



UNITED STATES
 CONSUMER PRODUCT SAFETY COMMISSION
 4330 EAST WEST HIGHWAY
 BETHESDA, MD 20814

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BALLOT VOTE SHEET

Date: February 2, 2011

TO : The Commission
 Todd Stevenson, Secretary

THROUGH: Kenneth R. Hinson, Executive Director
 Cheryl A. Falvey, General Counsel
 Philip L. Chao, Assistant General Counsel, RAD

FROM : Patricia M. Pollitzer, Attorney

SUBJECT : Petitions to Exempt Powder Formulations of Colesevelam Hydrochloride (Welchol®) (PP 10-1) and Sevelamer Carbonate (Renvela®) (PP 10-2) from Special Packaging Requirements of the Poison Prevention Packaging Act

BALLOT VOTE DATE: February 8, 2011

Attached is a briefing package from the staff concerning the following requests for exemption from special packaging requirements under the Poison Prevention Packaging Act (“PPPA”): (1) a petition submitted by Daiichi Sankyo, Inc., requesting an exemption for the powder formulation of colesevelam hydrochloride, which it markets as Welchol®, and (2) a petition submitted by Genzyme Corporation requesting an exemption for the powder formulation of sevelamer carbonate, which it markets as Renvela®. The staff recommends that the Commission grant the petitions and publish a notice of proposed rulemaking. A draft *Federal Register* notice is provided at Tab F of the briefing package.

Please indicate your vote on the following options:

- A. Petition PP 10-1 Requesting Exemption for Powder Formulations of Colesevelam Hydrochloride (Welchol®)
- I. Grant Petition PP 10-1 and approve publication in the *Federal Register* of the draft notice of proposed rulemaking without change.

 Signature

 Date

II. Grant Petition PP 10-1 and approve publication in the *Federal Register* of the draft notice of proposed rulemaking with changes (please specify changes):

Signature

Date

III. Deny Petition PP 10-1 and direct the staff to prepare a letter of denial to the petitioner.

Signature

Date

IV. Defer decision on Petition PP 10-1.

Signature

Date

V. Take other action (please specify):

Signature

Date

B. Petition PP 10-2 Requesting Exemption for Powder Formulations of Sevelamer Carbonate (Renvela®)

- I. Grant Petition PP 10-2 and approve publication in the *Federal Register* of the draft notice of proposed rulemaking without change.

Signature

Date

- II. Grant Petition PP 10-2 and approve publication in the *Federal Register* of the draft notice of proposed rulemaking with changes (please specify changes):

Signature

Date

- III. Deny Petition PP 10-2 and direct the staff to prepare a letter of denial to the petitioner.

Signature

Date

- IV. Defer decision on Petition PP 10-2.

Signature

Date

V. Take other action (please specify):

Signature

Date



Briefing Package

Petitions to Exempt Powder Formulations of
Colesevelam Hydrochloride (Welchol[®])
(PP 10-1) and Sevelamer Carbonate (Renvela[®]) (PP 10-2) from the Special
Packaging Requirements of the Poison Prevention Packaging Act

For Information:
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Tab A Petitions (PP 10-1 and PP10-2) for Exemption from Child-Resistant Packaging (For Official Use Only) REMOVED
Tab B Memorandum from Adrienne R. Layton, Ph.D., HS, to Mary Ann Danello, Ph.D., HS, 'Toxicity Review of Colesevelam Hydrochloride (Welchol®) and Sevelamer Carbonate (Renvela®)'
Tab C Memorandum from Craig W. O'Brien, EPHA, to Adrienne R. Layton, Ph.D., HS, 'Reported Incidents for Colesevelam Hydrochloride (Welchol®), Sevelamer Carbonate (Renvela®) and Related Drugs, 2000-2009'
Tab D Memorandum from Catherine A. Sedney, HF, to Adrienne R. Layton, Ph.D., HS, 'Petitions for Exemption from PPPA Requirements for Child-Resistant Packaging'
Tab E Memorandum from Jill L. Jenkins, Ph.D., EC, to Adrienne R. Layton, Ph.D., HS, 'Colesevelam Hydrochloride (Welchol®) and Sevelamer Carbonate (Renvela®) Petitions for Exemption from the Child-Resistant Packaging Requirements of the Poison Prevention Packaging Act - Economic Considerations'
Tab F Draft Notice of Proposed Rulemaking

Executive Summary

The powder forms of the marketed drugs colesevelam hydrochloride (Welchol[®]), produced by Daiichi Sankyo, Inc., and sevelamer carbonate (Renvela[®]), produced by the Genzyme Corporation, recently have been approved by the U.S. Food and Drug Administration. The companies have petitioned the Commission to exempt these drugs from the child-resistant packaging (CRP) requirements of the Poison Prevention Packaging Act (PPPA). The requested exemption from the PPPA is for the powder dosage forms of the drugs only; the marketed tablets will continue to meet the requirements detailed in the PPPA in 16 CFR 1700, by being packaged in child-resistant packages.

Colesevelam hydrochloride (Welchol[®]) and sevelamer carbonate (Renvela[®]) are used therapeutically to bind bile acids and phosphate, respectively. CPSC staff is processing the petitions together because the request is the same (*i.e.*, exemption of powders from CRP requirements), and the drugs have similar chemical and biological properties.

Staff believes that available data support the following conclusions: that colesevelam hydrochloride (Welchol[®]) and sevelamer carbonate (Renvela[®]) have low oral toxicities following clinical use of the drugs; there are no serious adverse event data associated with their accidental ingestion; and there appears to be little risk that children under five years old will ingest large amounts of the powdered products. Colesevelam hydrochloride (Welchol[®]) and sevelamer carbonate (Renvela[®]) are not absorbed from the gastrointestinal tract. The acute toxicity of both drugs is mild to moderate and may include indigestion, diarrhea, flatulence, constipation, nausea and vomiting, and muscle pain. Similar drugs—cholestyramine and colestipol—have already been exempted from CRP. For these reasons, staff recommends that the Commission grant the petitions to exempt the powder formulation of colesevelam hydrochloride (Welchol[®]) containing no more than 3.75 grams per package from special packaging requirements and exempt the powder formulation of sevelamer carbonate (Renvela[®]) containing no more than 2.4 grams per package from special packaging requirements.



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February 2, 2011

MEMORANDUM

To: The Commission
Todd Stevenson, Secretary

Through: Cheryl A. Falvey, General Counsel
Kenneth R. Hinson, Executive Director

From: Robert J. Howell, Associate Executive Director
Office of Hazard Identification and Reduction
Adrienne R. Layton Ph.D., Project Manager
Directorate for Health Sciences

Subject: Petitions to Exempt the Powder Formulations of Colesevelam
Hydrochloride (Welchol[®]) and Sevelamer Carbonate (Renvela[®]) from the
Special Packaging Requirements of the PPPA

I. Introduction

The Poison Prevention Packaging Act (PPPA) requires child-resistant packaging (CRP) for oral prescription drugs. The Commission can exempt a substance from CRP if the packaging is not necessary to protect young children from serious illness or injury due to a lack of toxicity and lack of adverse human experience for the substance.

Daiichi Sankyo, Inc. and the Genzyme Corporation have petitioned the U.S. Consumer Product Safety Commission (CPSC) to exempt the powder forms of their marketed drugs, colesevelam hydrochloride (Welchol[®]) and sevelamer carbonate (Renvela[®]), from the special packaging requirements of the PPPA, as detailed in 16 CFR 1700. Currently, colesevelam hydrochloride (Welchol[®]) and sevelamer carbonate (Renvela[®]) are marketed in tablet and powder form and dispensed in CRP. The U.S. Food and Drug Administration (FDA) approved the new powder formulations of the drugs on October 2, 2009, and August 12, 2009, respectively. The requested petitions for exemptions are for the powder dosage forms of colesevelam hydrochloride (Welchol[®]) and sevelamer carbonate (Renvela[®]) only; the tablets will continue to meet PPPA requirements. Because colesevelam hydrochloride (Welchol[®]) and sevelamer carbonate (Renvela[®]) have similar chemical structures, biological properties, and powder formulations, staff is handling the petitions together in one briefing package.

Colesevelam Hydrochloride (Welchol[®])

Colesevelam hydrochloride (Welchol[®]) is indicated to reduce elevated low density lipoprotein (LDL) cholesterol levels and improve glycemic (blood glucose) control in adults with type 2 diabetes mellitus (Jialal, 2009). The new dosage form of colesevelam hydrochloride (Welchol[®]) is available in two strengths, providing either 1.875 g or 3.75 g of the powdered drug in unit dose packages,¹ to be mixed with water and taken orally as a suspension. Daiichi Sankyo requested an exemption from the special packaging requirements for the powder dosage form containing no more than 3.75 grams of colesevelam hydrochloride (Welchol[®]).

Sevelamer Carbonate (Renvela[®])

Sevelamer carbonate (Renvela[®]) is used for the control of elevated serum phosphorous in chronic kidney disease (CKD) patients on dialysis (Burke 2000). Sevelamer carbonate (Renvela[®]) tablets are marketed with a pill crusher for those patients who find the tablets too large to swallow. To provide an alternative dosage form for these patients, sevelamer carbonate (Renvela[®]) was formulated as a powder to be taken orally as a suspension. The new dosage form of sevelamer carbonate (Renvela[®]) provides either 0.8 g or 2.4 g of sevelamer carbonate (Renvela[®]) powder in unit dose packages¹ to be mixed with water and taken orally as a suspension (Drug Facts and Comparisons, 2010). Genzyme requested an exemption from the special packaging requirements for the powder dosage form containing no more than 2.4 grams of sevelamer carbonate (Renvela[®]).

Both petitioners maintain that CRP is not necessary to protect young children from serious injury or illness. Genzyme supported its request for exemption by arguing that: (1) prior to being suspended in water, sevelamer carbonate powder is likely to be unpalatable to children; (2) the risk of systemic toxicity is low because the drug is not absorbed from the gastrointestinal (GI) tract; (3) sevelamer has been well-tolerated in the clinical studies performed in normal volunteers, adult CKD patients, and pediatric CKD patients on dialysis; and (4) no reports of overdose with sevelamer have been reported (Genzyme Corporation, March 6, 2009).

II. Discussion

A. Toxicity

The Directorate for Health Sciences staff reviewed the toxicity of colesevelam hydrochloride (Welchol[®]) and sevelamer carbonate (Renvela[®]) (Tab B). One conclusion from the toxicology review was that colesevelam hydrochloride (Welchol[®]) and sevelamer carbonate (Renvela[®]) are not absorbed from the gastrointestinal (GI) tract,

¹ A unit dose package of colesevelam hydrochloride (Welchol[®]) or sevelamer carbonate (Renvela[®]) is a pouch that contains an individual dose. The drugs are each available in unit dose packaging in two different dosages.

thereby limiting the systemic toxicities of the drugs. This property has been established in nonclinical and clinical pharmacokinetic studies. Precise toxic doses have not been established for either colesevelam hydrochloride (Welchol[®]) or sevelamer carbonate (Renvela[®]). In children 10 to 17 years old with familial hypercholesterolemia, the usual dosage is 3.75 grams (g) powder daily or 1.875 g powder taken twice daily with meals. The maximum daily dose of sevelamer carbonate (Renvela[®]) studied in adult kidney disease patients was 14 g daily (Drug Facts and Comparisons, 2010). Renvela[®] is not approved for use by children, although it has been studied in children (11 months to 18 years) at a dose of 5.4 g/day (Pieper, 2006). The usual dose for adults is 7.2 g per day. There are no data indicating that either colesevelam hydrochloride (Welchol[®]) or sevelamer carbonate (Renvela[®]) cause serious acute toxicity, the type of toxicity of concern in determining whether a drug should be dispensed in CRP. The types of toxicity seen, even in patients chronically taking these drugs, include: diarrhea, nausea, constipation, flatulence, and dyspepsia (Burke 2000, Davidson 2000).

Staff identified cases of serious toxicity associated with chronic use of Welchol[®] and Renvela[®]. Hemorrhage was observed in animal studies following 3- and 6-month administration of colesevelam hydrochloride (Welchol[®]) and sevelamer carbonate (Renvela[®]), respectively; however, this was not directly related to the mechanism of action of the drugs, but rather to a side effect involving the inhibition of vitamin K absorption. Colesevelam hydrochloride (Welchol[®]) and sevelamer carbonate (Renvela[®]) cause an alteration in the absorption of vitamins A, D, E, and K. Vitamin K is required by the liver to produce functional blood clotting factors. When vitamin K levels are low, nonfunctional blood clotting factors are produced, which can lead to hemorrhage (Majerus and Tollefsen, 2009). This can occur following the chronic administration of these drugs, but not after an acute exposure.

In general, chronic studies are not useful in determining whether a drug should be in CRP. In the case of colesevelam hydrochloride (Welchol[®]) and sevelamer carbonate (Renvela[®]), the toxicity resulting from chronic administration of these drugs is not relevant to an acute exposure.

There is one report of a four-year-old child who was prescribed colesevelam hydrochloride (Welchol[®]) off-label² to treat skin irritation secondary to liver disease. She died from an intracranial hemorrhage. The death occurred following a fall, and after chronic, not acute exposure. Because of the confounding factors, the death cannot be attributed solely to colesevelam hydrochloride (Welchol[®]). A trial of sevelamer hydrochloride (Renagel[®]) in a limited number of pediatric patients (18) for eight weeks resulted primarily in GI effects (Pieper et al. 2006). These effects would occur after chronic, but not acute exposure. The metabolic acidosis which was observed may be attributed to the hydrochloride released from Renagel[®] (Oka, 2008).

If a child accidentally ingests colesevelam hydrochloride (Welchol[®]) or sevelamer carbonate (Renvela[®]), the potential for occurrence of mild to moderate GI discomfort,

² Off-label refers to when a drug is prescribed to treat an indication for which it has not been approved by the FDA.

such as indigestion, constipation, nausea and vomiting, or muscle pain does exist. Therefore, based upon this information, staff believes that both colesevelam hydrochloride (Welchol[®]) and sevelamer carbonate (Renvela[®]) powders lack the potential to cause serious illness or injury in an acute poisoning scenario. Any serious toxicity with these drugs would result only after chronic administration.

Data that support a finding that child-resistant packaging is not necessary for the powdered forms of colesevelam hydrochloride (Welchol[®]) or sevelamer carbonate (Renvela[®]) containing no more than 3.75 grams/package for colesevelam hydrochloride (Welchol[®]) and containing no more than 2.4 grams/package for sevelamer carbonate (Renvela[®]), includes that these products: (1) have low oral toxicities following clinical use of the drugs; (2) lack adverse human experience associated with acute ingestion; and (3) are unlikely, in the powder form, to be ingested in large quantities by children under five years of age.

