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

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BALLOT VOTE SHEET

Date: July 6, 2011

TO : The Commission
Todd A. 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 : Final Rule 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: July 12, 2011

Attached is a briefing package from the staff recommending that the Commission issue a final rule to exempt two drugs from special packaging requirements under the Poison Prevention Packaging Act ("PPPA"). The rulemaking is based on petitions submitted by: (1) Daiichi Sankyo, Inc., requesting an exemption for the powder formulation of colesevelam hydrochloride, which it markets as Welchol®, and (2) Genzyme Corporation requesting an exemption for the powder formulation of sevelamer carbonate, which it markets as Renvela®. The Commission previously voted to grant the petitions and publish a notice of proposed rulemaking. A draft *Federal Register* notice for a final rule 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 the Powder Formulation of Colesevelam Hydrochloride (Welchol®)

I. Approve publication in the *Federal Register* of the draft final rule without change.

_____ _____
Signature Date

II. Approve publication in the *Federal Register* of the draft final rule with changes (please specify changes):

_____

_____

_____

_____ _____
Signature Date

III. Do not approve publication in the Federal Register of the draft final rule.

_____ _____
Signature Date

IV. Take other action (please specify):

_____

_____

_____

_____ _____
Signature Date

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

I. Approve publication in the *Federal Register* of the draft final rule without change.

_____ _____
Signature Date

II. Approve publication in the *Federal Register* of the draft final rule with changes (please specify changes):

_____

_____

_____

_____ _____
Signature Date

III. Do not approve publication in the *Federal Register* of the draft final rule.

_____ _____
Signature Date

IV. Take other action (please specify):

_____

_____

_____

_____ _____
Signature Date

Final Rule 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

7/6/2011

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Executive Summary

In response to petitions submitted to the U.S. Consumer Product Safety Commission ("Commission" or "CPSC") by Daiichi Sankyo, Inc. and Genzyme Corporation, the Commission proposed to exempt the powder formulations of colesevelam hydrochloride (Welchol®) and sevelamer carbonate (Renvela®) from the child-resistant packaging ("CR packaging" or "CRP") requirements of the Poison Prevention Packaging Act (PPPA). Colesevelam hydrochloride (Welchol®) is a cholesterol-lowering agent, and sevelamer carbonate (Renvela®) is used to bind phosphate in patients with chronic kidney disease. The requested exemption is for the powder dosage forms of colesevelam hydrochloride (Welchol®) and sevelamer carbonate (Renvela®) only; the tablet dosage forms will continue to be subject to the child-resistant packaging requirements detailed in the PPPA at 16 CFR § 1700. Staff 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. A notice of proposed rulemaking was published in the Federal Register on February 16, 2011. The Commission received 27 comments in response to the notice of proposed rulemaking. Fifteen comments supported and 12 comments opposed the proposed rule. Most comments expressed general opinions but provided little or no evidence to support their opinions. Staff received no information that changes its recommendation.

Based on available information, colesevelam hydrochloride (Welchol®) and sevelamer carbonate (Renvela®) have low oral toxicities; lack adverse human experience associated with acute ingestion; and, in powder form, pose little risk that children less than 5 years old will ingest large amounts. Serious toxicity is unlikely after acute ingestion because colesevelam hydrochloride (Welchol®) and sevelamer carbonate (Renvela®) are not absorbed by the body. Adverse effects would be limited and include gastrointestinal effects (*e.g.*, indigestion, constipation, flatulence, nausea, and vomiting) and muscle pain. Moreover, there are no reports of acute poisoning associated with two similar drug powders, colestipol (44 FR 6343) and cholestyramine (44 FR 21625), which the Commission exempted from special packaging in 1979.

Staff recommends that the Commission issue a final rule to exempt the powdered dosage forms of colesevelam hydrochloride (Welchol®) and sevelamer carbonate (Renvela®) from CRP requirements.

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

This document has been electronically approved and signed.

Memorandum **Date: July 6, 2011**

To: The Commission
Todd A. 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: Final Rule to Exempt the Powder Formulations of Colesevelam Hydrochloride (Welchol®) and Sevelamer Carbonate (Renvela®) from the Special Packaging Requirements of the PPPA

I. Background

The U.S. Consumer Product Safety Commission ("Commission" or "CPSC") requires "special" or child-resistant packaging ("CR packaging" or "CRP") for oral prescription drugs under the Poison Prevention Packaging Act (PPPA) (16 CFR § 1700). The Commission's regulations allow exemptions from this requirement for substances with low acute toxicity (16 CFR § 1702).

