	(b) (4)			
Sucralose				
Mango flavor (b) (4)				
Fruit Punch flavor (b) (4)				
Citric acid (encapsulated)***				

* All active ingredients and excipients are contained in a single pouch.

** All active ingredients and excipients are contained in pouch A and pouch B.

*** Of note the citric acid used in the NER1006 formulation is encapsulated (b) (4)

(b) (4) All ingredients are generally recognized as safe (GRAS).

2.3.2 Comments on Novel Excipients

The two flavoring agents used in the drug product have not been used previously in FDA-approved products. They are

- Fruit punch flavor # (b) (4)
- Mango flavor # (b) (4)

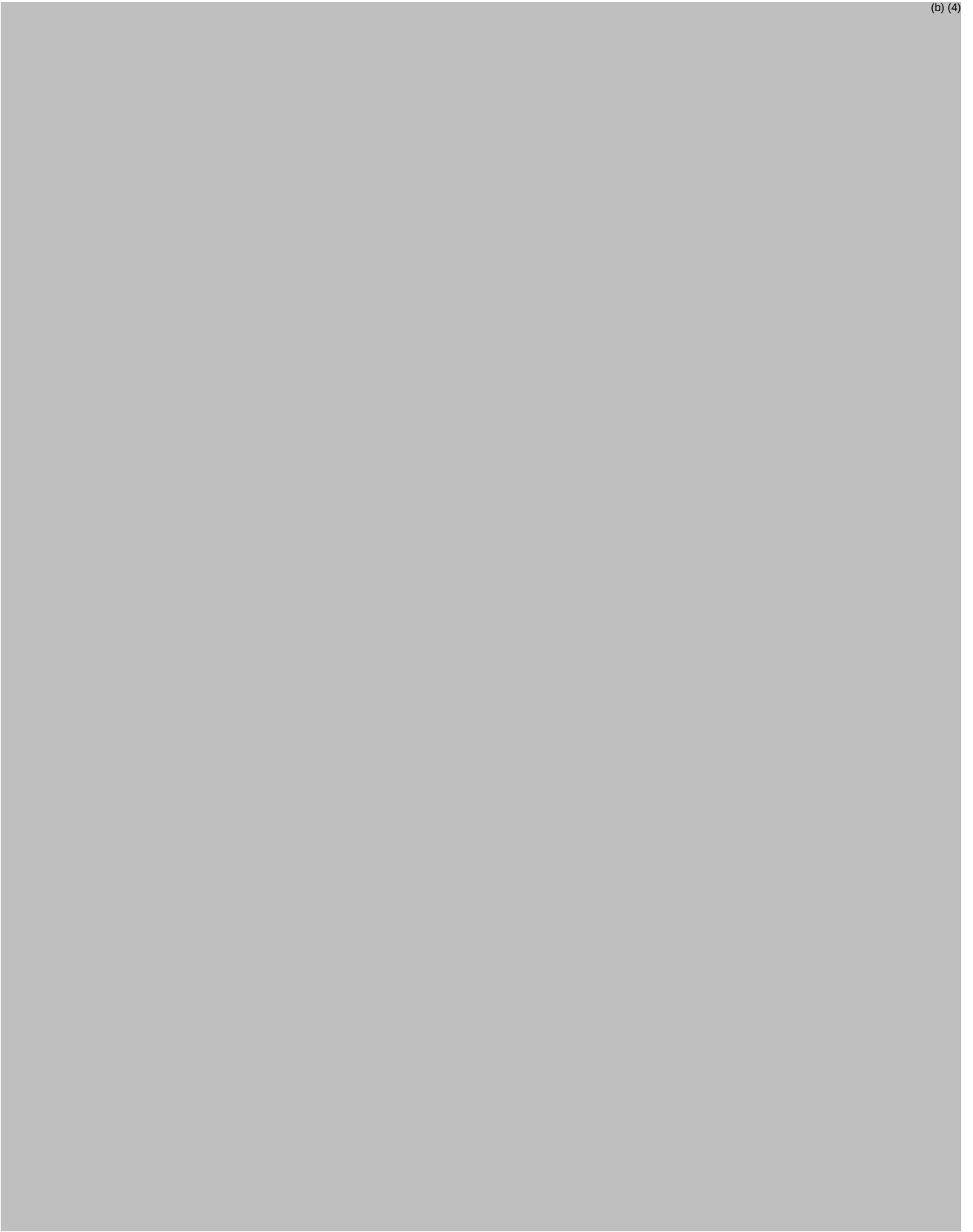
Fruit punch flavor # (b) (4) :

Fruit punch flavor # (b) (4) is not present in any FDA approved product. Fruit punch flavor # (b) (4) is made up of

(b) (4)

The composition of Fruit Punch # (b) (4) is shown in the Table below (from the Sponsor's submission).

(b) (4)



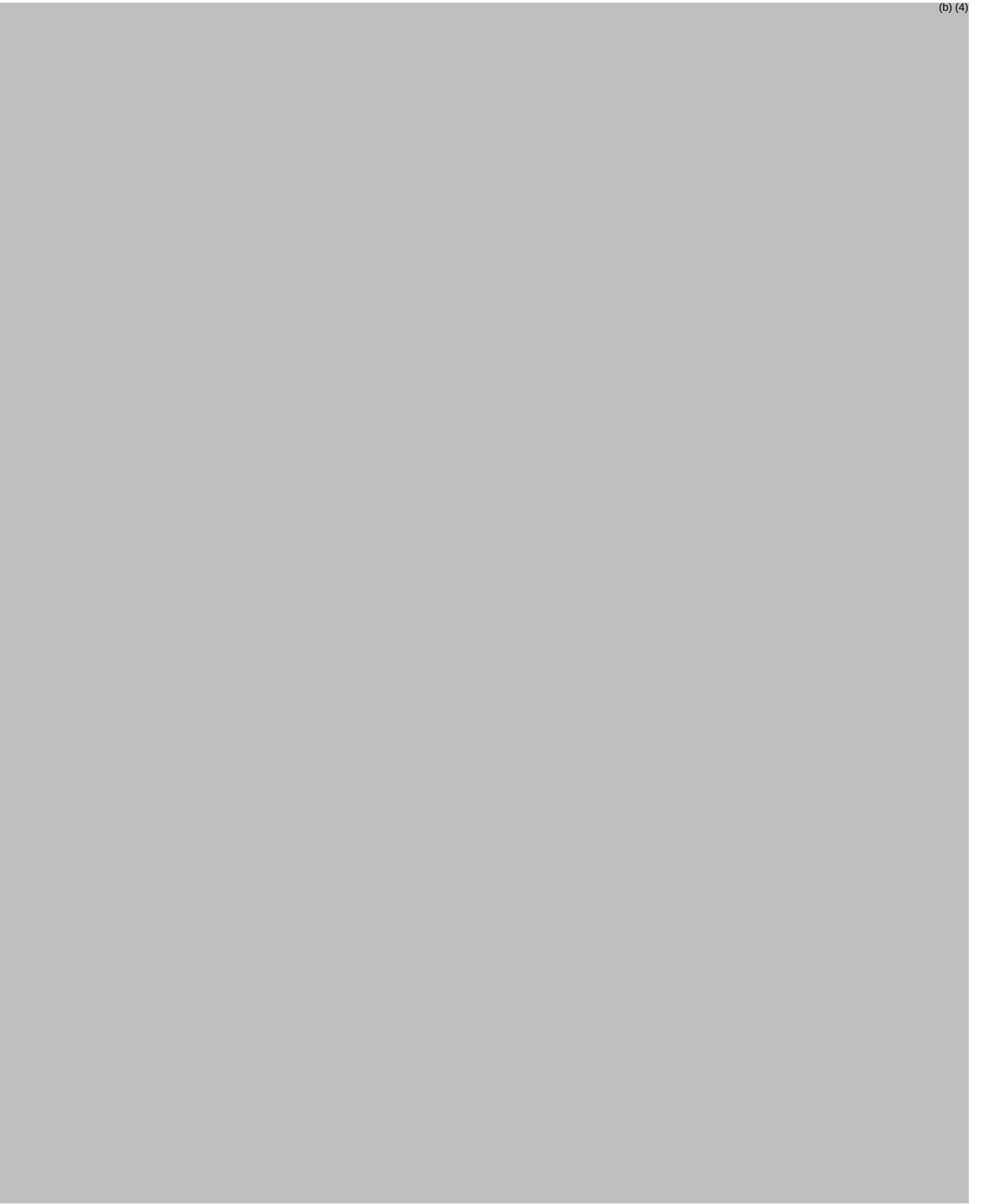
(b) (4)



Mango flavor # (b) (4)

Mango flavor # (b) (4) has not been approved by FDA. It contains following ingredients.