Further, the powder forms of two bile acid sequestrants, cholestyramine and colestipol, which have similar chemical profiles to colesevelam hydrochloride (Welchol[®]) and sevelamer carbonate (Renvela[®]) (Mahley, R.W. and Bersot, T.P., 2009), already have been exempted from child-resistant packaging by the CPSC (CFR1700.14(10)(v)(xv)). Anhydrous cholestyramine was exempted in powder form, and colestipol was exempted in powder form in packages containing not more than five grams of the drug, and containing no other substance subject to the provisions of CFR§1700.14. Furthermore, CPSC staff did not find any articles in the medical literature, from 1975 through 2010, describing toxic effects in humans following the acute ingestion of cholestyramine or colestipol.

B. Database Searches

The Directorate for Epidemiology staff searched the following databases for incidents from 2000 through 2009, related to colesevelam hydrochloride (Welchol[®]) and sevelamer carbonate (Renvela[®]): the Injury and Potential Injury Incident database (IPII), the National Electronic Injury Surveillance System database (NEISS), and the Death Certificates database (DTHS) (Tab C). Medwatch³ reports obtained from the FDA were also analyzed. Only one report of acute ingestion involving Welchol[®] tablets was found in the NEISS database. Eleven-month-old twin boys were taken to the emergency room after they possibly ingested Welchol[®] and diltiazem (a calcium channel antagonist). Five

³ MedWatch is FDA's program for reporting a [serious adverse event](#), product quality problem, product use error, or therapeutic inequivalence/failure that may be associated with the use of an FDA-regulated drug, biologic, medical device, dietary supplement, or cosmetic. (See <http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm>. Accessed 11/3/2010.) Although Medwatch data are useful to identify adverse events which occur while patients are taking medication, there are some limitations to the data: FDA receives some adverse event and medication error reports directly from health care professionals (such as physicians, pharmacists, and nurses) and consumers (such as patients or family members); there is no certainty that the reported event was actually due to the product since the FDA does not require that a causal relationship between a medication and an adverse event be proven, and often reports do not contain enough detail to properly evaluate an event. In addition, the FDA does not receive all adverse event reports that occur with a certain product.

to six Welchol[®] tablets were missing, and a Welchol[®] tablet was found in one boy's mouth. It is not clear exactly how many pills were ingested by the boys, but they were treated and released the same day (O'Brien, October, 2010). Poisindex[®], Pub Med, and Google also were searched for Welchol[®], Renvela[®], Colestipol, and Cholestyramine; and no incidents of acute poisoning in humans were found.

The FDA provided CPSC staff with 151 distinct incidents of adverse events associated with colesevelam hydrochloride (Welchol[®]) reported through the MedWatch system. Health Sciences staff reviewed the reports to exclude incidents where other medications may have caused the adverse event reported, resulting in 21 in-scope incidents.⁴ Adverse events included GI effects (e.g., upset stomach, constipation, and bloating) (7 out of 22), and muscle pain (4 out of 22). Also, three patients had a problem swallowing the pills (3 out of 22), and another (1 out of 22) had chronic gall bladder disease. Adverse effects reported in the "other" (7 out of 22) category, included: throat cancer, blood pressure increase, elevated ALT,⁵ rash, feeling "out of sorts," death from natural causes, and cholesterol increase. Therefore, most incidents reported from Medwatch were gastrointestinal or involved muscle pain, which is to be expected, considering the adverse effects reported from clinical trials of Welchol[®].

CPSC staff also received reports from the FDA of 40 distinct incidents of adverse events associated with sevelamer carbonate (Renvela[®]). Health Sciences staff reviewed the reports to exclude incidents where other medications may have caused the adverse event reported, resulting in five in-scope incidents. One 65-year-old female on hemodialysis, died from unknown causes after being treated with sevelamer carbonate (Renvela[®]). Another female, a 50-year-old with end stage renal disease on dialysis, died from unknown causes following treatment with sevelamer carbonate (Renvela[®]). These deaths are related most likely to the underlying disease and not sevelamer carbonate (Renvela[®]) treatment. A 45-year-old male, treated with sevelamer carbonate (Renvela[®]) for several months, developed an intestinal obstruction and perforation and an abdominal fistula (abnormal opening in the stomach or bowel, which allows the contents to leak), which were thought to be related to sevelamer carbonate (Renvela[®]) by his physician. Of the remaining patients, one experienced gastroenteritis, thought not to be related to sevelamer carbonate (Renvela[®]); and the other, who had asthma and chronic obstructive pulmonary disease, suffered severe breathing problems while on Renvela[®], which is most likely coincidental to Renvela[®] treatment.

C. Human Factors Assessment

The Division of Human Factors (HF) staff evaluated the likelihood of children younger than five years old ingesting powdered substances (Tab D). Both petitioners suggest that children will not ingest large amounts of either the colesevelam hydrochloride (Welchol[®]) or sevelamer carbonate (Renvela[®]) powder formula because they are unpalatable. However, because both products contain citrus flavoring and non-

⁴ One patient reported both GI and muscle effects as one incident report, resulting in 22 adverse events and 21 incidents.

⁵ Alanine transaminase (ALT) is a liver enzyme that is released upon damage to the liver. Some medications also release ALT.

caloric sweeteners, Human Factors staff believes that neither flavor nor “mouth feel” is likely to be a strong deterrent to ingestion.

According to HF staff, children under five may try to ingest either of these powdered products directly because they are hungry or curious, or might mix them in a liquid, in imitation of an adult, for example, or as part of their role-playing activities. However, the powder form of the substances makes them more difficult to ingest than most medicines, and is likely to deter children from ingesting significant quantities. Poisoning due to ingestion of large amounts of powder is relatively rare compared to other formulations. In fact, formulating a substance as a powder is considered a way to lower the toxicity of a substance, because less of the substance is usually ingested, not because the drug has lower toxicity (Done, 1970). For example, using a powdered household chemical, rather than a liquid, is considered a preventive measure for accidental ingestion (Writer, 1993).

Human Factors staff believes that it would be difficult for children under five to eat large amounts of powder quickly without aspirating or coughing. It would also be difficult for children to thoroughly mix powder in a liquid; and the resulting lumpy quality may be unappealing to children who try to drink it. Although children are likely to be able to tear open the non-child-resistant packets used for colesevelam hydrochloride (Welchol[®]) and sevelamer carbonate (Renvela[®]), they are just as likely to spill much of the contents; therefore, they would have to open a number of packages to access a significant quantity of drug. Most unintentional poisonings among children occur during short lapses in direct visual supervision. The difficulty posed by ingestion of powder introduces a delay in the poisoning scenario, and supervision is likely to resume before a child can ingest a significant quantity (Sedney, 1995). Colesevelam hydrochloride (Welchol[®]) and sevelamer carbonate (Renvela[®]) are provided in small, foil-lined packages that contain individual doses. The sevelamer carbonate (Renvela[®]) package is only easy to tear at the notch. Because the package must be opened at a precise location, it is less accessible, especially to young children. The colesevelam hydrochloride (Welchol[®]) package does not have a notch and has uniform resistance to tearing, which makes it more difficult to open than sevelamer carbonate (Renvela[®]). Although both packages tear easily enough to be opened by children under five, the fine motor skills of this age group of children are still developing, and children, particularly those age two and younger, are more likely to spill a majority of the powder than ingest it.

D. Economic Information

The Directorate for Economic Analysis staff provided market information on colesevelam hydrochloride (Welchol[®]) and sevelamer carbonate (Renvela[®]), as well as indicated the possible economic effects of the petition (Tab E). Daiichi Sankyo, Inc., a subsidiary of the Japanese firm Daiichi Sankyo Co., Ltd., markets tablets of colesevelam hydrochloride under the trade name of Welchol[®]. Daiichi Sankyo employs approximately 1,500 people in the United States. Net sales of Welchol[®] were approximately \$243.1 million in 2008.

Genzyme Corporation currently markets sevelamer carbonate in tablet form under the trade name of Renvela[®]. Genzyme Corporation is a U.S. firm, headquartered in Cambridge, Mass., with more than 12,000 employees worldwide. For 2008, annual revenue was \$4.6 billion. Renvela[®] along with Renagel[®], is a market leader in the treatment of kidney disease, with more than 50 percent of the prescriptions in the United States for this indication. Sales revenue for Renvela[®] and three other cardiometabolic and renal drugs was \$1 billion in 2008.

Because the affected firms are requesting the exemption, the action is unlikely to impose a significant impact. Additionally, given that both of the firms that would be affected by a CR packaging exemption for colesevelam hydrochloride (Welchol[®]) and sevelamer carbonate (Renvela[®]) are large, the data would support a conclusion that the exemption would not have any significant economic effect on a substantial number of small entities.

III. Options

1. Colesevelam Hydrochloride (Welchol[®])

- A. Grant the petition and propose a rule to exempt the powder formulation of colesevelam hydrochloride (Welchol[®]) containing no more than 3.75 g per package from special packaging requirements.

The Commission may grant the petition and issue a notice of proposed rulemaking if it preliminarily concludes that exempting colesevelam hydrochloride (Welchol[®]) from child-resistant packaging requirements at this level will not present a risk of serious personal injury or illness to young children.

- B. Deny the petition.

The Commission may deny the petition if it concludes that there is insufficient evidence to show that colesevelam hydrochloride (Welchol[®]) at this level would not be hazardous to young children.

- C. Defer the petition.

The Commission may defer the petition if it concludes that more information on colesevelam hydrochloride (Welchol[®]) is needed to make a decision.

2. Sevelamer Carbonate (Renvela[®])

- A. Grant the petition and propose a rule to exempt the powder formulation of sevelamer carbonate (Renvela[®]) containing no more than 2.4 g per package from special packaging requirements.

The Commission may grant the petition and issue a notice of proposed rulemaking if it preliminarily concludes that exempting sevelamer carbonate (Renvela[®]) from child-resistant packaging requirements at this level will not present a risk of serious personal injury or illness to young children.

B. Deny the petition.

The Commission may deny the petition if it concludes that there is insufficient evidence to show that sevelamer carbonate (Renvela[®]) at this level would not be hazardous to young children.

C. Defer the petition.

The Commission may defer the petition if it concludes that more information is needed on sevelamer carbonate (Renvela[®]) to make a decision.

IV. Conclusions and Recommendation

Data that support a finding that child-resistant packaging is not necessary for the powdered forms of colesevelam hydrochloride (Welchol[®]) or sevelamer carbonate (Renvela[®]) containing no more than 3.75 grams/package for colesevelam hydrochloride (Welchol[®]) and containing no more than 2.4 grams/package for sevelamer carbonate (Renvela[®]), includes that these products: (1) have low oral toxicities following clinical use of the drugs; (2) lack adverse human experience associated with acute ingestion; and (3) are unlikely, in the powder form, to be ingested in large quantities by children under five years of age.

Staff recommends that the Commission grant the petition from Daiichi Sankyo requesting an exemption from CRP for its powder formulation containing no more than 3.75 g of colesevelam hydrochloride (Welchol[®]) per package. The staff further recommends that the Commission grant the petition from Genzyme to exempt from CRP the powdered form of sevelamer carbonate (Renvela[®]) containing no more than 2.4 g per package, which is the level requested by the company. Colesevelam hydrochloride (Welchol[®]) and sevelamer carbonate (Renvela[®]) lack the potential to cause serious illness or injury in an acute poisoning scenario. Data that support a finding that packaging is not necessary for the powdered forms of colesevelam hydrochloride (Welchol[®]) or sevelamer carbonate (Renvela[®]) are: (1) their low acute toxicity; (2) the lack of serious adverse human experience data associated with acute ingestion; and (3) the powder form of the drugs makes it unlikely that a child under five years of age could ingest large quantities.

V. References

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Tab A

Tab B



**United States
CONSUMER PRODUCT SAFETY COMMISSION
4330 East West Highway, Bethesda MD 20814**

MEMORANDUM

November 1, 2010

To: Mary Ann Danello, Ph.D., Associate Executive Director, Directorate for Health Sciences

Through: Lori E. Saltzman, M.S., Division Director, Directorate for Health Sciences

From: Adrienne Layton, Ph.D., Pharmacologist, Directorate for Health Sciences

Subject: Toxicity Review of Colesevelam Hydrochloride (Welchol[®]) and Sevelamer Carbonate (Renvela[®])

Introduction

Daiichi Sankyo, Inc. and the Genzyme Corporation have petitioned the Consumer Product Safety Commission (CPSC) to exempt the powder forms of their marketed drugs, colesevelam hydrochloride (Welchol[®]) and sevelamer carbonate (Renvela[®]), respectively, from the requirements of the Poison Prevention Packaging Act (PPPA), as detailed in 16 CFR 1700. The PPPA requires child-resistant packaging (CRP) for oral prescription drugs. The Commission can exempt a substance from CRP, if the packaging is not necessary to protect young children from serious illness or injury due to a lack of acute toxicity and lack of adverse human experience for the substance. Although colesevelam hydrochloride (Welchol[®]) and sevelamer carbonate (Renvela[®]) currently are marketed in tablet and powder form and sold in child-resistant packaging, the U.S. Food and Drug Administration recently has approved the new dosage forms of the drugs, namely powders, to be taken orally as suspensions.

Colesevelam hydrochloride (Welchol[®]) is a polymeric⁶ cholesterol-lowering agent, which binds bile acids (i.e., a bile acid sequestrant). It is prescribed to reduce elevated LDL⁷ cholesterol levels found in patients. It is also used in combination with other cholesterol reducing agents, such as statins,⁸ which work through a different

⁶ A polymer is a high molecular weight molecule made up of repeating units.

⁷ LDL is low density lipoprotein.

⁸ A statin is a cholesterol lowering drug such as simvastatin and lovastatin.

mechanism than bile acid sequestrants⁹ (Davidson, 2000). Colesevelam hydrochloride (Welchol[®]) also improves glycemic control¹⁰ in adults with type 2 diabetes, which is indicated by reducing hemoglobin A1C levels, a marker of long-term blood glucose control (Jialal, I. et al., 2009). The usual daily dose of colesevelam hydrochloride (Welchol[®]) in adults is 3.75 grams (g), taken as a single or divided dose. In children 10 to 17 years old with familial hypercholesterolemia,¹¹ the usual dosage is 3.75 grams (g) powder daily or 1.875 g powder, taken twice daily with meals (Drug Facts and Comparisons, 2010). The new powder formulation is available in either 1.875 g or 3.75 g unit dose packages.

