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APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	206679
Supporting document/s:	SDN10, SN0000
Applicant's letter date:	June 22, 2015
CDER stamp date:	June 22, 2015
Product:	Simvastatin oral suspension
Indication:	Treatment of primary and homozygous familial hypercholesterolemia in adults and for the treatment of heterozygous familial hypercholesterolemia in adult and pediatric patients (≥10 years)
Applicant:	Rosemont Pharmaceuticals (a wholly owned subsidiary of Perrigo Pharmaceuticals, U.S. agent)
Review Division:	Division of Metabolism and Endocrinology Products
Reviewer/Team Leader:	C. Lee Elmore, PhD
Division Director:	Jean-Marc Guettier, MD
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1 Executive Summary

1.1 Introduction

Perrigo Pharmaceuticals (U.S. agent) has submitted a New Drug Application (NDA 206679) on behalf of Rosemont Pharmaceuticals (the Applicant) via the 505(b)(2) regulatory pathway of the FD&C Act for Simvastatin oral suspension 20 mg/5 mL and 40 mg/5 mL for the treatment of primary and homozygous familial hypercholesterolemia in adults and for the treatment of heterozygous familial hypercholesterolemia in adult and pediatric patients (≥10 years). The listed drug identified in the FDA Orange Book is Zocor® (simvastatin tablets, hereafter referred to simiply as Zocor®) marketed by Merck & Co. under the approved NDA 019766.

1.2 Brief Discussion of Nonclinical Findings

No nonclinical studies were submitted to support a scientific bridge between Simvastatin oral suspension and the listed drug Zocor® to establish safety. Instead, the applicant is relying upon physicochemical (chemistry, manufacturing, and controls, CMC) characterization or has provided scientific justification for the safety of all components of Simvastatin oral suspension. The active pharmaceutical ingredient (simvastatin, USP) is manufactured by (b) (4)., located in (b) (4). The applicant refers to DMF (b) (4) for detailed manufacturing information regarding the simvastatin drug-substance. The simvastatin drug substance produced by (b) (4) under DMF (b) (4) is also the source of the drug substance (b) (4).

The FDA Office of Pharmaceutical Quality CMC review did not identify any impurity or degradant in the drug substance or drug product for Simvastatin oral suspension requiring qualification per ICH Q3A and ICH Q3B, respectively. No components were identified as requiring additional qualification per ICH M7. No leachables or extractables of toxicological concern were identified for this liquid formulation. In conclusion, there were no safety issues identified from the CMC perspective that would require additional nonclinical toxicology studies. See the CMC review for NDA 206679 for additional details.

As an orally administered suspension, it is expected that the proposed Simvastatin oral suspension product would require alternate/additional excipients compared to Zocor® tablets. Three excipients were identified as potentially exceeding the amounts present in other U.S. approved drugs (as listed in the FDA Inactive Ingredients Database, IID) at similar or greater amounts, for similar duration and for a comparable patient population. Two are esters of p-hydroxybenzoic acid (i.e., parabens), ethylparaben and propylparaben, and the third is an (b) (4) strawberry flavoring mixture. Ethylparaben and propylparaben are added for their (b) (4) properties, but potentially exceed the IID levels. The novel flavoring agent, Strawberry Flavouring (b) (4) was added to enhance the palatability of the liquid preparation, but is not present in any U.S. approved product per the IID. The Applicant identified propylene glycol as potentially exceeding IID levels; this reviewer identified propylene glycol in the

IID at higher amounts for drugs approved for chronic oral administration than levels in Simvastatin oral suspension. Therefore, the levels of propylene glycol are safe.

Ethylparaben

The Joint FAO/WHO Expert Committee on Food Additives, a recognized panel of international experts, established a total paraben (the sum of methyl-, ethyl-, and propylparaben) acceptable daily intake (ADI) of 0-10 mg/kg body weight[1], although propylparaben was later recommended for exclusion from the total paraben ADI in a subsequent report of the same committee[2]. Therefore, using the 10 mg/kg ADI upper limit, total paraben (methyl- and ethylparaben) of up to 600 mg/day is safe, based on a 60 kg patient body weight. The total amount of combined methyl- and ethylparaben in Simvastatin oral suspension at the maximum recommended dose of 80 mg simvastatin is (b) (4) mg/day, which represents approximately (b) (4) % of the ADI for total parabens as defined by the Joint FAO/WHO Expert Committee on Food Additives. The concentration of ethylparaben is below the use limit levels of 0.1% cited in 21 CFR184.1670, Subpart B, for direct food substances affirmed as GRAS intended for use as (b) (4) Therefore, proposed amounts of ethylparaben in Simvastatin oral suspension are considered safe at the amounts specified (≤ (b) (4) mg/day), based on the findings of the Joint Food and Agriculture Organization of the United Nations/World Health Organization (FAO/WHO) Expert Committee on Food Additives and the determination that ethylparaben is present at amounts consistent with its designation as Generally Recognized as Safety (GRAS) for use as an (b) (4) in foods.