(b) (4)



On November 3, 2017, the Agency sent an information request to the Applicant asking the following.

“The anticipated total exposure of (b) (4) from the excipients and flavors (sucralose, aspartame, mango flavor and fruit punch flavor) used in the PLENVU formulation is >5-fold higher than the ICH Q3D recommended daily exposure limit for (b) (4) at the stated specifications. You need to adjust specifications for (b) (4) in at lower levels so that the exposure to (b) (4) from PLENVU does not exceed the permitted daily exposure of 5 mcg/day. Otherwise, you need to provide an appropriate justification for the (b) (4) level in your formulation.”

On November 13, 2017, the Applicant submitted a response to the above IR regarding the Agency’s concern about the exposure of (b) (4) from PLENVU®. The Applicant stated that the potential maximum exposure of (b) (4) specified by the manufacturers of the individual excipients and flavors (sucralose, aspartame, mango flavor and fruit punch flavor) present in PLENVU® is theoretically higher than the ICH Q3D recommended daily exposure; as this calculation is based on data available from the suppliers. To mitigate this risk, samples of all exhibit batches of PLENVU® (all 3 formulations: Dose 1, Dose 2 Pouch A and Dose 2 Pouch B) were tested by (b) (4). The results are presented in the Applicant’s Table below.

Table 1.11.1-1: Quantity of (b) (4) in Samples of all Exhibit Batches of PLENVU

Batch number	Formulation	(b) (4)
15G001	TF067 (Dose 1)	(b) (4)
15G004	TF067 (Dose 1)	
15G007	TF067 (Dose 1)	
15G002	TF079a (Dose 2 Pouch A)	
15G005	TF079a (Dose 2 Pouch A)	
15G008	TF079a (Dose 2 Pouch A)	
15G003	TF079b (Dose 2 Pouch B)	
15G006	TF079b (Dose 2 Pouch B)	
15G009	TF079b (Dose 2 Pouch B)	

¹Limit of Detection (b) (4)

The results showed that the actual levels of (b) (4) were (b) (4) (Limit of Detection; LOD) of the method) for all drug product samples tested. Based on a complete preparation of (b) (4) of PLENVU, this would equate to a maximum exposure of (b) (4) of (b) (4) which is well below the 5 µg/day limit recommended by ICH Q3D Guidance.

2.3.3 Comments on Impurities/Degradants of Concern

The Applicant listed the potential impurities and degradation products that have been associated with PEG 3350 and which could potentially be observed in the drug product.

They include

(b) (4)

have also been assessed in PEG 3350, and none of the potential degradants were detected. The name, structure and origin of potential impurities are presented in the Applicant's Table below.

Table 3.2.S.3.2-1: Structure and Origin of Potential Impurities

(b) (4)

PEG 3350 contains no Class 1 solvents. Only trace amounts of the Class 2 solvents, (b) (4) and the Class the 3 solvents (b) (4) were present in the drug product. The potential residual solvents of PEG 3350 are listed in the Applicant's Table below.

Table 3.2.S.3.2-2 Potential residual solvents in PEG 3350

Solvent	USP <467> classification	ICH Q3C / USP limits	Nominal values
(b) (4)			

The residual solvents detected in the drug product are qualified according to ICH Q3C(R5) guidance.

The release and stability specifications for the drug product (Dose 1 and Dose 2 Pouch A) are provided in the Applicant's Tables below and are acceptable.

Table 2.3.P-26: Specification for NER1006 Dose 1 (Formulation TF067)

Table 2: 2.9.5. Specification for (b) (4) (Formulation 1) (b) (4)

Test	Method	Specification	
		Release	Stability
Description of product	Visual	White to off-white powder	White to slightly yellow powder
Description of packaging	Visual	Not tested for release	Tear resistant packaging. No damage or defects.
Water Content	Karl Fisher	Not more than (b) (4)%	Not more than (b) (4)%
pH of Solution	USP <791>	(b) (4)	
Reconstitution Time	Visual	Not more than (b) (4) seconds	Not more than (b) (4) seconds
Color of Solution	USP <631>	Not more intensely colored than ref. solutions A-T	Not more intensely colored than ref. solution D-T
Uniformity of Dosage Units			
Uniformity of Mass	Ph. Eur. 2.9.5	Complies with Ph. Eur. 2.9.5	Not tested for stability
Content Uniformity – Potassium	USP <905>	Complies with USP <905>	
Content Uniformity - Chloride	USP <905>	Complies with USP <905>	
Identification			
Polyethylene Glycol 3350	USP <197>	FTIR Comparable to standard	Not tested for stability
	HPLC	Retention time of reference standard ± 5%	Not tested for stability

Test	Method	Specification	
		Release	Stability
Sodium	USP <191>	(b) (4)	Not tested for stability
	IC	Retention time of reference standard ± 5%	Not tested for stability
Sulfate	USP <191>	(b) (4)	Not tested for stability
	IC	Retention time of reference standard ± 5%	Not tested for stability
Potassium	USP <191>	(b) (4)	Not tested for stability
	IC	Retention time of reference standard ± 5%	Not tested for stability
Chloride	USP <191>	(b) (4)	Not tested for stability
	IC	Retention time of reference standard ± 5%	Not tested for stability
Assay (Active ingredient)			
Polyethylene Glycol 3350	HPLC	(b) (4)	
Potassium	IC		
Sodium	IC		
Sulfate	IC		
Chloride	IC		
Polyethylene Glycol 3350 impurities*		(b) (4)	Not conducted on stability
			Not conducted on stability
Microbiological Attributes			
Total Aerobic Microbial Count	USP <61>	Not tested for release	(b) (4)cfu/g
Total Combined Yeast/Mold Count	USP <61>	Not tested for release	(b) (4)cfu/g
Escherichia Coli	USP <62>	Not tested for release	Absent in 1 g

*Conducted on NER1006 registration/validation batches only

Table 2.3.P-27: Specification for NER1006 Dose 2 Pouch A (Formulation TF079a)

Table 2.3.1-27. Specification for LER1000 Dose 2 Pouch A (Formulation 110754)

Test	Method	Specification	
		Release	Stability
Description of product	Visual	White to off white powder	White to slightly yellow powder
Description of packaging	Visual	Not tested for release	Tear resistant packaging. No damage or defects.
Water Content	Karl Fisher	Not more than (b) (4) %	Not more than (b) (4) %
pH of Solution	USP <791>	(b) (4)	
Reconstitution Time	Visual	Not more than (b) (4) seconds	Not more than (b) (4) seconds
Color of Solution	USP <631>	Not more intensely colored than ref. solutions A-T	Not more intensely colored than ref. solution D-T
Uniformity of Dosage Units			
Uniformity of Mass	Ph. Eur. 2.9.5	Complies with Ph. Eur. 2.9.5	Not tested for stability
Content Uniformity Potassium	USP <905>	Complies with USP <905>	
Content Uniformity Chloride	USP <905>	Complies with USP <905>	
Identification			
Polyethylene Glycol 3350	USP <197>	FTIR Comparable to standard	Not tested for stability
	HPLC	Retention time of reference standard $\pm$ 5%	
Sodium	USP <191>	(b) (4)	Not tested for stability
	IC	Retention time of reference standard $\pm$ 5%	
Potassium	USP <191>	(b) (4)	Not tested for stability
	IC	Retention time of reference standard $\pm$ 5%	
Chloride	USP <191>	(b) (4)	Not tested for stability
	IC	Retention time of reference standard $\pm$ 5%	
Assay (Active ingredient per theory pouch)			
Polyethylene Glycol 3350	HPLC	(b) (4)	
Potassium	IC		
Sodium	IC		

Test	Method	Specification	
		Release	Stability
Chloride	IC	(b) (4)	
Polyethylene Glycol 3350 impurities*			
			(b) (4)
			Not tested on stability
			Not tested on stability
Microbiological Attributes			
Total Aerobic Microbial Count	USP <61>	Not tested for release	(b) (4)-cfu/g
Total Combined Yeast/Mold Count	USP <61>	Not tested for release	(b) (4)-cfu/g
Escherichia Coli	USP <62>	Not tested for release	Absent in 1 g

*Conducted on NER1006 registration/validation batches only.