Sevelamer carbonate (Renvela[®]) is a calcium- and aluminum-free phosphate binder used for patients with end-stage renal disease (Burke 1997, Rosenbaum 1997, Storms 2006, Tonelli 2010). In addition to the tablet form, sevelamer carbonate (Renvela[®]) has been formulated as a powder for suspension, to provide an alternative dosage form for patients who have difficulty using solid dosage forms of medications or for those who require multiple tablets with each meal. When sevelamer carbonate (Renvela[®]) is marketed in tablet form, a pill crusher is provided with the tablets, so that the pills can be crushed prior to ingestion, if the patient cannot swallow the large tablet.

The maximum daily dose of sevelamer carbonate (Renvela[®]) studied in chronic kidney disease (CKD) patients was 14 g daily (Facts and Comparison, 2010). Renagel[®] is the trade name of the 400 and 800 mg tablets of sevelamer hydrochloride, which has the same active moiety and therapeutic use as sevelamer carbonate (Renvela[®]). Renvela[®] is the trade name of the oral 800 mg tablet, composed of sevelamer carbonate and the powder for suspension. Sevelamer carbonate (Renvela[®]) is not approved for use in children, although it has been studied in children (11 months to 18 years) at a dose of 5.4 g/day (Pieper, 2006). The usual dose in adults is 7.2 g per day. The new dosage form of sevelamer carbonate (Renvela[®]) will provide either 0.8 g or 2.4 g anhydrous sevelamer carbonate (Renvela[®]) powder in unit dose packages, which are to be mixed with water and taken orally as a suspension (Drug Facts and Comparisons, 2010).

The requested exemption from the PPPA is for the powder dosage forms containing no more than 3.75 grams colesevelam hydrochloride (Welchol[®]) or 2.4 grams sevelamer carbonate (Renvela[®]) only; the tablets for both drugs will continue to meet the requirements detailed in the PPPA in 16 CFR 1700, by being marketed in child-resistant packages.

Chemistry

1. Colesevelam hydrochloride (Welchol[®])

Colesevelam hydrochloride (Welchol[®]) is a highly positively charged polymer of poly(allylamine hydrochloride) cross-linked with epichlorohydrin and then alkylated with

⁹ A bile acid sequestrant is a cholesterol-lowering drug that binds bile acids and aids in their elimination.

¹⁰ Glycemic control refers to controlling blood glucose levels.

¹¹ Familial hypercholesterolemia is an inherited condition with high lipid levels in the blood.

approximately equal amounts of decylbromide and 6-trimethylammonio hexyl- bromide. The polymer is insoluble in aqueous environments because the particles are positively charged; it faces a significant barrier to absorption through the negatively charged mucus layer that lines the intestinal wall. Consequently, due to its charge and large size, absorption in the GI tract of intact particles of colesevelam hydrochloride (Welchol[®]) is negligible. Colesevelam hydrochloride (Welchol[®]) is sugar-free and citrus-flavored (Daiichi Sankyo, Inc., February 24, 2009). Table 1 shows the amount of colesevelam hydrochloride (Welchol[®]) contained within unit dose packages.

Table 1. Formulated Drug Amounts

Drug	Amount of Drug Powder (g)	Unit Dose Pack Weight (g)
Welchol [®]	1.875	2.6
Welchol [®]	3.75	5.2
Renvela [®]	0.8	NA
Renvela [®]	2.4	2.5

NA=not available

2. Sevelamer carbonate (Renvela[®])

Sevelamer carbonate (Renvela[®]) is a cross-linked polymeric phosphate binder, known chemically as poly(allylamine-co-N,N'-diallyl-1,3-diamino-2-hydroxypropane), carbonate salt, 2-propen-2-amine, polymer with (chloromethyl) oxirane, carbonate salt. Sevelamer carbonate (Renvela[®]) is not soluble in water and has ionizable amine groups. It is designed to bind anions, such as phosphate (Genzyme Corporation, March 6, 2009). Due to the large size of sevelamer carbonate (Renvela[®]), it is not absorbed from the gastrointestinal (GI) tract. According to Genzyme, sevelamer carbonate (Renvela[®]) powder, if ingested dry, may lead to an overall unpleasant dry mouth feeling.

Various ingredients (e.g., flavors, artificial sweeteners) are added to enhance the palatability and appearance of the product, including propylene glycol alginate (to improve “mouth feel”); sodium chloride sucralose (a nonsugar sweetening agent); and ferric oxide (a colorant) (Genzyme Corporation, March 6, 2009). Table 1 shows the amount of sevelamer carbonate (Renvela[®]) contained within unit dose packages.

Pharmacokinetics

Colesevelam hydrochloride (Welchol[®]) and sevelamer carbonate (Renvela[®]) are polymers that are not readily absorbed by the intestines and have been evaluated in both nonclinical and clinical pharmacokinetic studies (Rosenbaum, D.P. et al., 1997; Burke, S.K. et al., 1997; Mahley, R. and Bersot, T.P., 2010; Heller, D.P., 2002). Because neither of the two drugs is absorbed, pharmacokinetic studies were performed using radiolabeled forms of the drugs, and metabolism studies were not conducted.

1. Colesevelam Hydrochloride (Welchol[®])

Animal Studies

Six rats/group were dosed once orally via gavage with ^{14}C (radiolabeled) colesevelam hydrochloride (Welchol[®]), followed by unlabeled colesevelam hydrochloride (Welchol[®]) for four days, *ad libitum* (at their pleasure), at a target dose of 3 g/kg/day. It is not possible to determine the exact amount the rats ate because the method used to calculate the exact amount is not stated. Urine and fecal samples were collected from 0 to 24, 24 to 48, 48 to 72, and 72 to 96 hours. [^{14}C] was eliminated between 48 and 96 hours, with a total mass balance of 99.58 percent being recovered in the feces. No detectable levels of [^{14}C] were measured in the tissues, blood, or plasma; and the stomach contained less than 0.01 percent of the total radioactive dose administered (Daiichi Sankyo, Inc., February 24, 2009).

Another study was performed using radiolabeled colesevelam hydrochloride (Welchol[®]) in male beagles (6/group). Pharmacokinetics, tissue distribution, and excretion of radioactivity was determined following a single oral administration of [^{14}C]-colesevelam hydrochloride (Welchol[®]). The dogs were given [^{14}C]-colesevelam hydrochloride (Welchol[®]) at a target dose level of 100 mg/kg and 167 $\mu\text{Ci}/\text{dog}$. At 72 hours post dosing, blood and plasma radioactivity levels were below the lower limit of quantification at all time points. No radioactivity was measured for the kidneys, muscle, stomach, and stomach content. Radioactivity was almost recovered exclusively in the feces, with negligible amounts detected in the urine and cage rinses. The lack of urinary excretion and the recovery of radioactivity in the feces support a conclusion that there was no significant absorption of colesevelam hydrochloride (Welchol[®]) (Daiichi Sankyo, Inc., February 24, 2009).

Human Studies

Total radioactivity was measured in 16 healthy adult volunteers following a single acute dose of [^{14}C]-colesevelam hydrochloride (Welchol[®]). Radioactivity in the whole blood was 0.04 percent of the dose 96 hours after administration of the radiolabeled dose. The mean cumulative recovery of total radioactivity in urine throughout 96 hours was 0.05 ± 0.01 percent of the administered dose, while cumulative fecal recovery of [^{14}C]-colesevelam hydrochloride (Welchol[®]) among the 16 subjects was greater than 80 percent in eight subjects; between 60 percent to 80 percent in six subjects; and less than 25 percent in two subjects. The large variability in fecal excretion data may be due to incomplete fecal collection of the samples. Loss of even a single specimen could account for the low cumulative excretion in these patients. Assuming that incomplete fecal collection occurred in the two subjects with less than 25 percent fecal collection, this study, although limited, demonstrates that colesevelam hydrochloride (Welchol[®]) is essentially unabsorbed in humans (Heller, D.P., 2002).

Only 0.05 percent of a single [^{14}C]-labeled colesevelam hydrochloride (Welchol[®]) dose was excreted in the urine of 16 healthy volunteers following 28 days of administration of 3.8 g/day of colesevelam hydrochloride (Welchol[®]) in two daily divided doses (Melian, E.B., 2001). This study, again limited in size, demonstrates that this dose of drug was not absorbed into the body and excreted by the kidneys.

2. Sevelamer Carbonate (Renvela[®])

Animal Studies

Since Renagel[®], the hydrochloride salt of sevelamer was marketed first, many of the early animal studies were performed with Renagel[®]. Studies were performed later to verify that the carbonate salt of sevelamer carbonate (Renvela[®]) and the hydroxide salt of sevelamer (Renagel[®]) had equivalent actions *in vivo*.

Pharmacokinetic studies were performed with radiolabeled sevelamer hydrochloride to determine the amount of sevelamer hydrochloride that was absorbed. *In vivo* studies in rats given [³H]-Renagel[®] (sevelamer hydrochloride) (215 mg/kg) (Plone M.A. et al 2002) and dogs given [³H]-Renagel[®] (120 mg/kg) show that [³H]-Renagel[®] is not absorbed into the body and excreted entirely into the feces (Rosenbaum, D.P., 1997).

Human Studies

Human absorption of [¹⁴C]-sevelamer hydrochloride was investigated in a study of seven adults. No [¹⁴C]- sevelamer hydrochloride was detected in the whole blood of any subject at any time during the study. A very small amount (0.2 percent or less) of the administered dose (2.325 g of [¹⁴C]-labeled Renagel[®]) was recovered in the urine of the seven subjects. The mean percent of [¹⁴C]- sevelamer hydrochloride in the feces was 99.57 percent for all of the subjects. The results of this study confirm the results of the animal studies that sevelamer hydrochloride at this dose is not absorbed when administered orally (Plone, M.A. et al., 2002).

Toxicology

1. Colesevelam Hydrochloride (Welchol[®])

Animal Studies

There are no single-dose, acute toxicity data for colesevelam hydrochloride (Welchol[®]). In one chronic study, dogs (6/sex/group) were dosed at 0.2, 0.67, and 2.0 g/kg/day of colesevelam hydrochloride (Welchol[®]), for a minimum of 13 weeks, and no overt or dose-limiting toxicity was seen. Similarly, when rats were treated with colesevelam hydrochloride (Welchol[®]) at doses of 0.2, 1.2, or 2.4 g/kg/day for 26 weeks, no adverse clinical signs were seen, although vitamin E consistently was lower in both male and female rats. In addition, male rats had decreased vitamin D levels compared to the control group at week 26. Based upon the above data, the no observable adverse effect level (NOAEL) for six months of dietary exposure to colesevelam hydrochloride (Welchol[®]) was 0.2 g/kg/day (Daiichi Sankyo, Inc., February 24, 2009).

The toxicity of colesevelam hydrochloride (Welchol[®]) was studied in rats at doses of 0.3, 1.5, and 3.0 g/kg/day for a minimum of 92 days. Toxicity was noted primarily in male rats exposed to colesevelam hydrochloride (Welchol[®]) at a dose of 3.0 g/kg/day for

90 days, where 8 of 10 male rats were found dead or were euthanized before the end of the study. Based upon macroscopic and microscopic evidence, death was most likely due to primary hemorrhage or secondary effects of hemorrhage, such as anemia and tissue hypoxia. No such evidence of hemorrhage was found in female rats. Vitamin E levels were lower than the control values at termination for the 3.0 g/kg/day dose group in both male and female rats. Vitamins A and D significantly were decreased from the basal control values at week 13 for the high-dose male group. Since the levels of the fat soluble vitamins A, D, and E were decreased, it is likely that vitamin K was also decreased, although it was not measured. It is believed that the hemorrhage was not caused by a *direct* effect of colestevam hydrochloride (Welchol[®]), because it is not absorbed from the GI tract, but rather an *indirect* effect of the drug resulting in interference with the absorption of vitamin K, a fat soluble vitamin.

To prove that the hemorrhage from the colestevam hydrochloride (Welchol[®]) treatment was caused by a vitamin K deficiency in rats, vitamin K was given to rats treated with colestevam hydrochloride (Welchol[®]), and the hemorrhage reversed (Daiichi Sankyo, Inc., February 24, 2009).

Bile acid sequestrants, such as colestevam hydrochloride (Welchol[®]), are known to interfere with the absorption of the fat soluble vitamins A, D, E, and K (Vroonhof et al., 2003). Because vitamin K is required for production of functional coagulation factors, interference with the production of clotting factors can lead to a hemorrhagic syndrome. Therefore, it is believed that colestevam hydrochloride (Welchol[®]) interfered with the absorption of vitamin K, which led to the hemorrhagic syndrome in the male rats. Based upon the above data, the NOAEL for this three-month study was 0.3 g/kg/day (Daiichi Sankyo, Inc., February 24, 2009).

Daily dosing of colestevam hydrochloride (Welchol[®]) to beagles (4/sex/group) at doses of 0, 0.20, 0.60, and 2.0 g/kg/day for one year, was well tolerated, although some clinical pathology changes occurred. These include decreased phospholipids, red blood cells, hemoglobin, vitamin A, D, and E levels, as well as increased chloride ions and increased mean cell volume for both males and females. Reduced weight gain occurred for the females at the 2.0 g/kg/day dose. The NOAEL for colestevam hydrochloride (Welchol[®]) is 0.60 g/kg/day, based upon reduced weight gain in females at 2.0 g/kg/day, over the period of a year (Daiichi Sankyo, Inc., February 24, 2009).

Human Data

According to the Poisindex[®] System,¹² because colestevam hydrochloride (Welchol[®]) is not absorbed from the GI tract, the risk of toxicity is low. Doses up to 4.5 g/day, which are greater than the single unit dose packages of 3.75 g, have been well-tolerated, although GI effects such as constipation, indigestion, and nausea have been observed. Although overdose information is limited, it is anticipated that colestevam

¹² The Poisindex[®] System is a comprehensive database which identifies the toxicity of commercial, biological and pharmaceutical products.

hydrochloride (Welchol[®]) overdose may result in the extension of the GI effects observed at therapeutic doses (Poisindex, 2010).

2. Sevelamer Carbonate (Renvela[®])

Animal Data

Single-dose acute toxicity studies were performed for sevelamer hydrochloride (Renvela[®]). Because the poisoning of a child is an acute event, single-dose studies are the most relevant type of toxicology study to perform when studying poisoning. A single dose (1.0 or 2.0 g/kg) of sevelamer hydrochloride was administered orally to rats (5/sex/group), and the animals were observed for 14 days. Following treatment, no deaths were observed in any group. Furthermore, no abnormalities were found at autopsy. Therefore, Genzyme concluded that the maximum tolerated dose of sevelamer hydrochloride in rats following a single oral administration was greater than 2.0 g/kg. This led to a second single dose acute toxicology study where one dog of each sex was given 2.0 or 4.0 g/kg sevelamer hydrochloride and clinical signs were investigated for 14 days. The only clinical sign noted was vomiting of the sevelamer hydrochloride 1 to 1.5 hours after administration by all animals, except males in the low-dose group. The drug, which was vomited, was readministered to the dogs, and no further vomiting occurred. Consequently, it was concluded that the maximum tolerated dose of sevelamer hydrochloride in dogs, after single, oral-dose administration, was 4.0 g/kg or higher (Genzyme Corporation, March 6, 2009).