In February 2011, the Commission considered petitions from Daiichi Sankyo, Inc. and Genzyme Corporation to exempt from CRP the powder forms of their marketed drugs, colesevelam hydrochloride (Welchol®) and sevelamer carbonate (Renvela®), respectively. Colesevelam hydrochloride (Welchol®) is a cholesterol-lowering agent, and sevelamer carbonate (Renvela®) binds phosphate in patients with chronic kidney disease. Currently, colesevelam hydrochloride (Welchol®) and sevelamer carbonate (Renvela®) are marketed in tablet and powder form and dispensed in CRP.

The systemic toxicity of colesevelam hydrochloride (Welchol®) and sevelamer carbonate (Renvela®) is limited by their lack of absorption from the gastrointestinal (GI) tract. If accidentally ingested by a child, either of these drugs may cause mild to moderate GI discomfort (*e.g.*, indigestion, constipation, nausea and vomiting) or muscle pain. CPSC 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 because these

products: (1) have low oral toxicities following clinical use of the drugs; (2) lack adverse human experience associated with acute ingestion; and (3) in powder form, are unlikely to be ingested in large quantities by children under 5 years of age. Detailed information concerning this issue was provided to the Commission in a briefing package dated February 9, 2011 (Layton A.R. and Howell R.J., 2011).

On February 16, 2011, the Commission granted the petitions and published a notice of proposed rulemaking to exempt from special packaging no more than 3.75 g of the powder form of colesevelam hydrochloride (Welchol®) per package and no more than 2.4 g of the powder form of sevelamer carbonate (Renvela®) per package (76 FR 8942).

II. Discussion

A. Public Comments

The Commission received 27 comments in response to the notice of proposed rulemaking[1] (Tab B). Fifteen commenters supported the proposed exemptions.

Twelve commenters disagreed with the proposed exemptions, citing various reasons, including: (1) insufficient data; (2) the benefits of CRP in limiting ingestion; and (3) concerns about bowel obstruction, choking on the powder, and co-ingestion with other substances. Many commenters provided little or no information to support their arguments. Overall, no substantive evidence was provided to refute information CPSC staff compiled to support the exemptions.

B. Updated Injury Data

Hazard Analysis staff has updated the injury data since the proposed rule (Tab C). The Injury and Potential Injury Incident database (IPII), the National Electronic Injury Surveillance System database (NEISS), and the Death Certificates database (DTHS) were searched from 2000 through 2010, for incidents associated with colesevelam hydrochloride (Welchol®), sevelamer carbonate (Renvela®), and related drugs (*i.e.*, cholestyramine (Questran®) and colestipol (Colestid®).

There were no incidents related to Renvela,® Questran,® or Colestid,® and only one new Welchol®-related case was identified. This incident occurred in July 2010, when a 19-month-old boy was found in his crib with an open Tylenol® bottle. The bottle was used previously for carrying Welchol® tablets and other drugs while traveling. It was not clear if any Welchol® tablets were in the bottle when the child accessed it. The child was taken to the emergency department, held overnight for observation, and then released the next day.

Additionally, Health Sciences staff searched Poisindex®[2] and the medical literature for updated information on Welchol,® Renvela,® colestipol, and cholestyramine and found no incidents of acute poisoning in humans.

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[1] Http://www.regulations.gov/#!docketDetail;rpp=50;po=0;D=CPSC-2011-0007.

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

C. Economic Information

The Directorate for Economic Analysis provided an updated memo as shown in Tab E. Staff concluded that the CRP exemption for colesevelam hydrochloride (Welchol®) and sevelamer carbonate (Renvela®) would not have any significant economic effect on a substantial number of small entities because the affected firms are requesting the exemption, and both firms are large.

D. Effective Date

If the Commission issues a final rule to exempt these products, staff recommends that it take effect upon publication in the Federal Register because the rule does not put any new requirements into place, but removes the existing requirement that these drugs be packaged in CR packaging.

III. Options

A. Colesevelam hydrochloride (Welchol®)

1. The Commission may issue a rule exempting from the special packaging requirements the powder formulation of colesevelam hydrochloride (Welchol®) containing no more than 3.75 g per package, if it concludes that this product will not present a risk of serious personal injury or illness to young children when packaged in non-CR packaging.