The Applicant stated that there are no additional impurities or known degradation products observed in the Dose 2 Pouch B, apart from those found in the drug substances, namely (b) (4). The stability and release specifications for the drug product (Dose 2 Pouch B) are provided in the Applicant's Table below, and are acceptable.

Table 2.3.P-28: Specification for NER1006 Dose 2 Pouch B (Formulation TF079b)

Test	Method	Specification	
		Release	Stability
Description of product	Visual	White to yellow powder	White to yellow powder
Description of packaging	Visual	Not tested for release	Tear resistant packaging. No damage or defects.
Loss on drying	Ph. Eur. 2.2.32	Not more than (b) (4) %	Not more than (b) (4) %
pH of Solution	USP <791>	(b) (4)	
Reconstitution Time	Visual	Not more than (b) (4) seconds	Not more than (b) (4) seconds
Color of Solution	USP <631>	Not more intensely colored than ref. solutions A-T	Not more intensely colored than ref. solution D-T
Uniformity of Dosage Units			
Uniformity of Mass	Ph. Eur. 2.9.5	Complies with Ph. Eur. 2.9.5	Not tested at stability
Content Uniformity Sodium	USP <905>	Complies with USP <905>	
Identification			
Sodium	USP <191>	(b) (4)	Not tested at stability
	IC	Retention time of reference standard ± 5%	
Ascorbic Acid	USP Monograph	(b) (4)	Not tested at stability
	HPLC	Retention time of reference standard ± 5%	

Test	Method	Specification	
		Release	Stability
Assay (Active ingredient per theory pouch)			
Sodium	IC	(b) (4)	
Ascorbic Acid	HPLC		
Related Substances			
(b) (4)	HPLC		
	HPLC		
Microbiological Attributes			
Total Aerobic Microbial Count	USP <61>	Not tested for release	(b) (4) cfu/g
Total Combined Yeast/Mold Count	USP <61>	Not tested for release	(b) (4) cfu/g
Escherichia Coli	USP <62>	Not tested for release	Absent in 1 g

HPLC: High Performance Liquid Chromatography

IC: Ion chromatography

Dose 2 Pouch B contains ascorbic acid. The potential degradation products of ascorbic acid (b) (4). The specifications for these two impurities are NMT (b) (4) are acceptable.

2.4 Proposed Clinical Population and Dosing Regimen

PLENVU® is an osmotic laxative indicated for cleansing of the colon in preparation for colonoscopy in adults 18 years or older. There are two proposed dosing regimens, two day split-dosing regimen and one day morning dosing regimen. In two-Day split-dosing regimen, the individual will receive Dose 1 in the evening before the colonoscopy (approximately 18:00H). The next morning, on the day of the colonoscopy, the individual will receive Dose 2 (Pouch A and Pouch B). In one-day morning dosing regimen, the individual will receive Dose 1 in the morning of the colonoscopy (approximately 05:00H), and dose 2 (Pouch A and B) will be administered approximately 2 hours after starting Dose 1.

2.5 Regulatory Background

A type B meeting was held on April 16, 2014 at the end of Phase 2 clinical study. In response to the Sponsor's nonclinical question, the following recommendations provided by the Agency.

Question 4

Does the Agency agree that the available nonclinical safety information is sufficient to support NER1006 for the Phase III clinical studies and the NDA?

FDA Response to Question 4:

We have identified the following issues that need to be addressed prior to phase 3:

- The proposed specification for (b) (4) (NMT (b) (4)%) and (b) (4) (NMT (b) (4)%) in NER1006 formulation Pouch b TF073 is above the ICH qualification threshold (ICHQ3A) of (b) (4)% and is not acceptable.
- You need to provide toxicological qualification of (b) (4) in the drug product to support the specification of NMT (b) (4)%.
- (b) (4) is weakly genotoxic and showed positive results in 2-year carcinogenicity studies in male rats and mice (NTP). The specification of (b) (4) in the drug product (Pouch b) has to be set per the draft ICH M7 Guidance [Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic

Risk, February 2013] at a level (b) (4) such that daily exposure to (b) (4) from the drug product does not exceed (b) (4) per day.

- You need to provide the levels of the following impurities if present in the drug substance/drug product: (b) (4) These impurities have been associated with PEG 3350. In addition, you also need to qualify the levels of these impurities if they exceed the acceptable limits. [ICH Q3A and ICH Q3B(R2)]

A pre-NDA meeting was held on 02 February 2016, and the following response to the nonclinical question was communicated to the Applicant.

Question 1: *Based on provision of a complete nonclinical package with all nonclinical reports provided, does the Agency agree that no additional nonclinical studies/data are needed to support a 505(b)(1) NDA for NER1006?*

FDA Response to Question 1: The non-clinical package appears to be adequate to support the NDA. However, if you intend to rely, in part, on information required for approval that comes from studies not conducted by you or for you (e.g., published literature, FDA's finding of safety and/or effectiveness for a listed drug) and for which you have not obtained a right of reference, then your marketing application will be a 505(b)(2) NDA. You must establish a "bridge" between your proposed product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. You must also establish that reliance on studies described in the published literature is scientifically appropriate.

See the 505(b)(2) REGULATORY PATHWAY section below for additional information on submitting a 505(b)(2) NDA.

3 Studies Submitted

The Applicant did not submit any nonclinical studies of NER1006 (PLENVU®) in the NDA. For nonclinical safety, the Applicant relied on their approved NDA for MOVIPREP® and published literatures.

3.1 Studies Reviewed

The Applicant relied on their approved NDA for MOVIPREP® for nonclinical safety of PLENVU®, and did not conduct any nonclinical studies in support of the NDA; however, published studies were submitted in support of the safety of some components of the drug product. Relevant published studies were reviewed.

3.2 Studies Not Reviewed

N/A.

3.3 Previous Reviews Referenced

Pharmacology review of NDA 21-881 (MOVIPREP®, reviewed by Ke Zhang, Ph.D.) is referenced in this application.

4 Pharmacology

The applicant did not submit any pharmacology studies of (PLENVU®). For pharmacology studies, the Applicant relied on the nonclinical review of MOVIPREP® (NDA 21-881) reviewed by Dr. K. Zhang dated February 24, 2006.

See nonclinical review of NDA 21-881 for additional information.

5 Pharmacokinetics/ADME/Toxicokinetics

The applicant did not submit any pharmacokinetic studies with PLENVU®. The Applicant relied on their approved NDA (21-881) for pharmacokinetic studies reviewed by Dr. K. Zhang dated February 24, 2006.

The applicant submitted available published studies of PEG, sodium sulfate and sucralose, and the relevant studies are reviewed below.

Absorption of Polyethylene Glycols 600 Through 2000: The Molecular Weight Dependence of Gastrointestinal and Nasal Absorption (Donovan, M. D., Flynn, G. L. and Gordon L. Amidon, G. L. *Pharmaceutical Research*, 1990, Vol. 7, No. 8, 863-868).

Absorption of PEGs was determined in 9-13 weeks old male SD rats. Animals were fasted for 12 to 18 hours and 5% PEGs 600, 1000 and 2000 were administered orally by gavage. Urine samples were collected over a 6 hr collection period to determine the individual oligomers by HPLC. The mean excretion of these oligomers over 6 hr decreased up to 35%, 9% and 1.8% for PEGs 600, 1000 and 2000, respectively.

Cosmetic Ingredient Review Expert Panel (USA). Final report on the safety assessment of polyethylene glycols (PEGs)-6, -8, -32, -75, -150, -14M, -20M. *Journal of the American College of Toxicology* 1993;1(5).