Another toxicity study was performed in the rat (5/sex/group) at dose levels of 10.0, 15.0, or 20.0 g/kg/day, using sevelamer carbonate (Renvela[®]) mixed with rat chow over a 24-hour dosing interval. The rats were euthanized following a 14-day observation period, and tissues were collected. No unscheduled deaths or clinical signs were observed following treatment with 20.0 g/kg/day of sevelamer carbonate (Renvela[®]). Based on the experimental conditions of the study, it was concluded that the NOAEL for sevelamer carbonate (Renvela[®]), administered by dietary admixture over a 24-hour period, was 20.0 g/kg/day (Genzyme Corporation, March 6, 2009). Genzyme performed a calculation using a body surface area ratio for a 25-pound child and the NOAEL of 20.0 g/kg, and determined that the child would have to ingest approximately 32.5 g of sevelamer carbonate (Renvela[®]) or the equivalent of the contents of thirteen 2.4 g packages of sevelamer carbonate (Renvela[®]) to reach the 20 g/kg amount that was given to the rat. It is unclear whether safety factors were used in this calculation to account for interspecies variability.

Sevelamer carbonate (Renvela[®]) was administered orally to rats (15/sex/group), in their diet, at doses of up to 10 g/kg/day for one, three, and six months and to beagles (2/sex/group) in capsules for one, three, and 12 months at doses of up to 2 g/kg/day. Sevelamer carbonate (Renvela[®]) produced minimal toxicity. In rats, sevelamer carbonate (Renvela[®]) produced a decrease in fat-soluble vitamin E and decreased levels of fat-soluble vitamins D and K at high doses only (4.5–10 g/kg/day). Focal hemorrhages caused by these decreased fat-soluble vitamin levels have been observed only in the high-

dose group (4.5–10 g/kg/day) in male rats. These doses represent 60 to 140 times the maximum projected human dose of 75 mg/kg/day (Burke, S.K., 2000).

Human Data

According to Genzyme, there are no reports of overdose with sevelamer. Staff also searched the medical literature and did not find any cases of sevelamer carbonate (Renvela[®]) poisoning in humans.

Clinical Studies

1. Colesevelam Hydrochloride (Welchol[®])

The safety and efficacy of colesevelam hydrochloride (Welchol[®]) have been demonstrated in numerous clinical trials. The colesevelam hydrochloride (Welchol[®]) clinical trials include: (1) a randomized, double-blind evaluation of the safety and tolerance of single and multiple oral doses of 0.42, 1.7, or 5.1 grams of colesevelam hydrochloride (Welchol[®]) in normal subjects; (2) a randomized, double-blind, placebo-controlled evaluation of colesevelam hydrochloride (Welchol[®]) in lowering serum cholesterol in patients with primary hypercholesterolemia (PHCL); (3) another randomized, double-blind, placebo-controlled evaluation of colesevelam hydrochloride (Welchol[®]) in patients with PHCL; (4) a randomized, double-blind, placebo-controlled trial of once-per-day versus split-dosing of colesevelam hydrochloride (Welchol[®]) in patients with PHCL; (5) an extended-use study of colesevelam hydrochloride (Welchol[®]) in patients with PHCL; (6) an open-label, fixed dose, safety trial of colesevelam hydrochloride (Welchol[®]) tablets in normal volunteers; (7) a randomized double-blind placebo-controlled trial of once-per-day versus split-dosing of colesevelam hydrochloride (Welchol[®]) in patients with PHCL; and (8) studies with other cholesterol-lowering agents or drugs, in which colesevelam hydrochloride (Welchol[®]) may interfere with their absorption. The most frequently observed chronic adverse effects of colesevelam hydrochloride (Welchol[®]) in these human clinical trials included: constipation, indigestion, nausea, and flatulence (Daiichi Sankyo, Inc., February 24, 2009).

The efficacy and safety of colesevelam hydrochloride (Welchol[®]) were tested in the pediatric population of patients (ages 10–17) with hereditary high cholesterol. The dose given to the children was colesevelam hydrochloride (Welchol[®]) 1.875 g/day or 3.75 g/day, which represents the amount of drug in the unit dose packages. Colesevelam hydrochloride (Welchol[®]) significantly lowered LDL-cholesterol levels in children. The most common drug-related adverse events were gastrointestinal in nature, including diarrhea, nausea, vomiting, and abdominal pain. There were no deleterious effects of colesevelam hydrochloride (Welchol[®]) on adolescent growth or maturation (Stein, E.A. et al., 2010).

2. Sevelamer Carbonate (Renvela[®])

The safety and efficacy of sevelamer carbonate (Renvela[®]) in adult chronic kidney disease patients have been examined in numerous clinical trials, which include: (1) one double-blind, cross-over study with two 8-week treatment periods using sevelamer carbonate (Renvela[®]) tablets in hemodialysis patients (n=79); (2) one open-label, cross-over study with two 4-week treatment periods using sevelamer carbonate (Renvela[®]) in hemodialysis patients (n=31); (3) one randomized, open-label 24-week study using sevelamer carbonate (Renvela[®]) powder dosed once per day with the largest meal in hemodialysis patients (n=141); and (4) one open-label, single-arm, 8-week dose titration study using sevelamer carbonate (Renvela[®]) tablets in chronic kidney disease patients (n=49) not on dialysis. The most frequently observed chronic adverse effects encountered in the clinical trials of sevelamer carbonate (Renvela[®]) included: nausea, constipation, diarrhea, vomiting, abdominal pain, and flatulence. Similar side effects were encountered in clinical trials in the pediatric population (ages 0–17 years). The chronic adverse effects observed during the post-marketing phase are very similar to the adverse effects encountered during the clinical trials (Genzyme Corporation, March 6, 2009).

Sevelamer carbonate (Renvela[®]) (5.4 g/day) was also evaluated for eight weeks in a randomized, cross-over trial with 40 pediatric patients (ages 11 months to 18 years). The adverse events associated with sevelamer carbonate (Renvela[®]) include: abdominal pain (3 percent), diarrhea (3 percent), nausea (6 percent), vomiting (3 percent), muscle cramps (6 percent), headache (3 percent), hyperparathyroidism (9 percent), metabolic acidosis (19 percent), and hypocalcaemia (3 percent) (Pieper et al., 2006). In addition, a 19-month-old girl was treated with sevelamer carbonate (Renvela[®]) (130 mg/kg/day) for elevated serum phosphate levels for five days, and no adverse effects were noted (Storms et al., 2006). Sevelamer carbonate (Renvela[®]) is associated with “generally tolerable adverse effects that are chiefly GI in nature” (Sprague, S.M., 2007).

Post-Marketing Experience – CPSC Databases

1. Colesevelam Hydrochloride (Welchol[®])

One report of acute ingestion of colesevelam hydrochloride (Welchol[®]) tablets has been found in the NEISS database. Eleven-month-old twin boys were taken to the emergency room after they possibly ingested colesevelam hydrochloride (Welchol[®]) and another drug. Five to six colesevelam hydrochloride (Welchol[®]) tablets were missing, and a colesevelam hydrochloride (Welchol[®]) tablet was found in one boy’s mouth. It is not clear exactly how many pills were ingested by the boys, but they were treated and released the same day (O’Brien, October, 2010).

A four-year-old child was prescribed colesevelam hydrochloride (Welchol[®]) off-label¹³ by her doctor to treat pruritis (itching due to irritation of nerve endings) secondary to Byler disease (liver disease). At that time, she was also prescribed ADEK pediatric

¹³ Off-label is when a drug is used for a particular indication, even though the drug has not been approved by the U.S. Food and Drug Administration for that indication.

vitamin drops to compensate for a potential loss of vitamins A, D, E, and K caused by colesevelam hydrochloride (Welchol[®]) treatment. After taking colesevelam hydrochloride (Welchol[®]) for 19 months, the patient was admitted to the hospital with GI bleeding and a prolonged prothrombin time (PT). (This demonstrates that her functional coagulation factors were low. PT is a test of functional coagulation factor levels.) She was treated with vitamin K, taken off colesevelam hydrochloride (Welchol[®]), and released. One month later, following a fall, she was diagnosed with an intracranial hemorrhage and died from complications. Staff believes that her coagulation factors should have returned to normal levels after stopping colesevelam hydrochloride (Welchol[®]) treatment. However, her liver disease also contributed to the potential for bleeding since coagulation factors are produced by the liver. Apparently, the patient no longer had been taking the ADEK vitamin supplements prescribed for her at the time because the vitamin supplement had become unavailable from the manufacturer. It was reported that the intracranial hemorrhage was either due to, or exacerbated by, an effect of chronic colesevelam hydrochloride (Welchol[®]) treatment on vitamin K absorption and the lack of the vitamin supplement (Daiichi Sankyo, Inc., February 24, 2009).

2. Sevelamer Carbonate (Renvela[®])

As mentioned previously, there are no reports of overdoses with sevelamer carbonate (Renvela[®]) in humans (Genzyme Corporation, March 6, 2009). A decreased incidence of gastrointestinal adverse events was observed in a clinical trial of sevelamer carbonate (Renvela[®]) compared to sevelamer hydrochloride (Renagel[®]) (Delmez, J. et al., 2007). Sevelamer hydrochloride (Renagel[®]) is being removed from the market and replaced with sevelamer carbonate (Renvela[®]) because there are fewer side effects with the carbonate salt as compared to the hydrochloride salt.

Post-Marketing Experience—Medwatch Reports from the Food and Drug Administration (FDA)

MedWatch is the U.S. Food and Drug Administration's (FDA's) program for reporting serious drug and medical device reactions, as well as product quality problems, therapeutic inequivalence/failures, and product use errors with human medical products. Although MedWatch data are useful to identify adverse events that occur while patients are taking medication, there are some limitations to the data: (1) FDA receives some adverse event and medication error reports directly from health care professionals (such as physicians, pharmacists, and nurses) and consumers (such as patients or family members); (2) there is no certainty that the reported event was actually due to the product because the FDA does not require that a causal relationship between a medication and an adverse event be proven, and; (3) often, reports do not contain enough detail to properly evaluate an event. In addition, the FDA does not receive all adverse event reports that occur with a certain product.

1. Colesevelam Hydrochloride (Welchol[®])

The CPSC received MedWatch reports from the FDA containing 151 distinct incidents from patients experiencing adverse events while taking colesevelam hydrochloride (Welchol[®]) between 2001 and 2010. One hundred and thirty patients were on other medications, so it is uncertain whether the adverse events reported were due to colesevelam hydrochloride (Welchol[®]) alone. Health Sciences staff reviewed the reports to exclude incidents where other medications may have caused the adverse event reported, resulting in 21 in-scope incidents¹⁴. Adverse events included GI effects (e.g., upset stomach, constipation, bloating) (7 out of 22) and muscle pain (4 out of 22). Also three patients had a problem swallowing the pills (3 out of 22) and another (1 out of 22) had chronic gall bladder disease. Adverse effects reported in the “other” category (7 out of 22) included throat cancer, increased blood pressure, elevated ALT¹⁵, rash, feeling “out of sorts,” death from natural causes, and cholesterol increase. Therefore, most incidents reported from MedWatch were gastrointestinal or involved muscle pain, which is to be expected, considering the adverse effects reported from clinical trials.

Of those treated with other medications and colesevelam hydrochloride (Welchol[®]), there were 23 reports (23 out of 130) of gastrointestinal disturbances, including ileus (bowel obstruction), abdominal pain, nausea, indigestion, fecal impaction, flatulence, constipation, diverticulitis, and esophageal burning. There were 29 cases (29 out of 130) of myopathy (muscle cramps or stiffness) or increased creatine phosphokinase (CPK) levels (CPK is an enzyme released into the bloodstream after muscle damage). Eleven patients (11 out of 130) had difficulty swallowing the colesevelam hydrochloride (Welchol[®]) tablets. Two patients (2 out of 130) reported acute renal failure. A 44-year-old female taking colesevelam hydrochloride (Welchol[®]) for 12 days was diagnosed with rhabdomyolysis, a disease where muscles breakdown and proteins released from the muscles can cause kidney damage. The patient had been on a statin drug, which can also cause rhabdomyolysis; so it is unknown whether she had kidney damage prior to taking colesevelam hydrochloride (Welchol[®]). Nonetheless, while on colesevelam hydrochloride (Welchol[®]), she experienced acute renal failure, and when colesevelam hydrochloride (Welchol[®]) was discontinued, her renal failure resolved. She was on other medications, as well. The other report of acute renal failure occurred in a female patient following one dose of colesevelam hydrochloride (Welchol[®]). However, no detailed information, such as the patient’s age, medical condition, or concomitant medications is known about this case; so it is difficult to establish whether colesevelam hydrochloride (Welchol[®]) was responsible for the incident.

2. Sevelamer Carbonate (Renvela[®])

The CPSC received 40 MedWatch reports from the FDA of distinct incidents from chronic kidney disease patients who were on dialysis and experienced adverse events while taking sevelamer carbonate (Renvela[®]) between 2006 and 2010. Thirty-five of these patients (35 out of 40) were taking other medications; so it is uncertain whether

¹⁴ One patient reported both GI and muscle effects as one incident report, resulting in 22 adverse events and 21 incidents.

¹⁵ Alanine transaminase is a liver enzyme which is released upon damage to the liver. Some medications also release ALT.

the adverse events reported in these patients were due to sevelamer carbonate (Renvela[®]) alone. Five of the 40 patients reporting to the FDA were treated with sevelamer carbonate (Renvela[®]) only. A 45-year-old male, treated with sevelamer carbonate (Renvela[®]) for several months, developed an intestinal obstruction and perforation and an abdominal fistula (abnormal opening in the stomach or bowel that allows the contents to leak), which were thought to be related to sevelamer carbonate (Renvela[®]) by his physician. An 80-year-old female (1 out of 5) experienced gastroenteritis following treatment with sevelamer carbonate (Renvela[®]) for two days. One patient (1 out of 5) experienced an exacerbation of his preexisting asthma and chronic obstructive pulmonary disease. One 65-year-old female on hemodialysis died from unknown causes after being treated with sevelamer carbonate (Renvela[®]). Another female, a 50-year-old with end-stage renal disease, and on dialysis, died from unknown causes following treatment with sevelamer carbonate (Renvela[®]). Because limited data was provided on these cases, it is not possible to assign any cause and effect relationship between the deaths and sevelamer carbonate (Renvela[®]) and these effects occurred after chronic use.