Propylparaben

The Applicant preliminarily determined that levels of propylparaben exceeded those specified for other drugs in the FDA IID. Furthermore, propylparaben was recommended for exclusion from the total paraben ADI by a subsequent Joint FAO/WHO Expert Committee on Food Additives report, based concerns for endocrine disruptor properties of longer side-chain parabens at levels falling within the ADI range for total parabens[3]. However, the amount of propylparaben ((b) (4) mg/day) in Simvastatin oral suspension is less than that of another orally-administered U.S.-approved drug in the IID with a chronic indication. The levels of propylparaben in Simvastatin oral suspension are low, and fall below the use limit level of 0.1% cited in 21 CFR184.1670, Subpart B, for direct food substances affirmed as GRAS intended for use as (b) (4) This reviewer therefore concludes that the levels of propylparaben, which are necessary to (b) (4) and are lower in Simvastatin oral suspension than in another U.S. approved drug, are safe.

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[1] "Safety evaluation of certain food additives and contaminants". The 17 h report of the Joint Food Additives Organization of the United Nations/World Health Organization Expert Committee on Food Additives, 1974.

[2] "Evaluation of certain food additives and contaminants". The 67 h report of the Joint Food Additives Organization of the United Nations/World Health Organization Expert Committee on Food Additives, 2006.

[3] Oishi, S "Effects of propyl paraben on the male reproductive system" *Food Chem Toxicol* 2002; **40**:1807-1813.

Strawberry Flavouring [redacted] (b) (4)
Simvastatin oral suspension contains a novel flavoring agent that is not present in any U.S. approved drug per the FDA IID. This flavoring component, identified as Strawberry Flavouring [redacted] (b) (4), is added to improve the palatability of Simvastatin oral suspension. Strawberry Flavouring [redacted] (b) (4) is recognized to contain [redacted] (b) (4) % [redacted] (b) (4) but the formula for the remaining ingredients is proprietary and unavailable to the Applicant; the Applicant submitted no information to support the safety of Strawberry Flavouring [redacted] (b) (4) or its unidentified individual components. Instead, the Applicant secured right of reference to DMF [redacted] (b) (4), which is held by [redacted] (b) (4) where the formulation of Strawberry Flavouring [redacted] (b) (4) is semi-quantitatively described. The components of Strawberry Flavouring [redacted] (b) (4) and the maximum possible amounts of individual ingredients (reported as percent ranges) in the flavoring agent were provided in DMF [redacted] (b) (4) (a Pharmacology/Toxicology review for Strawberry Flavouring [redacted] (b) (4) was submitted to DMF [redacted] (b) (4)). All components of Strawberry Flavouring [redacted] (b) (4) have been designated as GRAS by the FDA as referenced in the CFR for each intended use. No toxicologic concern was identified for any component of the novel flavoring excipient Strawberry Flavouring [redacted] (b) (4) as described for inclusion in the Simvastatin oral suspension product to be chronically administered via the oral route. This reviewer therefore concludes that the inclusion of Strawberry Flavouring [redacted] (b) (4) in Simvastatin oral suspension for the purpose of improved palatability at the specified level is safe.

1.3 Recommendations

1.3.1 Approvability

In the absence of any substantial safety concerns identified, Pharmacology/Toxicology recommends Simvastatin oral suspension for approval.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

Product labeling for Simvastatin oral suspension for Sections 8.1 and 8.2 and 13.1 and 13.2 should be identical to the listed drug Zocor®, except "Zocor®" should be replaced by the trade name for "Simvastatin oral suspension", where applicable. When the term "simvastatin" is substituted for Zocor®, it may also be used for Simvastatin oral suspension.

Indications and Usage
Simvastatin oral suspension is an HMG-CoA reductase inhibitor (statin)…

Contraindications
• Women who are pregnant or may become pregnant. (4, 8.1)
• Nursing mothers. (4, 8.3)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X [See Contraindications (4).]

Simvastatin oral suspension is contraindicated in women who are or may become pregnant. Lipid lowering drugs offer no benefit during pregnancy, because cholesterol and cholesterol derivatives are needed for normal fetal development. Atherosclerosis is a chronic process, and discontinuation of lipid-lowering drugs during pregnancy should have little impact on long-term outcomes of primary hypercholesterolemia therapy. There are no adequate and well-controlled studies of use with Simvastatin oral suspension during pregnancy; however, there are rare reports of congenital anomalies in infants exposed to statins *in utero*. Animal reproduction studies of simvastatin in rats and rabbits showed no evidence of teratogenicity. Serum cholesterol and triglycerides increase during normal pregnancy, and cholesterol or cholesterol derivatives are essential for fetal development. Because statins decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, Simvastatin oral suspension may cause fetal harm when administered to a pregnant woman. If Simvastatin oral suspension is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

There are rare reports of congenital anomalies following intrauterine exposure to statins. In a review of approximately 100 prospectively followed pregnancies in women exposed to simvastatin or another structurally related statin, the incidences of congenital anomalies, spontaneous abortions, and fetal deaths/stillbirths did not exceed those expected in the general population. However, the study was only able to exclude a 3- to 4-fold increased risk of congenital anomalies over the background rate. In 89% of these cases, drug treatment was initiated prior to pregnancy and was discontinued during the first trimester when pregnancy was identified.