The extent of gastrointestinal absorption of PEGs was studied in rats. Groups of 30 rats were given 25% solutions of PEGs 32, 75, and 150, and rats were killed at hourly intervals for up to 5 hr after dosing. Gravimetric methods were used to determine the amount of PEG absorbed. Less than 2% of PEG-32 was absorbed in 5 hr. There was no evidence that PEG 75 or PEG 150 was absorbed, since the initial dose was recovered from the gastrointestinal tract.

Dow/Union Carbide. The excretion of C14 equivalents of CARBOW AX 4000 in rats dosed either perorally or intravenously. Mellon Institute Chemical Hygiene Fellowship Report No. 31-52; 4/15/1968. (unpublished).

Male Wister rats were orally administered [^{14}C] PEG 4000 (approximately 70 mg/kg). Urine samples and feces were collected for 7 days to determine the excretion of [^{14}C] PEG 4000 by scintillation counting. The result showed that only 4.1% [^{14}C] PEG 4000 was recovered in the urine up to 7 days. The remainder [^{14}C] PEG 4000 was eliminated in the feces.

Gastrointestinal Absorption of [^{14}C]Poly(ethylene glycol) 4000 (Yoshiyuki Koyama, Y., Tateishi, M., Kawaide, A. and Kojima, S., 1992: *Polymer Journal*, Vol. 24. No. 6, pp 583-589).

Absorption of [^{14}C] PEG 4000 was evaluated in mice following oral gavage (8 µg or 20-30 µg) in 0.4ml of phosphate buffered saline (PBS: pH 7.4) was administered into the

stomach of the mice using a narrow metallic tube with a round-tip end. After 1 h, mice were killed and the stomach and the whole intestines were removed. The intestines were sectioned into small pieces to facilitate the radio assay. In another experiment, the mice were anesthetized by urethane and the duodenum was exposed by abdominal incision. One cm closed loop was prepared by ligation to each end. Radiolabeled [^{14}C] PEG 4000 dissolved in 40 μl (1.7 μg) of phosphate-buffered saline was then injected into the loop with a small syringe. The loop was put back in the peritoneal cavity, and the incision was sutured. The loop was removed after a given time, and the absorption of PEG was determined by quantifying the radioactivity of the loop. In another intraduodenal injection experiment, the mice were anesthetized, and the duodenum was exposed by abdominal incision, to which [^{14}C] PEG 4000 in 50 μl (1, 100 or 2000 μg) of phosphate-buffered saline was injected. After 2 h, the stomach and the intestines were removed, and sectioned into seven pieces; the stomach, the duodenum, the upper and lower jejunum, the upper and lower ileum, the cecum, and the colon, and each part was radio-assayed separately.

The absorption of the polymer one hour after oral administration was 2% of the dose, while radioactivity recovered was 0.096% and 0.31% in the blood and urine, respectively. Although radioactivity levels in the tissues/organs were low (0.03%-0.06% of dose), highest levels were recovered in the liver, the mesenteric lymph nodes and the kidney. Results are shown in figure below.

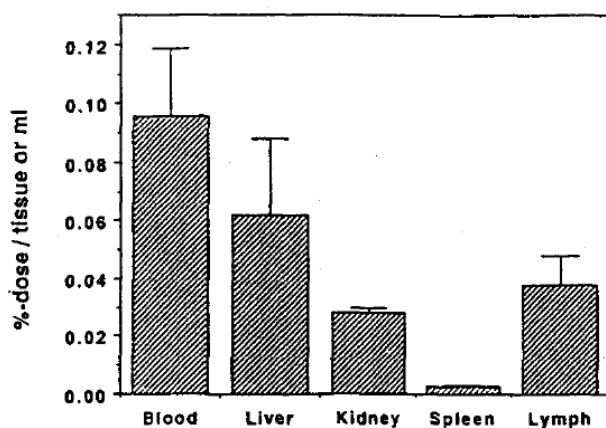


Figure 1. Body distribution of [^{14}C]PEG 4000 1 h after the oral administration (mean $\pm$ standard error).

In the isolated duodenum-jejunum loop, 15% of the [^{14}C] dose disappeared after 1 hour and 21% of the [^{14}C] dose disappeared after 2 hours, while 1.2% of the dose was found in the urine after 1 hour. The findings are shown in the figure below.

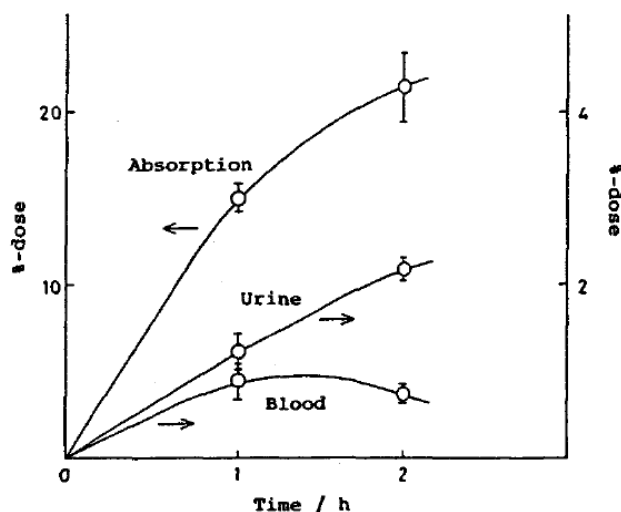


Figure 2. Absorption of [^{14}C]PEG 4000 from the duodenojejunal loop and its appearance in the blood and the urine (dose: 1.7 $\mu\text{g}/\text{mouse}$).

Following intraduodenal dosing, absorption decreased with increasing molecular weight of the dose, and was approximately 12%, 7% and 4% at doses of 1, 100 and 2000 μg , respectively. Results are shown in figure below.

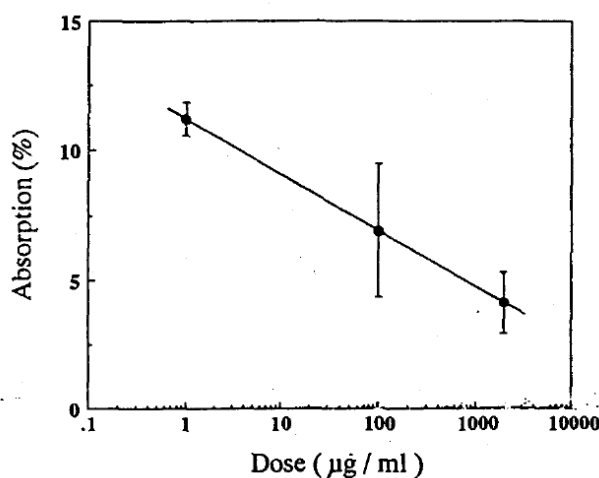


Figure 4. Absorption of [^{14}C]PEG 4000 2h after the intraduodenal administration.

Increased Permeability to Polyethylene Glycol 4000 in Rabbits With Experimental Colitis (Seidman, E. G., Hanson, D. G. and Walker, W. A.; *Gastroenterology* 1986; 90:120-126).

In vivo permeability of rabbit colon to [^{14}C] PEG 4000 at 1 mL/kg (7.5×10^6 cpm/ml) was examined in the presence of immune complex-mediated experimental colitis and compared with that of partially treated (control) and normal rabbits. Absorption was

estimated from measurements of PEG 4000 in the urine over 4 hours. Only 0.01% of the dose was recovered from control rabbits with a normal colon, whereas 2.06% of the dose was recovered from the urine of rabbits with colitis, indicating that the protective barrier of the colon is compromised. Data are shown in the Table below.

Table 1. Effect of Experimental Colitis on Uptake of [^{14}C]Polyethylene Glycol 4000 From Rabbit Colon In Vivo

	Dose excreted ^a (%)	Total urinary counts per minute ^{a,b}	
Colitis	2.06 ± 0.19	325,644 ± 20,750	$p < 0.001^c$ $p < 0.05^c$ $p < 0.001^c$
Controls	0.14 ± 0.04	21,600 ± 5,881	
Normals	0.01 ± 0.004	2,776 ± 834	

Permeability was assessed by urinary [^{14}C]polyethylene glycol 4000 (^{14}C -PEG) excretion for 4 h after rectal administration of 1 ml/kg of trace-labeled ^{14}C -PEG (0.1 mM in 0.9% NaCl, containing 7.5×10^6 cpm/kg). ^a Mean ± SEM of total urinary excretion at 4 h (n = 4). ^b In two-way analysis of variance: overall group effect F = 684.8 (2,9), p < 0.001. ^c Post hoc paired comparisons by Sheffé S test.