Of those treated with other medications, there were nine reports of GI disturbances, including abdominal pain, exacerbation of preexisting diverticulitis, constipation, bowel obstruction and perforation, gastroenteritis, vomiting, and nausea in these 35 patients. Based upon clinical trial data, these side effects are to be expected from patients treated with sevelamer carbonate (Renvela[®]).

Discussion

Overall, clinically relevant doses of colestevam hydrochloride (Welchol[®]) (up to 4.5 g/day) and sevelamer carbonate (Renvela[®]) (usual adult dose = 7.2 g/day) in humans are well-tolerated (Heller, D.P. et al., 2002; Burke, S.K. et al., 1997; Poisindex, 2010; and Drug Facts and Comparisons, 2010). The maximum daily dose of sevelamer carbonate (Renvela[®]) in adults is 14 g/day. Both drugs have been studied to some extent in pediatric populations. Colestevam hydrochloride (Welchol[®]) is used therapeutically at a dose of 3.75 g/day in children (10 to 17 years old) diagnosed with primary hypercholesterolemia. Radiolabeled drug studies in animals and humans have shown that these drugs are not absorbed from the GI tract. Therefore, it is unlikely that either drug will have any serious direct toxicity following ingestion. Adverse effects occurring during chronic dosing in clinical trials resulted in GI discomfort (nausea, vomiting, constipation, diarrhea, abdominal pain, and flatulence). If a child ingests colestevam hydrochloride (Welchol[®]) or sevelamer carbonate (Renvela[®]), toxic effects should be limited to mild to moderate GI discomfort and muscle pain.

While no acute animal toxicity data are available for colestevam hydrochloride (Welchol[®]), single doses of sevelamer carbonate (Renvela[®]) produced no toxicity in rats dosed at 2 g/kg and dogs dosed at 4 g/kg. However, chronic administration of colestevam hydrochloride (Welchol[®]) and sevelamer carbonate (Renvela[®]) resulted in hemorrhage in animals; and chronic administration of colestevam hydrochloride (Welchol[®]) resulted in hemorrhage in a 4-year-old child believed to be caused by interference with vitamin K absorption (Robinson et al., 1964; Vroonhof et al., 2003).

It is significant that it took a long duration of administration for the hemorrhage to develop in response to the drugs. Colesevelam hydrochloride (Welchol[®]) and sevelamer carbonate (Renvela[®]) were given to rats for three months and six months, respectively, prior to observing any hemorrhage. The four-year-old patient with Byler's disease took colesevelam hydrochloride (Welchol[®]) for 19 months before any toxicity (intracranial hemorrhage) was seen. In contrast, an acute administration of colesevelam hydrochloride (Welchol[®]) or sevelamer carbonate (Renvela[®]) will not have any influence upon clotting factor production, because it takes several days for enough altered clotting factors to be produced by the liver and have an effect.

Conclusions

Precise toxic doses have not been established for either colesevelam hydrochloride (Welchol[®]) or sevelamer carbonate (Renvela[®]). Overall, treatment with colesevelam hydrochloride (Welchol[®]) or sevelamer carbonate (Renvela[®]) is well tolerated (Heller, D.P. et al., 2002; Burke, S.K. et al., 1997), with gastrointestinal side effects seen at clinically relevant doses. If a child accidentally ingests colesevelam hydrochloride (Welchol[®]) or sevelamer carbonate (Renvela[®]), the potential for the occurrence of mild to moderate gastrointestinal discomfort, such as indigestion, constipation, nausea and vomiting, and muscle pain does exist (Burke 2000; Davidson 2000; Welchol[®] Tablet packet insert 2010). While chronic administration of colesevelam hydrochloride (Welchol[®]) or sevelamer carbonate (Renvela[®]) can result in a hemorrhagic syndrome by blocking vitamin K absorption, this effect will not occur after a single, accidental ingestion. Thus, both colesevelam hydrochloride (Welchol[®]) and sevelamer carbonate (Renvela[®]) powders lack the potential to cause serious illness or injury in an acute poisoning scenario.

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Tab C



**United States
CONSUMER PRODUCT SAFETY COMMISSION
4330 East West Highway, Bethesda MD 20814**

MEMORANDUM

Date: October 25, 2010

TO : Adrienne Layton, Pharmacologist
Directorate for Health Sciences

THROUGH: Gregory B. Rodgers, Ph.D., Acting Associate Executive Director
Directorate for Epidemiology

Kathleen A. Stralka, Division Director
Hazard Analysis Division

FROM : Craig W. O'Brien, Mathematical Statistician
Hazard Analysis Division

SUBJECT : Reported Incidents for Colesevelam Hydrochloride (Welchol[®]),
Sevelamer Carbonate (Renvela[®]), and Related Drugs, 2000–2009

This memo presents the results from searching U.S. Consumer Product Safety Commission (CPSC) databases and reviewing reports received from the U.S. Food and Drug Administration (FDA) for incidents associated with the drugs colesevelam hydrochloride (Welchol[®]) and sevelamer carbonate (Renvela[®]), to assist in assessing the toxicity of these substances. Also searched were data on the similar drugs Questran[®] and Colestid[®]. The databases searched were the Injury and Potential Injury Incident database (IPII); the National Electronic Injury Surveillance System database (NEISS); and the Death Certificates database (DTHS). The reports analyzed were from the FDA's MedWatch reporting system.

Database Searches

From 2000 through 2009, one incident was found for colesevelam hydrochloride (Welchol[®]). It involved twin boys, 11 months old, who possibly ingested Diltiazem[®] and/or colesevelam hydrochloride (Welchol[®]) in February of 2008. One of the boys had a colesevelam hydrochloride (Welchol[®]) tablet in his mouth, and the caregiver reported that five or six tablets were missing. The children were taken to the emergency room, treated, and released the same day.

From 2000 through 2009, no incidents were found in the CPSC databases related to Renvela[®].

From 2000 through 2009, no incidents were found in the CPSC databases related to Questran[®] or Colestid[®].

MedWatch Reports

The FDA provided CPSC staff with 203 reports of 151 distinct incidents of adverse events associated with colesevelam hydrochloride (Welchol[®]) reported through the MedWatch system. Health Sciences staff reviewed the reports to exclude incidents where other medications may have caused the adverse event reported, resulting in 21 in-scope incidents. The general area of the effect for the cases is detailed in Table 1.

Table 1: MedWatch Reports by Area of Adverse Effect

Area	Count
Gastrointestinal	7
Muscle	4
Problems Swallowing	3
Gall Bladder	1
Other	7
Total	21*

**One incident reported gastrointestinal and muscle effects, so 22 adverse effects.*

Effects reported in the “other” category included throat cancer, blood pressure increase, elevated ALT,¹⁶ rash, feeling “out of sorts,” death from natural causes, and cholesterol increase.

The FDA also provided CPSC staff with 40 reports of 40 distinct incidents of adverse events associated with Renvela.[®] Health Sciences staff reviewed the reports to exclude incidents where other medications may have caused the adverse event reported, resulting in five in-scope incidents. In two cases, the patients died of unknown causes after being treated with Renvela.[®] One of the decedents was a 50-year-old female with end-stage renal disease, and the other was a 65-year-old female on hemodialysis. One patient experienced intestinal problems possibly related to Renvela.[®] One patient experienced gastroenteritis that was not Renvela[®]-related in her physician’s opinion. One patient with asthma and chronic obstructive pulmonary disease suffered severe breathing problems while on Renvela.[®]

Methodology

The CPSC databases were searched in January 2010, for product codes 1931 (Tablet or capsule drugs), 1932 (Other drugs or medications), and 1929 (Drugs or medications, not specified). Incidents with narratives mentioning Welchol,[®] Colesevelam,[®] or Cholestigel[®] were assumed to be colesevelam hydrochloride (Welchol[®])-related. Incidents with narratives mentioning Renvela,[®] Sevelamer,[®] or Renagel,[®] were assumed to be sevelamer carbonate (Renvela[®])-related. Incidents with narratives mentioning Cholestyramine,[®] Questran,[®] Prevalite,[®] Colestipol,[®] or Colestid[®] were assumed to be related to either Questran[®] or Colestid.[®] The keywords used for these searches were provided by Health Sciences staff. The one incident found was in the NEISS database.

¹⁶ Alanine transaminase.

Deaths

CPSC staff purchases death certificates from all 50 states, New York City, the District of Columbia, and some territories. Only those certificates in certain E-codes (based on the World Health Organization's International Classification of Diseases ICD-10 system) are purchased. Subsequently, these death certificates are examined for product involvement before being entered into the CPSC's death certificate database. The result is neither a statistical sample nor a complete count of product-related deaths, nor does it constitute a national estimate. The database provides only counts for product-related deaths from a subset of E-codes. For this reason, these counts tend to be underestimates of the actual numbers of product-related deaths. Death certificate collection from the states also takes time. As of June 2009, the Death Certificates database was considered 98 percent complete for 2006; 84 percent complete for 2007; 62 percent complete for 2008; and 17 percent complete for 2009.

Injury or Potential Injury Incident Database (IPII)

IPII is a CPSC database containing reports made to the Commission of injuries or potential injuries. These reports come from news clips; consumer complaints received by mail or through the CPSC's telephone hotline or website; Medical Examiners and Coroners Alert Program (MECAP) reports; letters from lawyers; and similar sources. While the IPII database does not constitute a statistical sample, it can provide CPSC staff with guidance in investigating potential hazards. Because cases in this database may come from a variety of sources, some cases may be listed multiple times. To obtain a more accurate count of the number of reported incidents associated with each product, the cases were reviewed to eliminate duplicates.

National Electronic Injury Surveillance System (NEISS)

The estimate of emergency department-treated injuries was derived from NEISS, which is a probability sample of approximately 100 U.S. hospitals having 24-hour emergency departments (EDs) and more than six beds. NEISS collects injury data from these hospitals. Coders in each hospital code the data from the ED record, and subsequently, the data is transmitted electronically to the CPSC. Because NEISS is a probability sample, each case collected represents a number of cases (the case's *weight*) of the total estimate of injuries in the United States. Different hospitals carry different weights, based upon stratification by their annual number of emergency department visits (Schroeder and Ault, 2001).

MedWatch

MedWatch is a volunteer reporting system started by the FDA in 1993. It consists of voluntary reports of adverse events from health care professionals, consumers, and patients. These reports are submitted online, by fax, over the phone, and through the mail. While the system is mainly focused on prescription drugs, it also contains reports on other products under FDA jurisdiction, including dietary supplements, cosmetics, medical foods, and infant products.

Tab D



**United States
CONSUMER PRODUCT SAFETY COMMISSION
4330 East West Highway, Bethesda MD 20814**

MEMORANDUM

Date: November 22, 2010

TO:

Adrienne Layton, Ph.D., Project Manager
Directorate for Health Sciences

THROUGH:

Erlinda Edwards, Acting Associate Executive Director
Directorate for Engineering Sciences

Robert B. Ochsman, Ph.D., Director
Division of Human Factors

FROM:

Catherine A. Sedney, Engineering Psychologist
Division of Human Factors

SUBJECT:

Petitions for Exemption from PPPA Requirements for Child-Resistant
Packaging (PP 10-1 and PP 10-2)

Background

Daiichi Sankyo, Inc. and Genzyme Corporation have petitioned the Commission to exempt powder formulations of colesevelam hydrochloride (Welchol[®]) and sevelamer carbonate (Renvela[®]), respectively, from the child-resistant packaging requirements specified in 16 CFR 1700. The staff has addressed the two petitions in a single briefing package because the chemical structures of the two products are similar, and both are powder formulations in unit-dose packets. The following sections present basic information on the products and summarize the toxicology and epidemiology reviews performed by Health Sciences (HS) and Hazard Analysis (HA) staff.

Product Descriptions

As described in the petition, colesevelam hydrochloride (Welchol[®]) is a bile acid sequestrant used to reduce elevated LDL cholesterol levels in patients with primary hypercholesterolemia and to improve control of blood glucose levels in adults with type 2 diabetes (Daiichi Sankyo, Inc., February 24, 2009). The proposed powder form will be provided in unit-dose packages. The smaller dose will contain 1.875 grams (0.066 oz) of colesevelam hydrochloride (Welchol[®]) in 2.60 grams of powder (0.092 oz); the larger

size will consist of 3.75 grams (0.132 oz) of colestevam hydrochloride (Welchol[®]) in 5.20 grams (0.183 oz) of powder.

Sevelamer carbonate (Renvela[®]) is a phosphate binder used in the control of serum phosphorus in patients with chronic kidney disease (CKD) who are on dialysis. It was developed as an alternative to sevelamer hydrochloride (Renagel[®]), which has the same active component and has been more widely researched. Genzyme's proposed powder formulation will be provided in packets containing 2.40 grams (0.085 oz) sevelamer carbonate, along with agents intended to improve its taste, color, and texture (Genzyme Corporation, March 6, 2009).¹⁷ Both products contain citrus flavoring and a noncaloric sweetener. They are intended to be mixed with water and taken before meals.

Toxicological Review

HS staff's review of the available information on the products indicates that neither drug has serious direct toxicity because neither is absorbed from the gastrointestinal tract (Layton, November 1, 2010). Citing animal studies, HS staff reports that an acute dose of 20 g/kg (0.32 oz/lb) of sevelamer carbonate (Renvela[®]) was not toxic. Only chronic-dose rather than acute-dose studies of colestevam hydrochloride (Welchol[®]) have been reported; doses up to 2 g/kg daily for one year have resulted in only minor toxicity in dogs. Long-term use of either sevelamer carbonate (Renvela[®]) or colestevam hydrochloride (Welchol[®]) can affect the absorption of fat-soluble vitamins, such as vitamin K. However, per HS staff's assessment, these effects would develop over weeks and are not a concern in an acute ingestion. Adverse effects reported in clinical trials indicate that if a child ingests either colestevam hydrochloride (Welchol[®]) or sevelamer carbonate (Renvela[®]), toxic effects should be limited to mild to moderate gastrointestinal discomfort (e.g., nausea, constipation, diarrhea, vomiting, abdominal pain, and flatulence).