2. The Commission may decline to issue a rule exempting from the special packaging requirements the powder formulation of colesevelam hydrochloride (Welchol®) containing no more than 3.75 g per package, if it concludes that this product will present a risk of serious personal injury or illness to young children when packaged in non-CR packaging.

B. Sevelamer carbonate (Renvela®)

1. The Commission may issue a rule exempting from the special packaging requirements the powder formulation of sevelamer carbonate (Renvela®) containing no more than 2.4 g per package, if it concludes that this product will not present a risk of serious personal injury or illness to young children when packaged in non-CR packaging.

2. The Commission may decline to issue a rule exempting from the special packaging requirements the powder formulation of sevelamer carbonate (Renvela®) containing no more than 2.4 g per package, if it concludes that this product will present a risk of serious personal injury or illness to young children when packaged in non-CR packaging.

IV. Conclusion and Recommendation

Staff concludes that special packaging is not necessary for the powdered forms of colesevelam hydrochloride (Welchol®) or sevelamer carbonate (Renvela®) because of their low acute toxicity and the lack of serious adverse human experience data associated with acute ingestion. Moreover, powders are inherently difficult to ingest, decreasing the likelihood that young children would consume large quantities. Therefore, staff recommends that the Commission issue a rule to exempt from CRP the powder formulations of:

1. Colesevelam hydrochloride (Welchol®) containing no more than 3.75 g per package and;

2. Sevelamer carbonate (Renvela®) containing no more than 2.4 g per package.

TAB A: Federal Register Notice, February 16, 2011

Federal Register: February 16, 2011 (Volume 76, Number 32)
Proposed Rules
Page 8942-8945
From the Federal Register Online via GPO Access [wais.access.gpo.gov]
[DOCID:fr16fe11-16]

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CONSUMER PRODUCT SAFETY COMMISSION

16 CFR Part 1700

CPSC Docket No. CPSC-2011-0007

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 May 2, 2011.

ADDRESSES: You may submit comments, identified by Docket No. CPSC-2011-0007, 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 (e-mail) except through http://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.

FOR FURTHER INFORMATION CONTACT: Adrienne Layton, PhD, 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 that the substance poses to children is such that special packaging is not required to protect children against serious personal injury or serious illness (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 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, 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.

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.

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 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 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 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.

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.

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 Sec. 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 Sec. 1700.15 (a), (b), and (c), except for the following:

* * * * *

(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: February 10, 2011.

Todd A. Stevenson,

Secretary, Consumer Product Safety Commission.

[FR Doc. 2011-3437 Filed 2-15-11; 8:45 am]

BILLING CODE 6355-01-P

TAB B: Response to Comments on the Proposed Child-Resistant Packaging Exemptions for Colesevelam Hydrochloride (Welchol®) and Sevelamer Carbonate (Renvela®)

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

Memorandum **Date: May 27, 2011**

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 R. Layton, Ph.D., Pharmacologist, Directorate for Health Sciences

Subject: Response to Comments on the Proposed Child-Resistant Packaging Exemptions for Colesevelam Hydrochloride (Welchol®) and Sevelamer Carbonate (Renvela®)

Background

On February 16, 2011, the Commission proposed a rule (76 FR 8942) to exempt two drug powders, colesevelam hydrochloride (Welchol®) and sevelamer carbonate (Renvela®), from the special packaging requirements of the Poison Prevention Packaging Act (PPPA). The Commission received 27 comments, with 15 supporting the proposed rule and 12 opposing it (Table 1).[1] Outlined below are staff responses to comments from those opposing the exemptions. No new data were provided by the commenters to support their assertions.

[1] Http://www.regulations.gov/#!docketDetail;rpp=50;po=0;D=CPSC-2011-0007.

Table 1. Public Comment Information

Document Number	Supports Exemption	Opposes Exemption	Organization
0001	Federal Register Notice		
0002		X	Unaffiliated
0003	X		American Military University
0004		X	Georgetown University Law Center
0005	X		UUSP*
0006		X	UUSP*
0007		X	Unaffiliated
0008		X	Unaffiliated
0009		X	Unaffiliated
0010		X	UUSP*
0011		X	Unaffiliated
0012		X	Unaffiliated
0013	X		Unaffiliated
0014	X		UUSP*
0015	X		Unaffiliated
0016	X		Unaffiliated
0017	X		Unaffiliated
0018	X		Unaffiliated
0019		X	Unaffiliated
0020	X		UUSP*
0021	X		Unaffiliated
0022	X		Unaffiliated
0023		X	Unaffiliated
0024		X	UUSP*
0025	X		Unaffiliated
0026	X		Unaffiliated
0027	X		Unaffiliated
0028	X		Unaffiliated

* UUSP = Union University School of Pharmacy

Response to Public Comments

Comment:

Some commenters (4, 7, 8, 9, 10, 11, 12, 23, and 24) were concerned about the lack of data and thought that the drugs could be more harmful to children (*e.g*., cause bowel obstruction, electrolyte/serum glucose imbalance, death), particularly if ingested in large amounts. One commenter (4) also questioned the use of adverse effect data from adults and animals in predicting toxicity from accidental poisoning in children.