Simvastatin was not teratogenic in rats or rabbits at doses (25, 10 mg/kg/day, respectively) that resulted in 3 times the human exposure based on mg/m^2 surface area. However, in studies with another structurally-related statin, skeletal malformations were observed in rats and mice.

Women of childbearing potential, who require treatment with Simvastatin oral suspension for a lipid disorder, should be advised to use effective contraception. For women trying to conceive, discontinuation of Simvastatin oral suspension should be considered. If pregnancy occurs, Simvastatin oral suspension should be immediately discontinued.

8.3 Nursing Mothers

It is not known whether simvastatin is excreted in human milk. Because a small amount of another drug in this class is excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women taking simvastatin should not nurse their infants. A decision should be made whether to discontinue nursing or discontinue drug, taking into account the importance of the drug to the mother *[see Contraindications (4)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 72-week carcinogenicity study, mice were administered daily doses of simvastatin of 25, 100, and 400 mg/kg body weight, which resulted in mean plasma drug levels approximately 1, 4, and 8 times higher than the mean human plasma drug level, respectively (as total inhibitory activity based on AUC) after an 80-mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males with a maximum incidence of 90% in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls. No evidence of a tumorigenic effect was observed at 25 mg/kg/day.

In a separate 92-week carcinogenicity study in mice at doses up to 25 mg/kg/day, no evidence of a tumorigenic effect was observed (mean plasma drug levels were 1 times higher than humans given 80 mg simvastatin as measured by AUC).

In a two-year study in rats at 25 mg/kg/day, there was a statistically significant increase in the incidence of thyroid follicular adenomas in female rats exposed to approximately 11 times higher levels of simvastatin than in humans given 80 mg simvastatin (as measured by AUC).

A second two-year rat carcinogenicity study with doses of 50 and 100 mg/kg/day produced hepatocellular adenomas and carcinomas (in female rats at both doses and in males at 100 mg/kg/day). Thyroid follicular cell adenomas were increased in males and females at both doses; thyroid follicular cell carcinomas were increased in females at 100 mg/kg/day. The increased incidence of thyroid neoplasms appears to be consistent with findings from other statins. These treatment levels represented plasma drug levels (AUC) of approximately 7 and 15 times (males) and 22 and 25 times (females) the mean human plasma drug exposure after an 80 milligram daily dose.

No evidence of mutagenicity was observed in a microbial mutagenicity (Ames) test with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in vitro* alkaline elution assay using rat hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow.

There was decreased fertility in male rats treated with simvastatin for 34 weeks at 25 mg/kg body weight (4 times the maximum human exposure level, based on AUC, in patients receiving 80 mg/day); however, this effect was not observed during a subsequent fertility study in which simvastatin was administered at this same dose level to male rats for 11 weeks (the entire cycle of spermatogenesis including epididymal maturation). No microscopic changes were observed in the testes of rats from either study. At 180 mg/kg/day, (which produces exposure levels 22 times higher than those in humans taking 80 mg/day based on surface area, mg/m^2), seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. In dogs, there was drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration and giant cell formation at 10 mg/kg/day, (approximately 2 times the

human exposure, based on AUC, at 80 mg/day). The clinical significance of these findings is unclear.

13.2 Animal Toxicology and/or Pharmacology

CNS Toxicity

Optic nerve degeneration was seen in clinically normal dogs treated with simvastatin for 14 weeks at 180 mg/kg/day, a dose that produced mean plasma drug levels about 12 times higher than the mean plasma drug level in humans taking 80 mg/day.

A chemically similar drug in this class also produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose that resulted in a mean plasma drug level similar to that seen with the 60 mg/kg/day dose.

CNS vascular lesions, characterized by perivascular hemorrhage and edema, mononuclear cell infiltration of perivascular spaces, perivascular fibrin deposits and necrosis of small vessels were seen in dogs treated with simvastatin at a dose of 360 mg/kg/day, a dose that produced mean plasma drug levels that were about 14 times higher than the mean plasma drug levels in humans taking 80 mg/day. Similar CNS vascular lesions have been observed with several other drugs of this class.

There were cataracts in female rats after two years of treatment with 50 and 100 mg/kg/day (22 and 25 times the human AUC at 80 mg/day, respectively) and in dogs after three months at 90 mg/kg/day (19 times) and at two years at 50 mg/kg/day (5 times).