Incident Data

Epidemiology staff reviewed the CPSC databases¹⁸ for incidents involving colestevam hydrochloride (Welchol[®]) and sevelamer carbonate (Renvela[®]), as well as the similar drugs Questran[®] and Colestid[®] (O'Brien, October 25, 2010). The review identified no instances involving sevelamer carbonate (Renvela[®]) and one report involving colestevam hydrochloride (Welchol[®]) between 2000 and 2009. In the latter, 11-month-old twins may have ingested colestevam hydrochloride (Welchol[®]) tablets in combination with another drug. It is unknown how many tablets may have been ingested. It was reported that five or six colestevam hydrochloride (Welchol[®]) tablets were missing, and one of the twins had a tablet in his mouth. The boys were taken to the emergency department, treated, and released the same day.

¹⁷ The firm states that it may seek marketing approval for 1.60-g (0.06-oz) packages in the future. Also, since the petition was filed, Genzyme Corporation has begun marketing sevelamer carbonate in 0.80-gm (0.03-oz) unit-dose packages.

¹⁸ Injury and Potential Injury Incident database (IPII), the National Electronic Injury Surveillance System database (NEISS), and the Death Certificates database (DTHS).

CPSC staff also reviewed adverse event incidents associated with the two drugs that were reported to the U.S. Food and Drug Administration's (FDA's) MedWatch¹⁹ program (Layton, November 1, 2010; O'Brien, October 25, 2010). HS staff screened the reports to identify those patients taking only colesevelam hydrochloride or sevelamer carbonate. This resulted in 21 reports (of 151) related to colesevelam hydrochloride (Welchol[®]) and five reports (of 40) related to sevelamer carbonate (Renvela[®]). In addition to the expected gastrointestinal effects described above, reports related to those taking colesevelam hydrochloride included one or more instances of effects such as muscle pain, diverticulitis, allergic reaction, and a death thought to be unrelated to the drug. Regarding those using colesevelam hydrochloride, the reports included effects such as intestinal obstruction and perforation; gastroenteritis; exacerbation of pre-existing asthma and chronic obstructive pulmonary disease; and two deaths (one a patient on hemodialysis and the other a patient with end-stage renal failure) due to unknown causes.

Each of these events involved ill adults who typically used the product regularly over time. As such, they may not be relevant to the risks of acute ingestion among children younger than five years of age. Further, MedWatch does not include reports of all adverse effects, nor do the incidents reported constitute a representative sample of patients using the products. HS staff cautions that adverse event reports are filed by patients and family members, as well as health care professionals, and reports often lack sufficient detail for evaluation. Although useful, a causal relationship cannot be inferred from these data.

In addition to the above, HS staff discussed the death of a four-year-old child related to use of colesevelam hydrochloride (Welchol[®]) that was reported by Daiichi Sankyo, Inc. The child was prescribed the drug off-label to treat pruritis.²⁰ HS staff's summary of the case (Layton, November 1, 2010) is presented below:

“At that time she was also prescribed ADEK pediatric vitamin drops²¹ to compensate for a potential loss of vitamins A, D, E, and K caused by colesevelam hydrochloride (Welchol[®]) treatment. After taking colesevelam hydrochloride (Welchol[®]) for 19 months, the patient was admitted to the hospital with gastrointestinal bleeding and her prothrombin time (PT) was markedly elevated. (This demonstrates that her functional coagulation factors were low. PT is a test of functional coagulation factor levels.) She was treated with vitamin K, taken off colesevelam hydrochloride (Welchol[®]) and released. One month later, following a fall, she was diagnosed with an intracranial hemorrhage and died from complications. Staff believe that her coagulation factors should have returned to normal levels after stopping colesevelam hydrochloride (Welchol[®]) treatment. However, her liver disease also contributed to the potential for bleeding since coagulation factors are produced by the liver. Apparently, the patient no longer

¹⁹ MedWatch is the FDA's program for reporting a [serious adverse event](http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm), product quality problem, product use error, or therapeutic inequivalence/failure that may be associated with the use of an FDA-regulated drug, biologic, medical device, dietary supplement, or cosmetic. (See <http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm>. Accessed 11/3/2010.)

²⁰ An itching condition related to the liver disease that was the main cause of the child's illness.

²¹ A supplement containing the fat-soluble vitamins A, D, E, and K.

had been taking the ADEK vitamin supplements prescribed for her at this time since the vitamin supplement had become unavailable from the manufacturer. It was reported that the intracranial hemorrhage was either due to, or exacerbated by, an effect of chronic colesevelam hydrochloride (Welchol[®]) treatment on vitamin K absorption and the lack of the vitamin supplement.”

Both firms cite two factors in support of their requests. The first is the low toxicity of their products, which is supported by HS staff’s assessment. The second is that the products are unpalatable because of their gritty texture, making it unlikely that children would ingest them in large quantities. In addition, Genzyme Corporation contends that a child-resistant package that requires scissors to open may decrease patients’ adherence with their medication regimen. Human Factors staff was asked to assess the latter two claims with emphasis on the likelihood that children under five would ingest significant quantities of these drugs in powder form.

Discussion

Palatability and Likelihood of Powder Ingestion

Children ingest hazardous amounts of a variety of substances that are unpalatable, including powder-like products such as drain cleaner, dishwasher soap, and pesticides. Flavor, odor, and texture thus have little apparent effect in determining whether a product will be ingested, although studies using bitter additives have shown that flavor can influence the quantity ingested (e.g., Sibert & Frude, 1991; cf. Barone, January 24, 1990). In this case, palatability is unlikely to be the main deterrent to ingestion. Both products contain sweeteners and flavoring. Daiichi Sankyo, Inc. provided samples of its powdered colesevelam hydrochloride (Welchol[®]). Despite the firm’s claims, the author found it to be acceptable, particularly compared to many substances that children routinely put in their mouths. It is uncertain that children generally would find it unpleasant. In contrast, the powder form, as well as the packaging and the quantities available in the unit-dose packets, are likely to have a greater effect in limiting the total amount a child might ingest.

The staff addressed the topic of powder ingestions in a 1995 briefing package developed to respond to a similar request for exemption for a powdered dietary supplement, distributed in package amounts of up to 450 g (1 lb) that contained iron (Ferrante, March 17, 1995). Ingestion of iron can be fatal, and iron-containing substances are regulated under the Poison Prevention Packaging Act (PPPA).²² The Commission granted the exemption based on staff’s recommendation. The following points, drawn from the Health Sciences (Inkster, February 15, 1995) and Human Factors (Sedney, February 16, 1995) staff memos, along with more current sources, where available, summarize the results of that review regarding powder:

²² Child-resistant packaging is required for products containing 250 mg or more of elemental iron in a concentration of 0.025 percent or more on a weight-to-volume basis for liquids and 0.05 percent on a weight-to-weight basis for non-liquids [(16 CFR § 1700.14(a)(12–13)].

- Ingestion of large amounts of powder is rare relative to other formulations. It occurs primarily in pica, an eating disorder characterized by compulsive eating of inedible substances, including dirt, baking soda, and talc, as well as non-powder items (e.g., Rainville, 1998, and Sheahan, Page, Kemper & Suarez, 1988).
- With the exception of caustics, such as dishwasher detergent (e.g., Bertinelli, Hamill, Mahadevan & Miles, 2006), the primary risk of powdered products is aspiration, rather than ingestion. Powder form is a characteristic considered to lower the “potential toxicity” of a substance (Done, 1970),²³ and use of powdered household chemicals, rather than liquids, is considered a preventive measure (Writer, 1993).
- The powder form itself is likely to be a deterrent to ingestion in significant quantities. It must be eaten in small amounts at a time to allow the absorption of sufficient saliva before it can be swallowed. Too much placed in the mouth, or swallowing before it absorbs sufficient moisture, may result in aspiration or dry powder catching in the throat, causing coughing. Either outcome is unpleasant and would tend to inhibit, or at least delay, repeated attempts. Childhood poisoning incidents involve interruptions in direct visual supervision that typically are brief. The time needed to ingest powder successfully (i.e., without coughing or aspirating) increases the opportunity for adult intervention.
- Typical motivations, behaviors, and play patterns of the under-five age group tend not to support large-volume powder ingestion. Hunger is one possible motivation for a child to try to eat a powder. However, powdered food items are relatively uncommon and difficult to eat; it seems likely that children who have access to a powdered product may also have access to foods that, based on their experience, are more appealing.
- Children may also be motivated by curiosity to taste powdered products, or may incorporate them into role-play or pretend activities. Older preschool-aged children have been observed to test powder by dipping their fingers into it, then licking it from their fingers, or licking it from the table where it was placed (Block Drug Company, 1976). Either method is time-consuming and unlikely to result in ingestion of a significant amount in a short time.

²³ Done indicates that although, in general, only gross estimates can be made of the dose a child may have ingested, “experience has shown that liquids or pelleted materials are more likely to be ingested in large quantity than powders ... (p. 571).”

- Children of this age may also try adding a powder to liquid in imitation of an adult. They are unlikely to stir it thoroughly, however, which would result in a grainy or lumpy mixture. This quality is unfamiliar and unexpected in beverages, and may be perceived as unpleasant. Children may taste or even drink it, but not in large amounts. Younger toddlers tend to use less sophisticated techniques. For example, a child of this age may upend a container of powder into her mouth, or if enough is available, take a fistful and push it into her mouth with her palm. Both methods are awkward, and the child will spill much of the substance.

In addition to these factors, which apply to powders in general, there are features specific to the products in question. The iron-containing powdered food supplement that the staff evaluated in 1995 was sold in a cylindrical one-pound package with a plastic lid, similar in size and shape to a small coffee can or container of drink mix. This type of lid is relatively easy to remove, and the wide container opening makes it easy to access the entire contents at once. In contrast, the subject products are provided in small,²⁴ foil-lined packets containing individual doses. The sevelamer carbonate (Renvela[®]) package is very easy to tear at the notch, but not elsewhere. That it must be opened at this precise location makes it less accessible, especially to younger children, who have the highest frequency of exposure to household poisons.²⁵ The colesevelam hydrochloride (Welchol[®]) package has no notch, and its resistance to tearing seems uniform; it is somewhat more difficult to open than is the sevelamer carbonate (Renvela[®]) package at the notch. Although both packages tear easily enough to be opened by children under five, the fine motor skills and coordination of this age group are still developing. If they are able to open the packages, children, especially those two years old and younger, are likely to spill much of the powder. Alternatively, younger toddlers may mouth or chew the packages, and thereby ingest small, but not large, amounts.

Patient Compliance

Genzyme currently packages sevelamer carbonate (Renvela[®]) in a child-resistant packet that must be cut open with scissors. The medication must be taken with each meal. The firm contends that the need to have scissors at each meal is impractical, and the inconvenience may reduce patient compliance. Human Factors staff concurs that this is a possibility (although it seems unlikely that a package that requires scissors would be the only child-resistant option). Research on the effectiveness of warnings supports the firm's premise that the "cost of compliance" with prescribed treatments would influence the likelihood of compliance (Kalsher & Williams, 2006). Common costs include time, money, effort, discomfort, and inconvenience. Not surprisingly, the higher the perceived cost, the lower the likelihood of compliance. In addition to the potential gastrointestinal side effects mentioned previously, there appear to be other issues related to patient adherence to treatment regimes with phosphate binders (e.g., price, number of pills).²⁶

²⁴ Renvela[®] packages measure approximately 91.0 mm x 54.0 mm (3.6 in x 2.1 in), and Welchol[®] packages are approximately 104.0 mm x 75.0 mm (4.1 in x 3.0 in).

²⁵ Two years is the modal age among children under five involved in unintentional poisoning incidents.

²⁶ See <http://www.renalandurologynews.com/new-phosphate-binders-on-the-horizon/article/140045/> for a related discussion. Accessed 11/22/2010.

Given the factors that might affect those with chronic kidney disease who have chosen to use the powder product, it is impossible to determine that a non-child-resistant package necessarily would improve patient adherence. However, the inconvenience of opening a package with scissors at each meal adds an ongoing cost where compliance already may be a matter of concern. Because of the low toxicity of the product and the powder formulation, the introduction of even a small additional cost seems unnecessary.

Although the child-resistant version of their packaging also requires the use of scissors, the makers of colesevelam hydrochloride (Welchol[®]) did not include patient compliance as an issue in their request. As is true with sevelamer carbonate (Renvela[®]), despite the inconvenience of scissors, the choice of a product that can be mixed in a drink may be preferable for those who dislike taking pills. However, the regime and packaging may be less important factors in this case. Rather than being required with each meal, colesevelam hydrochloride (Welchol[®]) can be taken once or twice daily, and use of scissors may be less burdensome.²⁷ Nonetheless, the firm's child-resistant packaging, even if minimally inconvenient, appears to be unnecessary based on colesevelam hydrochloride's (Welchol[®]) low toxicity and the negligible risk that children will ingest it in significant quantities.

Conclusions

The staff's past and current reviews indicate that there is little risk that healthy children under age five will ingest large amounts of a powdered product. The risk of such incidents with either colesevelam hydrochloride (Welchol[®]) or sevelamer carbonate (Renvela[®]) is further lowered because each product is provided in a single-dose package that would make it difficult for children to access the contents in significant quantities. The sevelamer carbonate (Renvela[®]) treatment regime requires that the patient mix the drug with water and drink it before every meal on a consistent basis. The inconvenience of Genzyme's child-resistant packaging, which requires scissors to open, may exacerbate problems with patient compliance. The makers of colesevelam hydrochloride (Welchol[®]) did not raise the issue, suggesting it is of less concern. In both cases, however, child-resistant packaging seems unnecessary based on the low toxicity of the products, and the low likelihood that children will ingest them in large amounts.

²⁷ See "Dosage and Administration of Welchol" (http://www.welchol.com/hcp/about_welchol/dosage_administration.html). Accessed 11/22/2010.

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Tab E



**United States
CONSUMER PRODUCT SAFETY COMMISSION
4330 East West Highway, Bethesda MD 20814**

MEMORANDUM

Date: November 3, 2010

TO : Adrienne R. Layton, Ph.D.
Project Manager for Colesevelam Hydrochloride (Welchol[®])/Sevelamer Carbonate (Renvela[®])
Directorate for Health Sciences

THROUGH: Gregory B. Rodgers, Ph.D., Associate Executive Director
Directorate for Economic Analysis
Deborah V. Aiken, Ph.D., Senior Staff Coordinator
Directorate for Economic Analysis

FROM : Jill L. Jenkins, Ph.D., Economist
Directorate for Economic Analysis

SUBJECT : Colesevelam Hydrochloride (Welchol[®]) and Sevelamer Carbonate (Renvela[®]) Petitions for Exemption from the Child-Resistant Packaging Requirements of the Poison Prevention Packaging Act—Economic Considerations

Introduction

Daiichi Sankyo, Inc. and Genzyme Corporation have petitioned the U.S. Consumer Product Safety Commission (CPSC) to exempt powder formulations of their products, colesevelam hydrochloride (Welchol[®]) and sevelamer carbonate (Renvela[®]), respectively, from the child-resistant (CR) packaging requirements of the Poison Prevention Packaging Act (PPPA) (16 CFR §1700). Due to similarities between the two petitions (both are prescription drugs currently available in pill form seeking exemption for a new powder formulation), CPSC staff is addressing them in a single briefing package.