Distribution and Tissue Uptake of Poly(ethylene glycol) with Different Molecular Weights after Intravenous Administration to Mice (Yamaoka, T, Tabata, Y. and Ikada, Y. 1994; J Pharmaceutical Sciences 83 (4):601-605).

Radiolabeled [^{125}I]-PEG with different molecular weights (PEG 3000, 6000, 20000, 50000, 120000, 170000 and 190000) was administered intravenously to mice. The distribution and tissue uptake of [^{125}I]-PEG was assessed. The terminal half-life in blood increased from 18 minutes for PEG 6000 to 1 day for PEG 190000. PEG tended to distribute mainly into tissues/organs such as muscle, skin, bone and liver, irrespective of molecular weight. No radioactivity was observed in feces for any of the PEGs. The lower molecular weight PEGs (6000 and 20000) were rapidly distributed in extravascular tissues after intravenous administration, but returned to the blood circulation by diffusion and were then rapidly eliminated as demonstrated by the short terminal half-life. Large PEGs (50000 and 170000) translocated more slowly to extravascular tissues. Urinary clearance decreased with increasing molecular weight while liver clearance increased with increasing molecular weight after passing a minimum of about 50000. Results are shown in the Figures and Tables below.

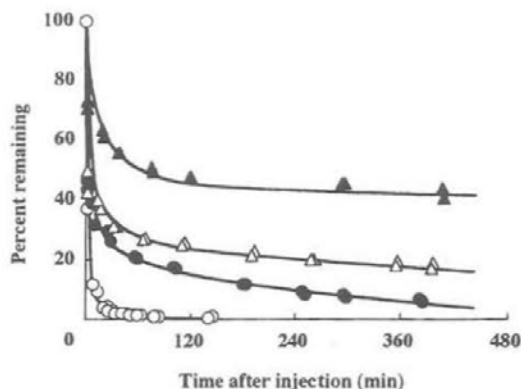


Figure 1—Decline of radioactivity from the blood after iv injection of PEG with different molecular weights. Key: (O) PEG-6; (●) PEG-20; (Δ) PEG-50; (▲) PEG-170.

Table 2—Body Distribution of PEG with Different Molecular Weights 4 h after Intravenous Administration

Distribution to	Percent Distribution			
	PEG-6	PEG-20	PEG-50	PEG-170
Blood	0.49 ± 0.12	18.74 ± 2.10	45.06 ± 3.87	58.01 ± 4.86
Heart	ND ^a	ND	0.29 ± 0.09	0.25 ± 0.11
Lung	ND	0.26 ± 0.09	ND	0.10 ± 0.03
Liver	2.57 ± 1.21	2.48 ± 1.15	1.65 ± 0.12	2.88 ± 1.82
Spleen	ND	0.13 ± 0.02	0.35 ± 0.03	0.22 ± 0.06
Kidney	0.29 ± 0.09	0.52 ± 0.13	0.46 ± 0.15	0.68 ± 0.13
GI	2.87 ± 1.65	13.53 ± 3.61	7.17 ± 1.86	4.87 ± 1.31
Thyroid Gland	ND	0.03 ± 0.01	ND	0.06 ± 0.02
Carcass	1.74 ± 0.31	17.67 ± 4.51	12.09 ± 2.01	7.70 ± 1.96
Excrements	91.93 ± 6.21	41.86 ± 6.12	33.57 ± 4.19	24.26 ± 3.89

^a ND, not detected.

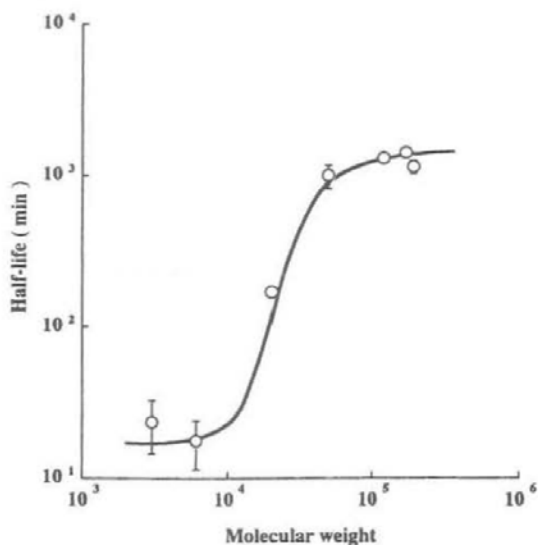


Figure 2—Relationship between the molecular weight of the PEG and its half-life in the circulation.

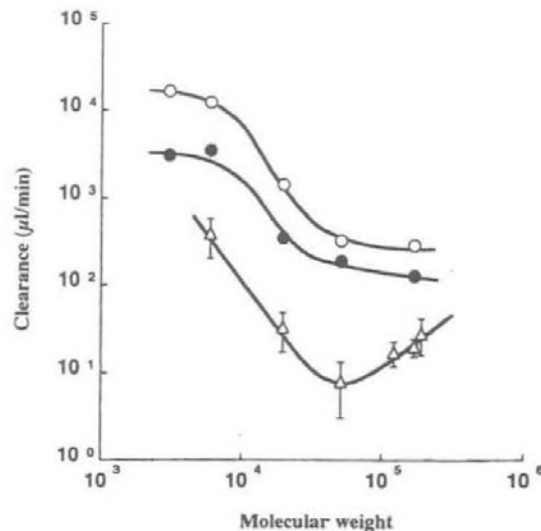


Figure 4—Effect of the molecular weight of PEG on the urinary, carcass, and liver clearances. Key: (O) urine; (●) carcass; (Δ) liver.

The metabolic sulphation of polyethyleneglycols by isolated perfused rat and guinea-pig livers (Roy, A. B., Curtis, C. G. and Powell, G. M., 1987; *Xenobiotica* 17(6):725-732).

Metabolism of PEGs with different molecular weights (200, 400, 1000 and 6000) was determined in the rat and guinea pig livers following perfusion techniques. Livers from male rats and female guinea pigs were isolated and perfused at 37°C. As soon as bile

flow was established, radiolabeled sulfate (^{35}S ; 100-300 μCi) was added to the perfusate. After one hour, PEG was added to the perfusate and perfusion continued for at least for another three hours. Bile samples were collected over 10 or 15 min periods throughout the experimental period. The concentration of ^{35}S was determined by liquid scintillation methods. Rat and guinea-pig perfused livers showed that PEGs 200, 400 and 1000, were metabolized by sulfation but PEG 6000 was not metabolized by sulfation. The sulfated PEG 200 was partially excreted in the bile.

Absorption, serum levels and urinary excretion of inorganic sulfate after oral administration of sodium sulfate in the conscious rat (Krijgsheld, K. R., Frankena, H., Scholtens, E., Zweens, J. and Mulder G. J. *Biochimica et Biophysica Acta*, 586 (1979) 492-500).

The absorption of anhydrous sodium sulfate after oral administration was investigated in rats. Radiolabeled sodium sulfate ($\text{Na}_2^{35}\text{SO}_4$) was administered orally to male Wistar rats. Blood samples were collected to determine the ^{35}S concentration in plasma. Urine was collected up to 7 days after oral sulfate administration. Radioactivity in serum and urine samples was determined by liquid scintillation method. Radioactivity in the serum samples was detected 15 minutes after oral administration and the plasma concentration reached a peak after about 1.5 to 2 hours. About 90% of the administered radioactivity was recovered in urine within 24 hours. In the following days, only a small additional amount was excreted, after a week a little more than 90% of the ^{35}S -radioactivity was recovered in the urine.

Sucralose-An Overview of the Toxicity Data (Grice, H. C. and Goldsmith, L. A. (*Food and Chemical Toxicology* 38 (Suppl. 2) (2000) S1-S6).