2 Drug Information

2.1 Drug

CAS Registry Number
79902-63-9

Generic Name
Simvastatin (oral suspension)

Code Name
N/A

Chemical Name
(b) (4)

Molecular Formula/Molecular Weight
$C_{25}H_{38}O_5$/418.57 g/mol

Figure 1: Structure of simvastatin

(b) (4)

Pharmacologic Class
HMG CoA-reductase inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA 019766, Zocor® (simvastatin) tablets, Merck & Co.
DMF (b) (4) simvastatin drug substance manufacturer (b) (4) source of drug substance is (b) (4) (DMF (b) (4))
(b) (4), manufacturer of Strawberry Flavouring (b) (4)

2.3 Drug Formulation

Table 1 shows the formulation of the lower strength, 20 mg in 5 mL Simvastatin oral suspension drug product. Table 2 shows the formulation of the higher strength, 40 mg in 5 mL Simvastatin oral suspension drug product.

Table 1: Composition of Simvastatin oral suspension 20 mg/5 mL

Component	Compendial Quality	Function	mg/5 mL Dose	Formulation %w/w
Simvastatin	USP	Active ingredient	20	0.4
Propylene Glycol	USP	(b) (4)		
Methylparaben	NF			
Ethylparaben	NF			
Propylparaben	NF			
Magnesium Aluminum Silicate	NF			
Carboxymethylcellulose Sodium	NF			
Simethicone Emulsion	USP			
Sodium Lauryl Sulfate	NF			
Acesulfame Potassium	NF			
Citric Acid Monohydrate	USP			
Sodium Phosphate, Dibasic, Anhydrous	USP			
Strawberry Flavoring (b) (4) (b) (4)	NA	Flavor	(b) (4)	
(b) (4) Water	USP	(b) (4)	N/A	NA

*Strawberry flavor contains (b) (4) % (b) (4) other ingredients are proprietary (Sponsor)

Table 2: Composition of Simvastatin oral suspension 40 mg/5 mL

Component	Compendial Quality	Function	mg/5 mL Dose	Formulation %w/w
Simvastatin	USP	Active ingredient	40	0.8
Propylene Glycol	USP	(b) (4)		
Methylparaben	NF			
Ethylparaben	NF			
Propylparaben	NF			
Magnesium Aluminum Silicate	NF			
Carboxymethylcellulose Sodium	NF			
Simethicone Emulsion	USP			
Sodium Lauryl Sulfate	NF			
Acesulfame Potassium	NF			
Citric Acid Monohydrate	USP			
Sodium Phosphate, Dibasic, Anhydrous	USP			
Strawberry Flavoring (b) (4) (b) (4)	NA	Flavor	(b) (4)	
(b) (4) Water	USP	(b) (4)	N/A	NA

*Strawberry flavor contains (b) (4) % (b) (4); other ingredients are proprietary (Sponsor)

2.4 Comments on Novel Excipients

Based on a maximum recommended human dose of 80 mg simvastatin per day, the safety of a total daily intake of any one component of Simvastatin oral suspension is

dependent on the safety evaluation of 10 mL of the 40 mg/5 mL product (see Total Daily Intake levels listed in Table 4).

The to-be-marketed formulation contains two excipients, ethylparaben and propylparaben, at levels preliminarily identified as potentially exceeding levels listed in the FDA Inactive Ingredient Database (IID). Simvastatin oral suspension contains a third excipient, a novel flavoring identified as Strawberry Flavouring (b) (4), which is not found in the IID. Refer to Table 3 and Table 4 for summaries of information supplied by the Applicant to identify potential safety concerns for components of Simvastatin oral suspension. The Applicant identified propylene glycol as potentially exceeding IID levels; this reviewer identified propylene glycol at higher amounts in other U.S. approved drugs for chronic oral administration than those present in Simvastatin oral suspension. The level of propylene glycol in Simvastatin oral suspension is therefore considered safe.

Table 3: Applicant Identified Inactive Ingredient Database Limits of Excipients in Simvastatin oral suspension 20 mg/5 mL

Component	mg/5 mL Dose	Total Daily Intake** (mg/day)	Formulation %w/w	IID*** (Oral Solid)
Simvastatin	20	40	0.4	NA
Propylene Glycol in formulation (b) (4)	(b) (4)	(b) (4)	(b) (4)	148.31 mg[1] (soft gel capsule)
Methylparaben	(b) (4)	(b) (4)	(b) (4)	50 mg (granual)
Ethylparaben	(b) (4)	(b) (4)	(b) (4)	0.66 mg (powder)[2]
Propylparaben	(b) (4)	(b) (4)	(b) (4)	0.216 mg (oral capsule sustained release)[3]
Magnesium Aluminum Silicate	(b) (4)	(b) (4)	(b) (4)	60 mg (tablet)
Carboxymethylcellulose Sodium	(b) (4)	(b) (4)	(b) (4)	160 mg (capsule)
Simethicone Emulsion	(b) (4)	(b) (4)	(b) (4)	15.63 mg (sustained release capsule)
Sodium Lauryl Sulfate	(b) (4)	(b) (4)	(b) (4)	51.96 mg (tablet)
Acesulfame Potassium	(b) (4)	(b) (4)	(b) (4)	117 mg (powder)
Citric Acid Monohydrate	(b) (4)	(b) (4)	(b) (4)	50 mg (tablet)
Sodium Phosphate, Dibasic, Anhydrous	(b) (4)	(b) (4)	(b) (4)	110 mg (sustained action tablet)
Strawberry Flavoring (b) (4)	(b) (4)	(b) (4)	(b) (4)	Not listed
(b) (4) Water (Applicant)	N/A	NA	NA	NA