Response:

Typically, Commission staff considers all available data in toxicity assessments, with human data taking precedence over animal data. While limited data are available on the acute toxicity of colesevelam hydrochloride (Welchol®) and sevelamer carbonate (Renvela®) in children, the adverse effects reported are similar to those in adults. Because these drugs are not absorbed systemically, acute adverse effects typically are limited to the gastrointestinal (GI) tract and are unlikely to be serious. An extension of these effects would be expected in an overdose scenario. Notably, intestinal obstruction has only been observed during therapeutic use in patients whose health has been compromised otherwise (*e.g*., low birth weight, chronic kidney disease, and adhesions). Cases of intestinal obstruction have been documented in infants and one child following treatment with a similar drug, cholestyramine (Cohen, M.I., 1969; Merten, D.F., 1979; Lloyd-Still, J.D., 1977; Tonstad, 1996). In addition, a 45-year-old male developed an intestinal obstruction, perforation, and an abdominal fistula (abnormal opening in the stomach or bowel, which allows the contents to leak) after several months of treatment with Renvela.® Intestinal obstruction has occurred very rarely after colesevelam hydrochloride (Welchol®) treatment. In fact, colesevelam hydrochloride has a greater specificity for bile acids than cholestyramine and colestipol and has been suggested to have greater gastrointestinal tolerance than the other two drugs (Jacobsen, T.A., 2007).

Health Sciences staff believes it is unlikely that an imbalance of electrolytes or glucose control would occur following an acute exposure to colesevelam hydrochloride (Welchol®) or sevelamer carbonate (Renvela®). No unexpected laboratory tests were seen following chronic administration of 3.75 grams g/day of colesevelam hydrochloride (Welchol®) to pediatric subjects with heterozygous familial hypercholesteremia (Stein, E.A., 2010) or 15 g/day of sevelamer carbonate (Renvela®) to normal volunteers (Burke, S.K., 1997). Chronic administration of colesevelam hydrochloride (Welchol®) decreased fasting glucose levels 3.9-15.9 mg/dl (Goldberg, R.B., 2008; Fonseca, V.A., 2008). Because the normal blood glucose levels in children are 100-180 mg/dl[3], it is unlikely that acute administration of Welchol® would cause hypoglycemia[4] in a child (less than 60 mg/dl) (Beck, R.W., 2010).

Moreover, there are no available poisoning data showing that these agents cause serious toxicity following an acute exposure. A previous search of CPSC databases found one incident

[3] Http://ndep.nih.gov/media/diabetes/youth/youth_FS.htm#Goals.
[4] Hypoglycemia is low blood sugar.

involving 11-month-old twins who were treated and released after playing with a grandparent's Welchol® tablets. It was unclear whether the children had ingested any tablets. Hazard Analysis staff provided an update of injury data on Welchol,® Renvela,® and two other similar drugs, cholestyramine and colestipol (Tab C). Since the proposed rule, there was one new incident involving a possible ingestion of Welchol® by a 19-month-old male in 2010. The child was found in his crib with an open Tylenol® bottle, which had been used to store Welchol® tablets and other drugs while traveling. Although it was unclear whether any Welchol tablets were in the bottle at the time of the incident, the child was taken to a hospital where he was held overnight for observation and then released.

Comment:

Some commenters (4 and 23) argued that: (1) the powder may present a choking hazard to children; and (2) there is little support for claims that the powders are more difficult for children to ingest, access from the packet without spilling, and mix thoroughly in a liquid.

Response:

The low acute toxicity of colesevelam hydrochloride (Welchol®) and sevelamer carbonate (Renvela®) is a key factor for the proposed exemptions. Additionally, Human Factors staff considered relevant data and medical literature to conclude that powders generally are a low-risk formulation because they are more difficult to ingest, particularly in large quantities (Tab D). Generally, with the exception of caustics, the primary exposure risk associated with powders is aspiration. Notably, any potential choking hazard with these drugs is comparable to that of any non-pharmaceutical powder formulation available in the household, such as soaps, baby powder, drink mixes, and food products.