The major portion of an oral dose of sucralose is unabsorbed and is excreted unchanged in the feces of rats, mice, rabbits, dogs and humans. The remainder of the dose is excreted largely unchanged in the urine. Sucralose is absorbed from the upper part of the gastrointestinal tract by passive diffusion as indicated by direct measurements in the rat. The peak blood level was determined in the rat, mouse, rabbit and human. There is considerable variation in the amount of absorption between individual animals; the approximate levels expressed as a percentage of dose are as follows: 10%, 15%, 20%, 30% and 35% in rats, human, rabbit, mouse and dogs, respectively. The rate of elimination is similar in the mouse, rat, dog and human, but excretion is prolonged in the rabbit. Unchanged sucralose was the predominant component in the urine accounting for 90% or more of the total urinary radioactivity following administration of ^{14}C -labelled sucralose. Two minor urinary metabolites have been identified in the human urine, accounting for approximately 2% of an oral dose. Evidence indicates that these metabolites are glucuronide conjugates of sucralose and also present in the rat, mouse and dog.

6 General Toxicology

6.4 6.1 Single-Dose Toxicity

No single-dose toxicology study of PLENVU[®] was submitted in this NDA. However, the applicant submitted available published single dose toxicology studies of individual ingredients of PLENVU[®], and relevant studies are summarized below.

Cavender, F. L. and Sowinski, E. J. (*Patty's industrial hygiene and toxicology, Fourth edition, volume 2, Part F, Edited by George D. Clayton and Florence E. Clayton. 1994; Glycol, Chapter 45 PP:4645-4719*).

Single oral dose toxicology studies of PEGs were conducted in rats and rabbits. PEGs had low acute oral toxicity in the rat and rabbit. The toxicity decreased as the molecular weight increased. Approximate LD₅₀s in rats for a variety of PEGs are as follows: PEG 200, 34000 mg/kg; PEG 400, 44000 mg/kg; PEG 4000, 59000 mg/kg; PEG 6000, >50000 mg/kg; PEG 10000, >50000 mg/kg. In rabbits, the LD₅₀s for a variety of PEGs are as follows: PEG 200, 20000 mg/kg; PEG 400, 27000 mg/kg; PEG 1500, 30000 mg/kg; PEG 4000, 76000 mg/kg.

Sodium sulfate (OECD, *SIDS Initial Assessment Report for SIAM 20, Paris, France, 19 – 22 April 2005*).

An oral LD₅₀ value of 5989 mg/kg has been reported in the mouse for sodium sulfate. In another single oral dose toxicity study in rats, sodium sulfate (in water) was administered orally to 10 rats, with an observation period of 8 days. No effects were observed and the LD₅₀ was determined to be >10000 mg/kg.

The acute oral toxicity of sodium chloride (Boyd, E. M. and Shanas, M. N.; *Arch. int. Pharmacodyn.*, 1963, 144, No 1-2).

Single oral dose of sodium chloride (in distilled water) was administered to Wister rats at dose levels of 0, 800, 3000, 3200, 3500, 3800, 4000, 5000, 10000 or 16000 mg/kg. Deaths occurred within approximately 0.5-10 hours after dosing, mainly at the two highest doses and primarily from respiratory failure, convulsions, acute encephalopathy, fulminating gastroenteritis, dehydration and vascular congestion of many organs. Survivors had polydipsia, convulsive movements, and gastrointestinal disturbances for 24-48 hours but recovered after that. The LD₅₀ was determined to be 3750 mg/kg.

The acute oral toxicity of potassium chloride (Boyd, E. M. and Shanas, M. N.; *Arch. int. Pharmacodyn.*, 1961, CXXXIII, No 3-4).

Single oral dose of potassium chloride was administered to Wister rats at dose levels of 0, 2100, 2400, 2700, 3300, 3600 or 3900 mg/kg. Most rats died within approximately 3 hours after dosing, primarily from respiratory failure, convulsions, gastroenteritis, dehydration, and renal tubular necrosis. Survivors had anorexia, polydipsia, polyuria,

fever, convulsive movements, and gastrointestinal disturbances for 24-48 hours but recovered after that. The LD₅₀ was determined to be 3020 mg/kg.

6.5 Repeat-Dose Toxicity

The applicant did not submit any repeat dose toxicity studies of PLENVU[®]. The Applicant cross referenced their NDA (21-881; MOVIPREP[®]) for repeat dose toxicity studies and reviewed by Dr. K. Zhang dated February 24, 2006.

The applicant also submitted available published literatures of repeat dose toxicology studies of PEGs, ascorbic acid, sodium sulfate, sodium chloride and sucralose, and relevant studies are reviewed below.

A 90-day oral (gavage) study of carbowax[®] peg-3350 in rats (b) (4)
Report, Vol 1-2; October 24, 2001; Study # 99U1792; Study conducted
by (b) (4).

In a 90-day oral (gavage) toxicity study in SD rats (10/sex/group), PEG (Carbowax) 3350 was administered once daily to 3 groups of rats at dose levels of 1.5, 3.0 and 6.0 g/kg/day. Control group received deionized water (vehicle). Animals were observed daily and were also assessed for physical examinations, body weights, food consumption, hematology, serum chemistry, urinalysis, ophthalmic examinations, and macroscopic examination, organ weights and microscopic pathology.

There were no test article-related effects on mean body weights, body weight gains, food consumption, clinical pathology (hematology, serum chemistry and urinalysis) parameters and organ weights. There were no treatment-related ophthalmological changes at any dose level. No test article-related effects were observed on macroscopic or microscopic examinations at the scheduled necropsy. The no-observed-effect level (NOEL) for carbowax[®] PEG-3350 for the 90 day study in rats was determined to be 6.0 g/kg/day.

The Chronic Oral Toxicology of the Polyethylene Glycols (Smyth, H., F., Carpenter, C. P. and Weil, C. S. 1955; J Am Pharmaceut Assoc Vol XLIV (1): 27-30).

PEGs 200, 300, 400, 600, 1000, 1500, 1540, 4000 and 6000 were administered to groups of rats (5/sex/group) in their diet for 90 days, at levels of 0, 2, 4, 8, 16 or 24% (about 1000-12000 mg/kg/day). Animals were assessed for clinical signs, body weight, liver weight, kidney weights and histopathology examinations of the liver and kidneys.

No deaths and no major signs of toxicity were recorded. There was a decrease in body weight (from 4000 mg/kg/day), and increased kidney and liver weight (from 8000 mg/kg/day) across groups. These findings were minimal with PEG 6000.

Effects of Polyethylene Glycol 400 (PEG 400) Following 13 Weeks of Gavage Treatment in Fischer-344 Rats (*Hermansky, S. J., Neptun, D. A., Laughran, K. A. and Leung, H. W. 1995; Food Chem Toxicol.; 33(2):139-49*).

Fischer-344 rats (10/sex/group) received PEG 400 by oral gavage at dose levels of 1.1, 2.8 and 5.6 g/kg/day at a volume of 1.0, 2.5 or 5.0 ml/kg, respectively for 5 days/week for 13 weeks. Animals in the control group received water by gavage (5.0 ml/kg body). An additional 10 rats/sex/group were assigned to the control and high-dose groups for a 6-week recovery period. Animals were assessed for clinical signs, body weight, food and water consumption, hematology, serum chemistry, urinalysis, organ weights, macroscopic and microscopic pathology.

One male and three females from the 1.1 g/kg/day group and two females from the 5.6 g/kg/day group died; these deaths were attributed to the gavage procedure and were not considered to be test article related. There was no test article related changes in hematology or clinical chemistry parameters. During the first week of dosing, animals in the 2.8 and 5.6 g/kg/day dose groups had transient loose feces, and slight decreases in food consumption and body weights. The highest dose group also had loose feces at the end of the study. Increased water consumption was noted in all dose groups, which may be due to a possible increase in urine osmolality. Increased urinary concentration of protein in female rats and decreased urine pH were observed in 2.8 and 5.6 g/kg/day dose groups. Males in all dose groups had increased urinary concentrations of bilirubin and protein. Females at 2.8 and 5.6 g/kg/day had increased urinary concentration of protein. Slight increases in absolute and/or relative kidney weight were observed in females in all dose groups. No microscopic pathological changes were observed in the kidneys or urinary bladder. A slight renal toxicity (increased protein and bilirubin concentrations, urinary vascular cell findings, and urinary N-acetyl- β -D-glucosaminidase activity) may have resulted in male rats at 2.8 g/kg/day, and in males and female rats at 5.6 g/kg/day. These effects and renal function returned to normal following the recovery period.