This memorandum provides some information on the markets for colesevelam hydrochloride (Welchol[®]) and sevelamer carbonate (Renvela[®]), as well as the possible economic effects of the petitions.

The Products and their Markets

Welchol[®] is the trade name under which Daiichi Sankyo, Inc. markets colesevelam hydrochloride. Colesevelam hydrochloride (Welchol[®]) is “a polymeric cholesterol-lowering agent which binds bile acids. It is indicated to reduce elevated LDL cholesterol levels found in patients.” It can be used alone or with other cholesterol-reducing agents, such as statins. Colesevelam hydrochloride is also used to improve “glycemic control in adults with type 2 diabetes.”²⁸ The product is currently marketed in tablet and powder form as a prescription. The powder formulation, for which Daiichi Sankyo, Inc. is seeking an exemption, is provided in unit-dose packages of 2.6 or 5.2 grams (containing 1.875 grams or 3.75 grams of colesevelam hydrochloride (Welchol[®]), respectively). The product contains citrus flavoring and noncaloric sweetener and is intended to be mixed with water and taken orally.²⁹

Daiichi Sankyo, Inc. is a subsidiary of, and owned in its entirety by, the Japanese firm Daiichi Sankyo Co., Ltd., and has approximately 1,500 employees in the United States.³⁰ U.S. sales for FY 2008 were approximately \$1.3 billion.³¹ Net sales of colesevelam hydrochloride (Welchol[®]) were approximately \$243.1 million.³²

Renvela[®] is the trade name under which Genzyme Corporation markets sevelamer carbonate. Sevelamer carbonate (Renvela[®]) is an anion exchange resin approved for the control of serum phosphorus in chronic kidney disease patients on dialysis. Sevelamer carbonate (Renvela[®]) is currently marketed in pill form and an alternative powder formulation to “benefit patients who dislike or have difficulty using solid dosage forms of medication and those who require multiple tablets with each meal.”³³ The powder formulation for which Genzyme Corporation is currently requesting an exemption will be provided in packets containing 0.8 grams or 2.4 grams of sevelamer carbonate (Renvela[®]).³⁴ The product contains other items intended to improve its color, flavor, and

²⁸ Daiichi Sankyo, Inc., “Petition for Exemption from Child-Resistant Packaging–Colesevelam Hydrochloride,” February 24, 2009, and Memorandum from Adrienne R. Layton, Ph.D., Directorate for Health Sciences, dated November 1, 2010, Subject: Toxicity Review of Colesevelam Hydrochloride (Welchol[®]) and Sevelamer Carbonate (Renvela[®]).

²⁹ Daiichi Sankyo, Inc., “Petition for Exemption from Child-Resistant Packaging–Colesevelam Hydrochloride,” February 24, 2009, and Memorandum from Catherine A. Sedney, Division of Human Factors, dated November 22, 2010, Subject: Petitions for Exemption from PPPA Requirements for Child-Resistant Packaging (PP 10-1 and PP 10-2).

³⁰ Dun & Bradstreet. According to a Daiichi Sankyo, Inc. press release (May 13, 2009), they have 830 employees based in New Jersey with 480 at their headquarters.

(http://www.dsi.com/news/pdfs/2_Hilton_Court_Alternate_Press_release.pdf)

³¹ “Strategic Moves: Daiichi Sankyo Co., Ltd. Annual Report 2009,”

([http://www.daiichisankyo.com/4less/cgi-bin/cs4view_obj.php/d_ir_public_n1_eng/352/DS\(AR\).pdf](http://www.daiichisankyo.com/4less/cgi-bin/cs4view_obj.php/d_ir_public_n1_eng/352/DS(AR).pdf)).

³² Net sales of colesevelam hydrochloride (Welchol[®]) for FY 2008 were 18.9 percent of total Daiichi Sankyo, Inc. net sales or approximately \$243.1 million (\$1.3 billion x 18.9 percent). Ibid.

³³ Genzyme Corporation, “Petition for Exemption from Poison Prevention Packaging Act; Request for Exemption from FOIA Disclosure,” March 6, 2009.

³⁴ They state that they may seek approval for smaller (1.6-gram) packages in the future.

texture, such as citrus flavorings and noncaloric sweeteners. It is intended to be mixed with water and taken orally.³⁵

Genzyme Corporation is a U.S. firm, headquartered in Cambridge, Massachusetts, with more than 12,000 employees world-wide.³⁶ Annual revenue for 2008 was \$4.6 billion.³⁷ Renvela[®], along with Renagel[®], is a market leader in the treatment of kidney disease with more than 50 percent of the prescriptions in the United States for this indication.³⁸ Sales revenue for sevelamer carbonate (Renvela[®]) and three other cardiometabolic and renal drugs were \$1 billion in 2008.³⁹

Risks Associated with Acute Ingestion

The risk associated with acute ingestion of colesevelam hydrochloride (Welchol[®]) and sevelamer carbonate (Renvela[®]), if they are approved for CR packaging exemption, appears to be very low. To date, there is only one known possible case of acute poisoning associated with colesevelam hydrochloride (Welchol[®]), sevelamer carbonate (Renvela[®]), or similar drugs, despite apparently large sales volumes.⁴⁰ The known incident involved twin boys (11 months old) who were taken to the emergency room following the possible ingestion of colesevelam hydrochloride (Welchol[®]) in combination with another drug. Five or six colesevelam hydrochloride (Welchol[®]) tablets were missing and a colesevelam hydrochloride (Welchol[®]) tablet was found in one boy's mouth. The children were treated and released the same day.⁴¹

The effects of accidental ingestions are likely to be minor. According to the toxicological review by Health Sciences (HS) staff,⁴² both colesevelam hydrochloride (Welchol[®]) and sevelamer carbonate (Renvela[®]) have low acute toxicity. The effects of

³⁵ Daiichi Sankyo, Inc. (February 24, 2009) and Memorandum from Catherine A. Sedney (November 22, 2010).

³⁶ Genzyme Corporation, 2008 Annual Report (http://www.genzyme.com/corp/investors/2008_annualreport.pdf), "Fast Facts About Genzyme Corporation" (<http://www.genzyme.com/corp/structure/fastfacts.asp>), and ReferenceUSAGov (http://www.referenceusagov.com/index_gov.asp?rusa=1).

³⁷ Genzyme Corporation, 2008 Annual Report.

³⁸ Ibid.

³⁹ Ibid. Note that based on "Fast Facts About Genzyme Corporation," the sales revenue for sevelamer carbonate (Renvela[®]) must have been less than \$263 million in 2008 or it would have been one of Genzyme Corporations top products.

⁴⁰ It should be noted, however, that there may be incidents that CPSC staff is unaware of because they did not result in an emergency room visit. For example, concerned parents might contact a poison control center, be told that gastrointestinal discomfort is the most likely result of accidental ingestion, and opt to treat at home.

⁴¹ Memorandum from Craig W. O'Brien, Hazard Analysis Division, Directorate for Epidemiology, dated October 25, 2010, Subject: Reported Incidents for Colesevelam Hydrochloride (Welchol[®]), Sevelamer Carbonate (Renvela[®]), and Related Drugs, 2000-2009 and Memorandum from Adrienne R. Layton, Ph.D. (November 1, 2010).

⁴² Memorandum from Adrienne R. Layton, Ph.D. (November 1, 2010).

ingestion, at most, would be the potential for “mild to moderate gastrointestinal discomfort.”⁴³

Additionally, Human Factors (HF) staff has identified several factors that would tend to further reduce or limit the risk associated with powder formulations of colesevelam hydrochloride (Welchol[®]) and sevelamer carbonate (Renvela[®]), including:⁴⁴

- Ingestion of powder is generally rare when compared to other formulations.
- The powder form, as well as the packaging and the quantities available in each packet, are likely to limit the total amount a child might ingest.
- Childhood behaviors are unlikely to result in large-volume powder ingestions.
- Children under age five are unlikely to be able to open these packages without substantial spillage.
- Mouthing or chewing on the unopened package would also result in lesser amounts being ingested.

Thus, any hazard associated with colesevelam hydrochloride (Welchol[®]) and sevelamer carbonate (Renvela[®]) in non-CR-packaged powder formulations is unlikely to impose a significant cost on society. The possible results (mild to moderate gastrointestinal discomfort) of acute ingestion are minor, and the number of incidents is likely to remain low as well.⁴⁵

Advantages of CR Packaging Exemption (Increased Patient Compliance)

The CR packaging for the powder sevelamer carbonate (Renvela[®]) and colesevelam hydrochloride (Welchol[®]) formulations requires having scissors on hand at every meal to open the medications, in addition to mixing the product in water. HF staff concurs with Genzyme Corporation that the CR packaging used for SC (Renvela[®]) may affect patients’ adherence to their medication regimen.⁴⁶ The CR packaging for CH (Welchol[®]) is similar and may, therefore, have a similar effect, although the makers did not include patient compliance as an issue in their exemption request. Exempting the powder formulations of CH (Welchol[®]) and SC (Renvela[®]) from the CR packaging requirements of the PPPA would allow these prescription drugs to be provided to patients in packages that could be torn open, rather than in packaging that would require scissors to open.⁴⁷

By approving the requested exemptions for these products, the Commission would reduce the potential inconvenience of the CR packaging of colesevelam hydrochloride (Welchol[®]) and sevelamer carbonate (Renvela[®]) in powder form and possibly would

⁴³ Ibid.

⁴⁴ Memorandum from Catherine A. Sedney (November 22, 2010).

⁴⁵ It should be noted that the powder forms of two bile acid sequestrants (cholestyramine and colestipol), which have chemical profiles similar to colesevelam hydrochloride and sevelamer carbonate, have already been exempted by the CPSC from CR packaging requirements.

⁴⁶ Ibid.

⁴⁷ Although, as noted by HF staff, it is unlikely that this would be the only child-resistant packaging option.

improve patient compliance. Given the low acute toxicity of these medications and the small risk that children will ingest significant quantities of powder, approving these exemptions seems reasonable.

Small Business Considerations

Because the affected firms are requesting the exemption, the action is unlikely to impose a significant impact. Additionally, given that both of the firms that would be affected by a CR packaging exemption for colesevelam hydrochloride (Welchol[®]) and sevelamer carbonate (Renvela[®]) are large, the data would support a conclusion that the exemption would not have any significant economic effect on a substantial number of small entities.

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[Billing Code 6355-01-P]

CONSUMER PRODUCT SAFETY COMMISSION

16 CFR Part 1700

CPSC Docket No. CPSC-2010-_____

Poison Prevention Packaging Requirements; Proposed Exemption of Powder Formulations of Colesevelam Hydrochloride and Sevelamer Carbonate

AGENCY: Consumer Product Safety Commission.

ACTION: Proposed rule.

SUMMARY: The Consumer Product Safety Commission (“CPSC,” “Commission,” or “we”) is proposing to amend its child-resistant packaging requirements to exempt powder formulations of two oral prescription drugs, colesevelam hydrochloride and sevelamer carbonate. Colesevelam hydrochloride, currently marketed as Welchol®, is available in a new powder formulation and is indicated to reduce elevated LDL cholesterol levels and improve glycemic control in adults with type 2 diabetes mellitus. Sevelamer carbonate, currently marketed as Renvela®, is available as a new powder formulation and is indicated for the control of elevated serum phosphorus in chronic kidney disease patients on dialysis. The proposed rule would exempt these prescription drug products on the basis that child-resistant packaging is not needed to protect young children from serious injury or illness from powder formulations of colesevelam hydrochloride and sevelamer carbonate because the products are not acutely toxic, lack adverse human experience associated with acute ingestion, and in powder form, are not likely to be ingested in large quantities by children under 5 years of age.

DATES: Comments on the proposal should be submitted no later than **[insert date 75 days after date of publication in the FEDERAL REGISTER]**.

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ADDRESSES: You may submit comments, identified by Docket No. **[insert CPSC docket number]**, by any of the following methods:

Electronic Submissions

Submit electronic comments in the following way:

Federal eRulemaking Portal: <http://www.regulations.gov>. Follow the instructions for submitting comments.

To ensure timely processing of comments, the Commission is no longer accepting comments submitted by electronic mail (email) except through www.regulations.gov.

Written Submissions

Submit written submissions in the following way:

Mail/Hand delivery/Courier (for paper, disk, or CD-ROM submissions), preferably in five copies, to: Office of the Secretary, U.S. Consumer Product Safety Commission, Room 820, 4330 East West Highway, Bethesda, MD 20814; telephone (301) 504-7923.

Instructions: All submissions received must include the agency name and docket number for this rulemaking. All comments received may be posted without change, including any personal identifiers, contact information, or other personal information provided, to <http://www.regulations.gov>. Do not submit confidential business information, trade secret information, or other sensitive or protected information electronically. Such information should be submitted in writing.

Docket: For access to the docket to read background documents or comments received, go to <http://www.regulations.gov>.

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FOR FURTHER INFORMATION CONTACT: Adrienne Layton, Ph.D., Division of Health Sciences, Directorate for Health Sciences, Consumer Product Safety Commission, Bethesda, MD 20814-4408; telephone (301) 504-7576; alayton@cpsc.gov.

SUPPLEMENTARY INFORMATION:

A. Background

1. The Poison Prevention Packaging Act of 1970 and Implementing Regulations

The Poison Prevention Packaging Act of 1970 (“PPPA”), 15 U.S.C. 1471–1476, gives the Commission authority to establish standards for the “special packaging” of household substances, such as drugs, when child-resistant (“CR”) packaging is necessary to protect children from serious personal injury or illness due to the substance and the special packaging is technically feasible, practicable, and appropriate for such substance. Accordingly, CPSC regulations require that oral prescription drugs be in CR packaging. 16 CFR 1700.14(a)(10). The powder forms of cholestyramine and colestipol, two drugs that are chemically similar to colesevelam hydrochloride and sevelamer carbonate, currently are exempt from CR packaging. *Id.* 1700.14(a)(10)(v) and (xv).

CPSC regulations allow companies to petition the Commission for exemption from CR requirements. 16 CFR Part 1702. Among the possible grounds for granting an exemption are that:

The degree or nature of the hazard to children in the availability of the substance, by reason of its packaging, is such that special packaging is not required to protect children from serious personal injury or serious illness resulting from handling, using or ingesting the substance.