* For proprietary reasons, levels of individual components of the flavoring ingredient other than (b) (4) content are not shown (refer to the nonclinical review in filed for DMF (b) (4)).
[1, 2, 3] Total daily intake is less than that identified by the Applicant for another U.S. approved ANDA not indicated for chronic use.
** The maximum recommended daily dose of Simvastatin oral suspension is 80 mg, and is considered to consist of 10 mL of the 40 mg/5 mL product.
*** Per the FDA IID

Table 4: Applicant Identified Inactive Ingredient Database Limits of Excipients in Simvastatin oral suspension 40 mg/5 mL

Component	mg/5 mL Dose	Total Daily Intake (mg/day)	Formulation %w/w	IID** (Oral Solid)
Simvastatin	40	80	0.4	NA
Propylene Glycol in formulation (b) (4)	(b) (4)			148.31 mg[1] (soft gel capsule)
Methylparaben				50 mg (granual)
Ethylparaben				0.66 mg (powder)[2]
Propylparaben				0.216 mg (oral capsule sustained release)[3]
Magnesium Aluminum Silicate				60 mg (tablet)
Carboxymethylcellulose Sodium				160 mg (capsule)
Simethicone Emulsion				15.63 mg (sustained release capsule)
Sodium Lauryl Sulfate				51.96 mg (tablet)
Acesulfame Potassium				117 mg (powder)
Citric Acid Monohydrate				50 mg (tablet)
Sodium Phosphate, Dibasic, Anhydrous				110 mg (sustained action tablet)
Strawberry Flavoring (b) (4)				Not listed
(b) (4) Water	N/A	NA	NA	NA

(Applicant)
* For proprietary reasons, levels of individual components of the flavoring ingredient other than (b) (4) content are not shown (refer to the nonclinical review in filed for DMF (b) (4)).
[1, 2, 3] Total daily intake is less than that identified by the Applicant for another U.S. approved ANDA not indicated for chronic use.

Parabens

Parabens (see Figure 2, below) are esters of ρ-hydroxybenzoic acid (most frequently encountered as methyl-, ethyl-, propyl- and butylparaben), which are used as (b) (4) and are naturally occurring in some foods (some fruit juices, wines, Bourbon vanillas, etc., which contain primarily methylparaben). Parabens do not accumulate in humans and share a common route of degradation regardless of side-chain length. The primary breakdown products include: ρ-hydroxybenzoic acid, and the glycine, glucuronic acid and sulfuric acid conjugates of ρ-hydroxybenzoic acid. Breakdown products are excreted predominantly in the urine.[4]

[4] Soni, MG et al. "Safety assessment of esters of ρ-hydroxybenzoic acid (parabens)" Food Toxicol 2005; 43:985-1015.

Figure 2: Chemical structures of parabens most commonly encountered in consumer products and foods

Darbre, PD and Harvey, PW. (2008)[5]

Safety concerns for parabens

The primary toxicological concern identified for parabens is their potential to induce endocrine disruption, with longer side-chain length parabens suspected of greater potency than shorter chain forms.[6] The Joint FAO/WHO Expert Committee on Food Additives provided the most robust publically available scientific evaluation of the safety of the use of parabens specific to foods. The Joint FAO/WHO Expert Committee on Food Additives set an acceptable daily intake (ADI of 0-10 mg/kg/day) for total methyl-, ethyl- and propylparaben.[7] It is notable that butylparaben was specifically excluded from the total paraben ADI of 0-10 mg/kg/day and that the Joint FAO/WHO Expert Committee on Food Additives later recommended propylparaben also be excluded from the total paraben ADI of 0-10 mg/kg/day, due to the finding that butylparaben, and later propylparaben, showed the potential for endocrine disruption[8]; propylparaben is

[5] Darbre, PD and Harvey, PW "Paraben esters: review of recent studies of endocrine toxicity, absorption, esterase and human exposure, and discussion of potential human health risks" *J Applied Toxicol* 2008; **28**:561-578.

[6] Boberg, J et al. "Possible endocrine disrupting effects of parabens and their metabolism" *Reprod Toxicol* 2010; **30**:301-312.

[7] "Safety evaluation of certain food additives and contaminants". The 17 h report of the Joint Food Additives Organization of the United Nations/World Health Organization Expert Committee on Food Additives, 1974.