Peroral Subchronic, Chronic Toxicity, and Pharmacokinetic Studies of a 100-Kilodalton Polymer of Ethylene Oxide (Polyox N-10) in the Fischer 344 Rat (*Leung, H. N., Ballantyne, B., Hermansky, S. J. and Franz, S. W.; 2000: Int J Toxicol 19:305-312*).

PEG (Polyox N-10) was administered orally in the diet to groups of 20 male and 20 female Fischer 344 rats at 0, 0.1, 0.5, 1.5 or 3%, (corresponding to levels of up to 2400-2667 mg/kg/day) for 13 weeks. An additional 10 animals/sex/group was assigned to the control and high dose groups for a 6-week recovery period. Animals were assessed for clinical signs, body weight, food and water consumption, ophthalmoscopy, clinical pathology, urinalysis, organ weights, macroscopic and microscopic pathology. All animals survived until the end of the study. Animals in the high dose group showed slight increases in food consumption and body weight gain. A dose-related increase in liver weight was observed, but this was not associated with any histopathology changes, and morphometric analysis showed no alteration in the number or size of the

hepatocytes. Because of the lack of correlative histopathology findings, the liver weight increase was considered not to be deleterious.

NTP Technical Report of L-ascorbic acid (vitamin c) in F-344/N rats and B6C3F1 mice (feed study) (NTP, Technical report series No. 247, 81-140-1983).

In the 14-day dose-range finding study, 6-week-old B6C3F1 mice (5 sex/dose) were fed with diets containing 0, 6000, 12500, 25000, 50000 or 100000 ppm of ascorbic acid/kg feed (equivalent to 0, 1128, 2350, 4700, 9400 and 18800 mg/kg/day for males and to 0, 1344, 2800, 5600, 11200 and 22400 mg/kg/day for females, respectively). Animals were observed twice daily for mortality and were weighed by cage on days 1 and 15. Necropsies were performed on all animals on day 15 or 16. All animals survived to the end of the dosing period. No compound-related clinical signs, gross or microscopic pathological effects were observed.

In the 14-day dose-range finding study, 6-week-old F344/N rats (5 sex/dose) were fed with diets containing 0, 6000, 12500, 25000, 50000 or 100000 mg ascorbic acid/kg feed (equivalent to 0, 708, 1475, 2950, 5900 and 11800 mg ascorbic acid/kg/day for males and to 0, 702, 1463, 2925, 5850 and 11700 mg ascorbic acid/kg/day for females, respectively). Animals were observed twice daily for mortality and were weighed by cage on days 1 and 15. Necropsies were performed on all animals on day 15 or 16. No compound-related clinical signs, gross or microscopic pathological effects were observed.

In the 13-week study, 7-week-old B6C3F1 mice (10 sex/dose) were given a diet containing 0, 25000, 50000 or 100000 ppm ascorbic acid/kg feed (equivalent to 0, 4225, 8450 and 16900 mg ascorbic acid/kg/day for males and to 0, 5375, 10750 and 21500 mg ascorbic acid/kg/day for females, respectively). Animals were checked for mortality and clinical signs twice daily. Each animal was clinically examined weekly, including palpation for tissue masses or swelling. Body weight and feed consumption were recorded weekly. Necropsies were performed on all animals on day 91 or 92. Mean body weight gain relative to controls was decreased by 37% in male mice in the 50000 and 100000 ppm dose groups. Weight gains of female mice were reduced by 10 to 13% in all dose groups compared with controls. Cystic endometrial glands were found in the uteri of four female mice in the 100000 ppm dose group. No other compound-related effects were observed. The NOAEL was determined to be 16900 or 21500 mg/kg/day for male and female mice, respectively.

In the 13-week study, 6-week-old rats (10/sex/dose) were fed a diet containing 0, 25000, 50000 or 100000 ppm of ascorbic acid/kg feed (equivalent to 0, 2045, 4050 and 8100 mg ascorbic acid/kg/day for males and to 0, 2275, 4550 and 9100 mg ascorbic acid/kg/day for females, respectively). No effects were seen in the male rats. Myeloid depletion was observed in two of the females in the 50000 ppm dose group and in four of the females in the 100000 ppm dose group. Reticulum cell hyperplasia was found in the bone marrow of two females in the 25000 ppm dose group, in one female in the

50000 ppm dose group and in four females in the 100000 ppm dose group. The NOAEL was determined to be 8100 or 9100 mg/kg/day for male and female rats, respectively.

Toxicity of Sucralose (Goldsmith, L. A. *Food and Chemical Toxicology* 38 (Suppl. 2) (2000) S53-S69).

In the 4 and 8 weeks dietary supplement study in SD rats, sucralose was admixed with diet at concentrations of 0, 10,000, 25,000 and 50,000 ppm (0, 1.0, 2.5 or 5% of the diet), which was equivalent to 737-1287, 1865-3218 and 2794-6406 mg/kg/day. Groups of 15 rats/sex/group were administered all dietary concentrations for 4 weeks and groups of 6 rats/sex/group were administered diets containing 0 or 5% sucralose for 8 weeks. Rats were observed for mortality, clinical signs, body weights, and food and water consumption. Blood and urine samples were collected for routine hematology, clinical chemistry and urinalysis parameters. All animals were subjected to necropsy and macroscopic examination, and all major organs were weighed. Microscopic examination was performed on the control and high dose groups. There were no unscheduled deaths. Body weight, food consumption and food conversion efficiency were slightly decreased relative to controls in rats of both sexes given 5% sucralose. Total leukocyte and lymphocyte counts were decreased for females and urinary volume was decreased for males given 5% sucralose during week 4, but these effects were not seen during week 8. Other effects of treatment observed at the 5% dose level included alterations in the weight or relative weight of a number of organs including the thymus, spleen, and the cecum. Microscopically, decreases in splenic or a diminution of the lymphocyte mass of the thymic cortex, were seen in females given 5% sucralose in diet. No toxicologically significant effects were observed at the 1.0% or 2.5% dietary levels.

In a 26-week chronic toxicity study in rats (20 rats/sex/group), sucralose was administered orally by gavage in tap water at 0, 750, 1500 or 3000 mg/kg/day. The dose was sub-divided for twice daily administration, 6 hours apart. Animals were observed for clinical signs, body weights, food and water consumption, ophthalmoscopy, hematology and blood clinical chemistry parameters. All animals were subjected to necropsy and macroscopic examination, and major organs from all animals were weighed. A comprehensive list of tissues was examined microscopically from control and high dose animals. There were no statistically significant differences in body weights, body weight gain, food consumption, ophthalmoscopy or clinical pathology parameters among sucralose-treated rats. Water consumption was higher (11% to 34%), in a dose-related manner, in all treated rats except males in the 750 mg/kg/day when compared with the controls. Absolute and relative (to body weight) weights of the cecum were higher than controls among all groups of males and females which received sucralose. In addition, body weight-relative kidney weights were slightly higher than controls among animals receiving 3000 mg/kg/day. Macroscopically, an elongated or distended cecum was noted for several animals in the 1500 or 3000 mg/kg/day dose groups and two males in the 750 mg/kg/day dose group. There were no microscopic changes considered to be related to treatment with sucralose.

7 Genetic Toxicology

No genetic toxicology studies of PLENVU® were submitted by the Applicant in this NDA. For genetic toxicology studies, the Applicant cross-referenced their previous NDA (21-881) and reviewed by Dr. K. Zhang dated February 24, 2006.

See nonclinical review of NDA 21-881 for additional information.

The applicant also submitted available published literatures of genotoxicity studies of sodium sulfate, sodium chloride, potassium chloride, citric acid and sucralose, and relevant studies are reviewed below.

Sodium sulfate (*SIDS Initial Assessment Report For SIAM 20 Paris, France, 19- 22 April 2005*).