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16 CFR 1702.17.

2. The Products for Which Exemptions Are Sought

a. Welchol® (Colesevelam Hydrochloride)

On February 24, 2009, Daiichi Sankyo, Inc. (“Daiichi”) petitioned the Commission to exempt the powdered form of colesevelam hydrochloride, which it markets as Welchol®, from the special packaging requirements for oral prescription drugs. The petitioner stated that the exemption is justified because of lack of toxicity and lack of adverse human experience with the drug. Welchol® has been marketed in tablet form and dispensed in CR packaging. On October 2, 2009, the U.S. Food and Drug Administration (“FDA”) approved a new powder formulation of the drug. The petition requested an exemption only for the powder dosage form of Welchol®. Tablets would continue to be in CR packaging.

Welchol® (colesevelam hydrochloride) is a bile acid sequestrant indicated as an adjunct to: (1) reduce elevated low-density lipoprotein cholesterol (LDL-C) levels; and (2) improve glycemic control in adults with type 2 diabetes mellitus. The new dosage form of Welchol® provides 1.875 g or 3.75 g of the powdered drug in unit dose packages to be mixed with water and taken orally as a suspension. (A unit dose package of Welchol® or Renvela® is a pouch that contains an individual dose.)

b. Renvela® (Sevelamer Carbonate)

On March 6, 2009, Genzyme Corporation (“Genzyme”) petitioned the Commission to exempt the powdered form of sevelamer carbonate, which it markets as Renvela®, from the special packaging requirements for oral prescription drugs. The

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petitioner stated that the exemption is justified because of lack of toxicity and lack of adverse human experience with the drug.

Renvela,[®] sevelamer carbonate, is a phosphate binder indicated for the control of serum phosphorus in patients with chronic kidney disease on dialysis. The tablets are marketed with a pill crusher for patients who have trouble swallowing the tablets. The company reformulated Renvela[®] as a powder to be taken as an oral suspension and received approval from FDA for this powder formulation on August 12, 2009. The new dosage form of Renvela[®] provides either 0.8 g or 2.4 g of Renvela[®] powder in unit dose packages to be mixed with 2 ounces of water.

B. Toxicity and Human Experience Data

Welchol[®] and Renvela[®] have similar chemical structures, biological properties, and powder formulations. Therefore, we are considering the two petitions together, and staff reviewed related toxicity data together. CPSC staff found that colesevelam hydrochloride and sevelamer carbonate are not absorbed from the gastrointestinal tract. This limits the systemic toxicity of the drugs.

No data indicate that either drug is acutely toxic, which is the type of toxicity of concern when considering whether CR packaging is appropriate. Even in patients taking these drugs chronically, the adverse effects are mostly minor, such as diarrhea, nausea, constipation, flatulence, and dyspepsia.

Generally, chronic studies are not useful in determining whether a drug should be in CR packaging (because CR packaging is intended to protect against the child's access and likely one-time use of the drug). Nevertheless, staff reviewed such data. Animal studies involving 3 to 6 month administration of Welchol[®] and Renvela,[®] respectively,

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resulted in hemorrhage. However, this result was not related directly to the mechanism of action of the drugs, but rather to a side effect involving the inhibition of vitamin K absorption. Chronic administration of Welchol[®] and Renvela[®] can cause an alteration in the absorption of vitamins A, D, E, and K. Vitamin K is required by the liver to produce functional blood clotting factors. When vitamin K levels are low, nonfunctional blood clotting factors are produced, which can lead to hemorrhage. This can occur following the chronic administration of a drug that inhibits vitamin K, but not after the acute administration of such a drug. Daiichi Sankyo's submission mentions one 4-year-old girl who was prescribed Welchol[®] off-label to treat a skin irritation secondary to liver disease. She died from an intracranial hemorrhage. There are confounding factors in this case, and the death occurred after chronic, not acute, exposure. Because of the confounding factors, the death cannot be attributed solely to Welchol[®]. A trial of Renvela[®] in a limited number of pediatric patients (18) for eight weeks resulted in primarily minor GI effects. (Pieper A.K., Haffner D., Hoppe B., Dittrich K., Offner G., Bonzel K.E., John U., Frund S., Klaus G., Stubinger A., Duker G. and Querfeld U. (2006).) Other effects, such as metabolic acidosis, can be attributed to the underlying chronic kidney disease in these children. These effects would occur after chronic, but not acute, exposure.

If a child were to ingest accidentally colesevelam hydrochloride (Welchol[®]) or sevelamer carbonate (Renvela[®]), the potential for the occurrence of mild to moderate GI discomfort, such as indigestion, constipation, nausea, and vomiting does exist. However, a review of relevant data indicates that an acute ingestion of these drugs would not result in serious toxicity. Any serious toxicity would result only after chronic administration.

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As noted, the CPSC's CR packaging regulations exempt cholestyramine and colestipol in powder form, two bile acid sequestrants that are similar chemically to Welchol[®] and Renvela[®]. CPSC staff has not found any articles in the medical literature describing toxic effects following the acute ingestion of either cholestyramine or colestipol from 1975 through 2010.

CPSC staff searched the following databases for incidents related to Welchol[®] and Renvela[®] occurring between 2000 and 2009: the Injury and Potential Injury Incident database ("IPII"), the National Electronic Injury Surveillance System database ("NEISS"), and the Death Certificates database ("DTHS"). Staff found one incident involving Welchol[®] in the NEISS database. In that incident, 11-month-old twin boys were taken to the emergency room after they had been playing with their grandmother's prescription medications. It is not clear how many, if any, pills the boys ingested, but the children were treated and released from the hospital. CPSC staff also searched Poisindex,[®] Pub Med, and Google for Welchol,[®] Renvela,[®] Colestipol, and Cholestyramine, and found no incidents of acute poisoning in humans.

CPSC staff also analyzed Medwatch reports obtained from the FDA. Medwatch is the FDA's program for reporting a serious adverse event, product quality problem, product use error, or therapeutic inequivalence/failure that may be associated with the use of an FDA-regulated drug, biologic, medical device, dietary supplement, or cosmetic. (See <http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm>.) There may be adverse events that have occurred and are not reported in the Medwatch database. Also, the existence of a report in the database does not mean necessarily that the product actually caused the adverse event.

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The FDA provided CPSC staff with 151 distinct incidents of adverse events associated with colesevelam hydrochloride (Welchol[®]) reported through the Medwatch system. CPSC staff excluded incidents where other medications may have caused the adverse event reported, resulting in 22 adverse events. Most adverse events reported to Medwatch were gastrointestinal or involved muscle pain, which is to be expected considering the adverse effects reported from clinical trials of Welchol.[®]

CPSC staff also received reports from the FDA of 40 distinct incidents of adverse events associated with sevelamer carbonate (Renvela[®]). CPSC staff excluded incidents where other medications may have caused the adverse event reported, resulting in five in-scope incidents. Two of the five incidents were deaths, which most likely were related to the underlying disease and not sevelamer carbonate (Renvela[®]) treatment. One of the five incidents involved intestinal obstruction and perforation, which the patient's physician thought were related to the patient's treatment with sevelamer carbonate (Renvela[®]). In the two remaining incidents, one patient experienced gastroenteritis, and the other (who had asthma and chronic obstructive pulmonary disease) suffered severe breathing problems while on Renvela.[®] Neither of these two results likely was related to sevelamer carbonate (Renvela[®]).

CPSC staff also evaluated the likelihood of children younger than 5 years old ingesting powdered substances. The powdered form of these substances makes them more difficult to ingest than medicines in other forms and therefore, likely will keep children from ingesting significant quantities. CPSC staff believes that it would be difficult for children under 5 years old to eat large amounts of powder quickly without aspirating or coughing. It would also be difficult for children to mix powder thoroughly

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in a liquid, and the resulting lumpy quality may be unappealing to children who try to drink it. Although children are likely to be able to tear open the non-child-resistant packets used for Welchol[®] and Renvela,[®] they are likely to spill much of the contents; therefore, they would have to open a number of packages to access a significant quantity of the drug. Most unintentional poisonings among children occur during short lapses in direct visual supervision. The difficulty posed by ingestion of powder introduces a delay in the poisoning scenario, and supervision is likely to resume before a child can take in a significant quantity.

The packages used with the powder formulations of Welchol[®] and Renvela[®] also reduce the likelihood of child poisoning. Both drugs are provided in small foil-lined packages containing individual doses. The Renvela[®] package is easy to tear only at the notch. Because the package must be opened at a precise location, it is less accessible, especially to young children. The Welchol[®] package does not have a notch and has uniform resistance to tearing, which makes it more difficult to open than Renvela.[®] Although both packages tear easily enough to be opened by children under 5 years of age, the fine motor skills of this age group of children are still developing, and children age 2 and younger are likely to spill most of the powder.

C. Action on the Petition

After considering the information provided by the petitioner and other available toxicity and human experience data, the Commission concluded preliminarily that the degree and nature of the hazard to children presented by the availability of powder formulations of colesevelam hydrochloride (currently marketed as Welchol[®]) and sevelamer carbonate (currently marketed as Renvela[®]) do not require special packaging

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to protect children from serious personal injury or serious illness resulting from handling, using, or ingesting the substance. Therefore, the Commission voted to grant the petition and begin a rulemaking proceeding to exempt powder formulations of colesevelam hydrochloride containing not more than 3.75 grams per package and sevelamer carbonate containing not more than 2.4 grams per package from the special packaging requirements for oral prescription drugs.

D. Regulatory Flexibility Act Certification

Under the Regulatory Flexibility Act, 5 U.S.C. 601 et seq., an agency that engages in rulemaking generally must prepare initial and final regulatory flexibility analyses describing the impact of the rule on small businesses and other small entities. Section 605 of the Act provides that an agency is not required to prepare a regulatory flexibility analysis if the head of an agency certifies that the rule will not have a significant economic impact on a substantial number of small entities.

The Commission's Directorate for Economic Analysis prepared a preliminary assessment of the impact of a rule to exempt powder formulations of colesevelam hydrochloride (currently marketed as Welchol®) and sevelamer carbonate (currently marketed as Renvela®) from special packaging requirements.

Daiichi Sankyo, Inc., a subsidiary of the Japanese firm Daiichi Sankyo Co, Ltd, the company that markets colesevelam hydrochloride under the trade name of Welchol®, employs approximately 1,500 people in the United States. Net sales of Welchol® were approximately \$243.1 million in 2008. Genzyme Corporation, the company that markets sevelamer carbonate under the trade name of Renvela®, is a U.S. firm headquartered in Cambridge, Mass., with more than 12,000 employees worldwide. Annual revenue for

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2008 was \$4.6 billion. Given that both firms that would be affected by a CR packaging exemption for these drugs are large, the exemption would not have a significant economic effect on a substantial number of small entities. Moreover, because the action at issue is an exemption from special packaging requirements, it would allow companies to avoid the costs associated with CR packaging.

Based on this assessment, we preliminarily conclude that the proposed amendment exempting powder formulations of colesevelam hydrochloride (currently marketed as Welchol[®]) and sevelamer carbonate (currently marketed as Renvela[®]) from special packaging requirements would not have a significant impact on a substantial number of small businesses or other small entities.

E. Environmental Considerations

Pursuant to the National Environmental Policy Act, and in accordance with the Council on Environmental Quality regulations and CPSC procedures for environmental review, we have assessed the possible environmental effects associated with the proposed PPPA amendment.

CPSC regulations state that rules requiring special packaging for consumer products normally have little or no potential for affecting the human environment. 16 CFR 1021.5(c)(3). Nothing in this proposed rule alters that expectation. Therefore, because the rule would have no adverse effect on the environment, neither an environmental assessment nor an environmental impact statement is required.

F. Executive Orders

According to Executive Order 12988 (February 5, 1996), agencies must state in clear language the preemptive effect, if any, of new regulations.

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The PPPA provides that, generally, when a special packaging standard issued under the PPPA is in effect, “no State or political subdivision thereof shall have any authority either to establish or continue in effect, with respect to such household substance, any standard for special packaging (and any exemption therefrom and requirement related thereto) which is not identical to the [PPPA] standard.” 15 U.S.C. 1476(a). A state or local standard may be excepted from this preemptive effect if: (1) the state or local standard provides a higher degree of protection from the risk of injury or illness than the PPPA standard; and (2) the state or political subdivision applies to the Commission for an exemption from the PPPA’s preemption clause and the Commission grants the exemption through a process specified at 16 CFR Part 1061. 15 U.S.C. 1476(c)(1). In addition, the federal government, or a state or local government, may establish and continue in effect a nonidentical special packaging requirement that provides a higher degree of protection than the PPPA requirement for a household substance for the federal, state or local government’s own use. 15 U.S.C. 1476(b).

Thus, with the exceptions noted above, the proposed rule exempting powder formulations of colesevelam hydrochloride (currently marketed as Welchol®) and sevelamer carbonate (currently marketed as Renvela®) from special packaging requirements, if finalized, would preempt nonidentical state or local special packaging standards for the substance.

List of Subjects in 16 CFR Part 1700

Consumer protection, Drugs, Infants and children, Packaging and containers, Poison prevention, Toxic substances.

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For the reasons given above, the Commission proposes to amend 16 CFR part 1700 as follows:

PART 1700--[AMENDED]

1. The authority citation for part 1700 continues to read as follows:

Authority: 15 U.S.C. 1471–76. Secs. 1700.1 and 1700.14 also issued under 15 U.S.C. 2079(a).

2. Section 1700.14 is amended by adding new paragraphs (a)(10)(xxii) and (xxiii) to read as follows:

Sec. 1700.14 - Substances requiring special packaging.

(a) *Substances*. The Commission has determined that the degree or nature of the hazard to children in the availability of the following substances, by reason of their packaging, is such that special packaging meeting the requirements of § 1700.20(a) is required to protect children from serious personal injury or serious illness resulting from handling, using, or ingesting such substances, and the special packaging herein required is technically feasible, practicable, and appropriate for these substances:

* * * * *

(10) *Prescription Drugs*. Any drug for human use that is in a dosage form intended for oral administration and that is required by Federal law to be dispensed only by or upon an oral or written prescription of a practitioner licensed by law to administer such drug shall be packaged in accordance with the provisions of § 1700.15 (a), (b), and (c), except for the following:

* * * * *

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(xxii) Colesevelam hydrochloride in powder form in packages containing not more than 3.75 grams of the drug.

(xxiii) Sevelamer carbonate in powder form in packages containing not more than 2.4 grams of the drug.

Dated: _____.

Todd A. Stevenson, Secretary
Consumer Product Safety Commission

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