[8] "Evaluation of certain food additives and contaminants". The 67 h report of the Joint Food Additives Organization of the United Nations/World Health Organization Expert Committee on Food Additives, 2006.

estrogenic and anti-androgenic in rats with the potential for similar effects in man at levels within the 0-10 mg/kg/day total paraben ADI.[9]

Each 40 mg/5 mL dose of Simvastatin oral suspension contains (b) (4) and (b) (4) mg of methyl-, ethyl-, and propylparaben, respectively, which provides a total daily intake of (b) (4) and (b) (4) mg/day, respectively, at the maximum recommended daily dose of Simvastatin oral suspension at 80 mg/day in 10 mL. Note: Simvastatin contains no isopropyl-paraben, butylparaben or benzylparaben.

Ethylparaben

The amount of ethylparaben, at (b) (4) mg/day, is present at higher levels than those in other U.S. approved drugs, as listed in the FDA IID (a maximum of 0.66 mg/day ethylparaben was identified in an oral powder formulation for a product with an expected short-term duration of use). However, an ADI of total parabens was suggested at 600 mg/day by the Joint FAO/WHO Expert Committee on Food Additives in 1974, based on an acceptable daily intake of 0-10 mg/kg/day parabens (excluding propyl- and butylparaben) for a 60 kg patient.[10] The proposed ethylparaben concentration represents a small fraction, or approximately (b) (4) %, of the ADI. When ethyl- and methylparaben are combined, the two represent approximately (b) (4) % of the paraben ADI. The concentration of ethylparaben is also below the use limit le els of 0.1% cited in 21 CFR184.1670, Subpart B, for direct food substances affirmed as GRAS intended for use as (b) (4), based on the weight of the suspension.

Propylparaben

In 2006, the Joint FAO/WHO Expert Committee on Food Additives amended their recommendations to exclude propylparaben from ADI of 0-10 mg/kg/day parabens (600 mg/day based on a 60 kg human body weight), because propylparaben was demonstrated to activate the estrogen receptor in vitro and in vivo.[11] However, propylparaben was observed to be approximately 30,000-fold weaker than estradiol at ERα and ERβ, in vitro, and failed to stimulate uterotrophic activity in vivo when administered to immature or ovariectomized rats at up to 100 mg/kg/day by oral gavage. Propylparaben was demonstrated to cause decreased testosterone in a dose dependent manner in male rats at exposures that approximated the 10 mg/kg/day ADI upper limit (600 mg/day based on a 60 kg adult human body weight). The amounts of propylparaben in Simvastatin oral suspension are expected to produce patient exposures that are estimated to be (b) (4) -fold below the lowest dose that caused decreased testosterone in rats. Sperm counts were more sensitive to propylparaben, and were decreased at all doses in male rats in the same study[12]. The lowest dose

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[9] "Evaluation of certain food additives and contaminants". The 67 h report of the Joint Food Additives Organization of the United Nations/World Health Organization Expert Committee on Food Additives, 2006.

[10] "Safety evaluation of certain food additives and contaminants". The 17th report of the Joint Food Additives Organization of the United Nations/World Health Organization Expert Committee on Food Additives, 1974.

[11] "Evaluation of certain food additives and contaminants". The 67th report of the Joint Food Additives Organization of the United Nations/World Health Organization Expert Committee on Food Additives, 2006.

tested represented an approximate 6 mg/day human dose (approximately (b) (4)-fold the (b) (4) mg/day exposure from Simvastatin oral suspension. A dose that failed to decrease sperm counts in male rats was not identified, although the clinical significance of these findings is unknown.

Established propylparaben use in U.S. approved drugs

Established precedent for the use of propylparaben should also be considered; propylparaben is contained in at least one U.S. approved product indicated for chronic administration at 3 mg/5mL, per the IID. For this oral liquid suspension product identified in the IID, with potential dosing up to 20 mL/day at the maximum recommended human dose per product labeling, the level of propylparaben of up to 12 mg/day exceeds the proposed amounts of propylparaben of (b) (4) mg/day contained in Simvastatin oral suspension at the maximum recommended human dose.

Propylparaben in foods

The acceptability of the use of propylparaben as an ingredient in foods should also be considered (refer to Table 5, below). The estimated total daily human intake (90th percentile) of all parabens consumed in food is approximately 155 mg/day (vs. (b) (4) mg/day from Simvastatin oral suspension), although it is recognized that the primary paraben in foods is methylparaben.

Table 5: Estimated total daily intake of parabens consumed in food in the U.S.

Food	Mean daily consumed over 3-day period (90th percentile) (g)[a]	Level of use (%)	Mean daily amount paraben consumed over 3-day period (g)
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Soni, MG et al. (2001)[13]

Recognized use of propylparaben as food (b) (4)

The concentrations of propylparaben in Simvastatin oral suspension are below the specified use limit of 0.1%, based on the mass of the entire suspension, cited in 21 CFR 184.1670, Subpart B, for direct food substances affirmed as GRAS permitted for

[12] Oishi, S "Effects of propyl paraben on the male reproductive system" *Food Chem Toxicol* 2002; **40**:1807-1813.

[13] Soni, MG et al. "Safety assessment of propyl paraben: a review of the published literature" *Food Chem Toxicol* 2001; **39**:513-532.