Sodium sulfate was not mutagenic in a GLP Ames test using *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 at up to 5 mg/plate, both in the presence and absence of S9 metabolic activation.

Amended Safety Assessment of Sodium Sulfate as Used in Cosmetics (CIR, March 7, 2016).

An Ames test was conducted to evaluate the effect of Sodium Sulfate (312.5 to 5000 µg per plate with 4 dilutions) on *Salmonella typhimurium* TA1535, TA1537, TA100, and TA98, both with and without metabolic activation. The results were negative for genotoxicity. No cytotoxicity was noted up to 5000 mg/L.

An *in vitro* mammalian chromosome aberration test (GLP compliant) was performed in Chinese hamster lung fibroblasts (V79). The test was performed with and without metabolic activation. Test concentrations with and without metabolic activation in experiment 1 were 11.1, 22.2, 44.4, 88.8, 177.5, 355.0, 710.0, and 1420.0 µg/mL of Sodium Sulfate. In experiment 2 with activation, concentrations tested were 177.5, 355.0, 710.0, and 1420.0 µg/mL of Sodium Sulfate. Test concentrations without metabolic activation in experiment 2 were 22.2, 44.4, 88.8, 177.5, 355.0, 710.0, and 1420.0 µg/mL of Sodium Sulfate. Negative solvent/vehicle controls and positive controls were used. Outcomes revealed that Sodium Sulfate did not induce structural chromosome aberrations in V79 cells of the Chinese hamster *in vitro* (non-clastogenic) up to 1420.0 µg/mL.

An *in vitro* mammalian cell gene mutation assay test was conducted in mouse lymphoma L5178Y cells. The test was performed with and without metabolic activation. The exposure duration of experiment 1 was 4 hours with and without metabolic activation. Experiment 2 exposure duration was 24 hours without metabolic activation and 4 hours with metabolic activation. Test concentrations used for experiments 1 and 2, both with and without metabolic activation, were 88.8, 177.5, 355, 710, and 1420 µg/mL Sodium Sulfate. Results were negative for genotoxicity and negative for cytotoxicity in the absence or presence of metabolic activation.

Sodium Chloride (*IUCLID, European commission-european chemical bureau, 2000*).

Sodium chloride was not mutagenic when tested in three *Salmonella typhimurium* reverse mutagenicity assays (Ames), with and without S9 metabolic activation. Sodium chloride was negative in a mouse lymphoma assay at 7 mg/mL.

Potassium chloride (SIDS Initial Assessment Report for 13th SIAM, Bern, 6-9 November 200 1).

In Ames test, doses of KCl between 0 and 10000 µg/plate were tested with and without metabolic activation. No significant increases in mutation frequencies were noted.

In L51784 mouse lymphoma mutation tests, KCl was found to be weakly mutagenic at high concentrations (above 7000 µg/ml without metabolic activation and above 4000 µg/ml with metabolic activation).

Aspartame: Review of Safety (*Butchko, H. H.; 2000: Regulat Toxicol Pharmacol 35:S1-93*).

In vitro study showed no evidence of genotoxicity in Ames test (at up to 5 mg/plate) or evaluation in chromosome aberration, SCE and human lymphocyte micronucleus tests (up to 2 mg/mL) or for DNA damaging activity in rat hepatocytes (at up to 10 mM). *In vivo* testing (host-mediated and dominant lethal mutation assays in rats at up to 8000 mg/kg orally, chromosome aberration assays in rats and/or mice at up to 4000 mg/kg orally) also gave negative results.

Citric acid (SIDS Initial Assessment Report for 11th SIAM, Orlando, FL, January 2001).

Citric acid was not mutagenic in a bacterial reverse mutation (Ames) test conducted at concentrations ranging from 500 to 2000 µg/plate in *Salmonella typhimurium* strains TA97, TA98, TA100 and TA104 with and without S9 metabolic activation. The same result also occurred in another Ames test using 6 strains of *Salmonella typhimurium* (TA92, TA94, TA98, TA100, TA1535 and TA1537) at up to 5000 µg/plate and in a bacterial reverse mutation test in *Escherichia coli* at 1000 µg/mL. Assessment of clastogenic effects in cultured Chinese hamster fibroblasts at up to 1000 µg/mL reported negative results. An *in vivo* chromosome aberration test in the rat reported negative results following oral administration at up to 3500 mg/kg (single dose) or up to 3000 mg/kg/day for 5 days.

The absence of genotoxicity of sucralose (*Brusick, D., Grotz, V. L., Slesinski, R., Kruger, C. L. and Hayes, A. W. 2010; Food Chem Toxicol 48:3067-3072*).

Sucralose was not genotoxic in the Ames (*Salmonella typhimurium*) test, an *in vitro* chromosome assay in human lymphocytes, mutation in TK +/- mouse lymphoma cells, an *in vivo* chromosome aberration test in rats.

8 Carcinogenicity

No carcinogenicity studies were submitted for PLENVU®.

9 Reproductive and Developmental Toxicology

No reproductive and developmental toxicology studies were submitted by the applicant. The applicant cross referenced NDA 21-881 for reproductive and developmental toxicology, and reviewed by Dr. K. Zhang February 24, 2006.

See nonclinical review of NDA (21-881) for additional information.

10 Special Toxicology Studies

No special toxicology studies were submitted.

11 Integrated Summary and Safety Evaluation

Under the current NDA, the applicant is seeking approval of PLENVU® (NER1006) as an osmotic laxative indicated for cleansing of the colon as a preparation for colonoscopy in adults 18 years or older. The initial approval for MOVIPREP® oral suspension was in 2006 under NDA 21-881. PLENVU® is a similar bowel-cleansing product to MOVIPREP®. The applicant's table below shows the formulation comparison of PLENVU® with MOVIPREP® and MOVICOL®. NER1006 has lower PEG 3350 and sodium sulfate and higher sodium ascorbate levels compared to MOVIPREP. The safety of the ascorbate/ascorbic acid levels in PLENVU® is supported by toxicology information from published literature. Sodium ascorbate is the sodium salt of ascorbic acid. In a 13-week repeat dose toxicity study with ascorbic acid, the NOAELs were reported to be 16900 and 21500 mg/kg/day for male and female mice, respectively, and 8100 and 9100 mg/kg/day for male and female rats, respectively. The NOAELS in rats and mice provide adequate safety margins for the proposed doses of ascorbic acid/sodium ascorbate.

Active Ingredient	NER1006		MOVIPREP®		MOVICOL®		
	Total Oral Administration		Total Oral Administration		Oral Dose (g/pouch)	Oral Dose ² (mg/kg/day)	Oral Dose ³ (mg/kg/day)
	g/person	mg/kg ¹	g/person	mg/kg ¹			
PEG 3350	140.00	2000	200	2850	13.125	563	1501
Sodium sulphate (b) (4)	9.00	129	15	214	-	-	-
Sodium ascorbate	48.11	687	11.8	169	-	-	-
Ascorbic acid	7.54	108	9.4	134	-	-	-
Sodium chloride	5.20	74	5.38	77	0.3507	15	40
Potassium chloride	2.20	31	2.03	29	0.0466	2	5
Sodium bicarbonate	-	-	-	-	0.1785	8	21

¹ bodyweight adjustment for a 70 kg person.

² following administration of 3 pouches/day for constipation to a 70 kg person

³ following administration of 8 pouches/day for fecal impaction to a 70 kg person

In this 505 (b)(2) NDA, the Applicant did not submit any nonclinical studies, and for nonclinical safety, the Applicant relied on the Agency's previous finding of safety of MOVIPREP®. In addition, the Applicant relied on published literature to support the safety of some components of the product. The nonclinical safety of MOVIPREP® was established under NDA 21-881 and are summarized briefly in this review. The Applicant used 2 novel excipients in the PLENVU®. They are fruit punch (b) (4) flavor and Mango # (b) (4) flavor. Safety assessment of individual ingredient of the two flavoring agents (b) (4)

(b) (4) were performed from the toxicology data available in the published literature, and were found to have no safety concerns.

From a nonclinical standpoint, no safety issues have been identified for the approval of PLENVU®.

12 Appendix/Attachments: None

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/s/

DINESH C GAUTAM
11/29/2017

SUSHANTA K CHAKDER
11/29/2017