(b) (4) (see Table 6, below), although total parabens (methyl-, ethyl- and propylparaben) are above the 0.1% use limit at approximately (b) (4)%. This higher percentage is due substantially to higher levels of the forms of least toxicologic concern (methylparaben – approximately (b) (4)%, and ethylparaben – approximately (b) (4)%). GRAS use limits for parabens are stated for individual paraben isoforms. Percentages were calculated based on the estimated weight of the total volume of the suspension administered.

Table 6: U.S. approved uses of propylparaben in food per 21 CFR

Citation	Food category	Permitted functionality	Use limits
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Soni, MG et al. (2001)[14]

Conclusion on ethyl- and propylparaben

Ethylparaben at (b) (4) mg/day, in combination with methylparaben at (b) (4) mg/kg/day, fall within the ADI recommended by the Joint FAO/WHO Expert Committee on Food Additives, and ethylparaben falls below the 0.1% use limit specified for FDA GRAS for this (b) (4) in foods. The levels of ethylparaben in Simvastatin oral suspension are therefore considered safe. While propylparaben levels are very low, they fall outside the ADI recommendations for parabens by the Joint FAO/WHO Expert Committee on Food Additives, based on its exclusion from the ADI. However, propylparaben is present at amounts in Simvastatin oral suspension consistent with its FDA GRAS use as an (b) (4) by the oral route. Propylparaben levels in Simvastatin oral suspension are below the IID levels for at least one other U.S.-approved drug indicated for chronic oral administration. Therefore, based on the totality of the information for consideration, the levels of propylparaben in Simvastatin oral suspension are considered safe.

[14] Soni, MG et al. "Safety assessment of propyl paraben: a review of the published literature" *Food Chem Toxicol* 2001; **39**:513-532.

Strawberry Flavouring [redacted] (b) (4)
All excipients in Simvastatin oral suspension are compendial with the exception of Strawberry Flavouring [redacted] (b) (4) which contains [redacted] (b) (4) % [redacted] (b) (4); specific amounts of the remaining ingredients are proprietary information. Refer to the Pharmacology/Toxicology review submitted to DMF [redacted] (b) (4) for the evaluation of the safety of ingredients at the amounts specified for Strawberry Flavouring [redacted] (b) (4) Each individual component of Strawberry Flavouring [redacted] (b) (4) was identified as FDA GRAS for the intended use by the oral route, which is comparable to the route of administration for Simvastatin oral suspension. FDA GRAS notice statements in the CFR were evaluated to address the intended use of each component and no applicable restrictions were identified.

2.5 Comments on Impurities/Degradants of Concern

The Agency's Office of Pharmaceutical Quality (CMC) review indicates there are no impurities or degradants observed in the drug substance or drug product that would require additional qualification per ICH Q3A and ICH Q3B. None were identified that would require qualification per ICH M7.

2.6 Proposed Clinical Population and Dosing Regimen

Adults with heterozygous familial and non-familial hypercholesterolemia are instructed to take up to 80 mg/day Simvastatin oral suspension and pediatric patients with heterozygous familial hypercholesterolemia are instructed to take up to 40 mg/day Simvastatin oral suspension.

2.7 Regulatory Background

The Sponsor requested a Type B pre-NDA meeting in a letter dated January 6, 2014. Pre-NDA written responses were provided to the Sponsor on March 21, 2014. NDA 206679 was submitted for review on June 22, 2015.

3 Studies Submitted

3.1 Studies Reviewed

No nonclinical study reports were submitted.

4 Pharmacology

4.1 Summary of Primary Pharmacology

HMG-CoA reductase inhibitors, of which simvastatin is a member, reduce the de novo production of cholesterol. In the liver, reduced hepatic cholesterol leads to increased expression of LDL receptors and enhances liver uptake of extrahepatic cholesterol (LDL-cholesterol). This leads to reduced plasma LDL-cholesterol and leads to reduced atherosclerosis and prevents cardiovascular mortality.

6 General Toxicology

According to the Zocor® label: Toxicity Optic nerve degeneration was seen in clinically normal dogs treated with simvastatin for 14 weeks at 180 mg/kg/day, a dose that produced mean plasma drug levels about 12 times higher than the mean plasma drug level in humans taking 80 mg/day.

A chemically similar drug in this class also produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean plasma drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose that resulted in a mean plasma drug level similar to that seen with the 60 mg/kg/day dose.

CNS vascular lesions, characterized by perivascular hemorrhage and edema, mononuclear cell infiltration of perivascular spaces, perivascular fibrin deposits and necrosis of small vessels were seen in dogs treated with simvastatin at a dose of 360 mg/kg/day, a dose that produced mean plasma drug levels that were about 14 times higher than the mean plasma drug levels in humans taking 80 mg/day. Similar CNS vascular lesions have been observed with several other drugs of this class.

There were cataracts in female rats after two years of treatment with 50 and 100 mg/kg/day (22 and 25 times the human AUC at 80 mg/day, respectively) and in dogs after three months at 90 mg/kg/day (19 times) and at two years at 50 mg/kg/day (5 times).

7 Genetic Toxicology

According to the Zocor® label: No evidence of mutagenicity was observed in a microbial mutagenicity (Ames) test with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an in vitro alkaline elution assay using rat hepatocytes, a V-79 mammalian cell forward mutation study, an in vitro chromosome aberration study in CHO cells, or an in vivo chromosomal aberration assay in mouse bone marrow

8 Carcinogenicity

According to the Zocor® label: In a 72-week carcinogenicity study, mice were administered daily doses of simvastatin of 25, 100, and 400 mg/kg body weight, which resulted in mean plasma drug levels approximately 1, 4, and 8 times higher than the mean human plasma drug level, respectively (as total inhibitory activity based on AUC) after an 80-mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid and high-dose males with a maximum incidence of 90% in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the Harderian gland (a gland of

the eye of rodents) were significantly higher in high-dose mice than in controls. No evidence of a tumorigenic effect was observed at 25 mg/kg/day.

In a separate 92-week carcinogenicity study in mice at doses up to 25 mg/kg/day, no evidence of a tumorigenic effect was observed (mean plasma drug levels were 1 times higher than humans given 80 mg simvastatin as measured by AUC).

In a two-year study in rats at 25 mg/kg/day, there was a statistically significant increase in the incidence of thyroid follicular adenomas in female rats exposed to approximately 11 times higher levels of simvastatin than in humans given 80 mg simvastatin (as measured by AUC).

A second two-year rat carcinogenicity study with doses of 50 and 100 mg/kg/day produced hepatocellular adenomas and carcinomas (in female rats at both doses and in males at 100 mg/kg/day). Thyroid follicular cell adenomas were increased in males and females at both doses; thyroid follicular cell carcinomas were increased in females at 100 mg/kg/day. The increased incidence of thyroid neoplasms appears to be consistent with findings from other statins. These treatment levels represented plasma drug levels (AUC) of approximately 7 and 15 times (males) and 22 and 25 times (females) the mean human plasma drug exposure after an 80 milligram daily dose.

9 Reproductive and Developmental Toxicology

According to the Zocor® label: There was decreased fertility in male rats treated with simvastatin for 34 weeks at 25 mg/kg body weight (4 times the maximum human exposure level, based on AUC, in patients receiving 80 mg/day); however, this effect was not observed during a subsequent fertility study in which simvastatin was administered at this same dose level to male rats for 11 weeks (the entire cycle of spermatogenesis including epididymal maturation). No microscopic changes were observed in the testes of rats from either study. At 180 mg/kg/day, (which produces exposure levels 22 times higher than those in humans taking 80 mg/day based on surface area, mg/m2), seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. In dogs, there was drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration and giant cell formation at 10 mg/kg/day, (approximately 2 times the human exposure, based on AUC, at 80 mg/day). The clinical significance of these findings is unclear.

Simvastatin was not teratogenic in rats or rabbits at doses (25, 10 mg/kg/day, respectively) that resulted in 3 times the human exposure based on mg/m^2 surface area. However, in studies with another structurally-related statin, skeletal malformations were observed in rats and mice.

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/s/

CALVIN L ELMORE
03/22/2016
Pharm/Tox recommends AP

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 206679 **Applicant:** Perrigo **Stamp Date:** 22 June 2015

Drug Name: simvastatin 20 mg/5 mL and 40 mg/5 mL oral suspension **NDA/BLA Type:** 505(b)(2)

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	Y		No studies submitted. Noncompendial (i.e., novel) excipient formulation is referenced in DMF (b) (4).
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	Y		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	Y		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	Y		Sponsor intends to rely upon the safety and efficacy of simvastatin demonstrated by Merck under NDA.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	n/a		Sponsor apparently intends to rely upon CMC bridging (comparison of physicochemical properties) for this 505(b)(2) application.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	n/a		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	n/a		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			The Division cautioned the Sponsor that a nonclinical bridging toxicity study might be essential to bridge to the LD. The Sponsor declined to perform this study.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	n/a		Labeling will be identical to the current Simvastatin PI.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	Y		This "Yes" is qualified by the fact that the Sponsor appears to be relying on a CMC (comparison of physicochemical properties) bridge, instead of head-to-head toxicity studies.
11	Has the applicant addressed any abuse potential issues in the submission?	n/a		There are no known abuse liabilities with the LD.
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			n/a

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

No filing issues. General comments for the 74-day filing letter are provided below:

Your drug product contains at least one novel excipient (Strawberry Flavouring (b) (4) (b) (4) that has not been used in any approved drug product in the United States. Because no nonclinical toxicology studies were provided to qualify this novel excipient or potential drug-related impurities, drug product safety will be dependent on review of the available toxicology and quality data and literature review provided.

C. Lee Elmore, Ph.D. 8/18/2015
Reviewing Pharmacologist Date

David Carlson, Ph.D. 8/18/2015
Team Leader/Supervisor Date

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/s/

CALVIN L ELMORE
08/18/2015

DAVID B CARLSON
08/18/2015