Based on available data, Human Factors staff maintains that a child would have difficulty opening the packet and mixing the powder with a liquid because of the lack of precision and control required (Tab D). Moreover, there are no available poisoning data with these agents or similar drugs (colestipol or cholestyramine) to indicate otherwise.

Comment:

One commenter (6) stated that the drug could be "mixed with something" to cause an adverse reaction.

Response:

The commenter provided no evidence to suggest that this is a likely event, and no information or examples of "benign substance(s)" that when mixed with colesevelam hydrochloride (Welchol®) or sevelamer carbonate (Renvela®) would interact to cause an adverse reaction (Tab D). As discussed in Human Factors staff's original memo, while it is possible that a child might mix the powder with a liquid in imitation of an adult, it is highly unlikely that a child would do so repeatedly because a small child can drink only a limited amount of liquid at

one time (Sedney, 2010). In addition, the consistency of incompletely mixed powder is likely to deter repetition.

Comment:

Some commenters (4 and 7) cited only limited benefits from CRP exemption: increased profits for the manufacturers of the drugs (4) and ease of opening the package (7).

Response:

Exempting from CRP requirements the powder forms of colesevelam hydrochloride (Welchol®) and sevelamer carbonate (Renvela®) may increase patient compliance. Poor adherence to medication regimens for chronic health issues is a well-established concern, human factors staff noted (Tab D). Easier access to these drugs could benefit patients with minimal or no risk to children.

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TAB C: Reported Incidents for Colesevelam Hydrochloride (Welchol®), Sevelamer Carbonate (Renvela®), and Related Drugs, 2000–2010

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

Memorandum **Date: May 17, 2011**

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

THROUGH: Kathleen A. Stralka, Associate Executive Director
Directorate for Epidemiology

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

SUBJECT : Reported Incidents for Colesevelam Hydrochloride (Welchol®), Sevelamer Carbonate (Renvela®), and Related Drugs, 2000–2010

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 2010, two incidents were found for colesevelam hydrochloride (Welchol®). The first incident involved twin boys, 11 months old, who possibly ingested Diltiazem® and/or colesevelam hydrochloride (Welchol®) in February 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.

The second incident involved a 19-month-old boy who was found in his crib with an open Tylenol® bottle in July 2010. The bottle had been used previously for carrying Welchol® and other drugs while travelling. However, it was not clear if any Welchol® tablets were in the bottle when the child accessed it. The child was taken to a hospital where he was held overnight for observation and then released.

From 2000 through 2010, no incidents were found in the CPSC databases related to Renvela.®

From 2000 through 2010, 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,[5] 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, which in her physician's opinion, was not Renvela®-related. One patient with asthma and chronic obstructive pulmonary disease suffered severe breathing problems while on Renvela.®

Methodology

The CPSC databases were searched in March 2011, 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 Cholestagel® 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. Both incidents found were in the NEISS database.

[5] 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 January 2011, the Death Certificates database was considered 87 percent complete for 2007; 77 percent complete for 2008; 61 percent complete for 2009; and 19 percent complete for 2010.

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 from health care professionals, consumers, and patients of adverse events, product quality problems, product use errors, or therapeutic inequivalence/failures. 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. As with IPII, MedWatch is not a statistical sample. Furthermore, the FDA does not require proof of a causal relationship between the medication and the adverse event. MedWatch data can still be useful in indentifying adverse events that occur while patients are taking medication.

TAB D: Response to Comments—Proposed Rule on Exemptions from PPPA Requirements for Child-Resistant Packaging (PP 10-1 and PP 10-2)

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

MEMORANDUM **Date: May 25, 2011**

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

Through: George A. Borlase, Ph.D., P.E., 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: Response to Comments—Proposed Rule on Exemptions from PPPA Requirements for Child-Resistant Packaging (PP 10-1 and PP 10-2)

Background

Daiichi Sankyo, Inc. and Genzyme Corporation 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. Welchol,® or colesevelam hydrochloride (CH), 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 CH (Welchol®) in 2.60 grams of powder (0.092 oz); the larger size will consist of 3.75 grams (0.132 oz) of CH (Welchol®) in 5.20 grams (0.183 oz) of powder. Renvela,® or sevelamer carbonate (SC), is a phosphate binder used in the control of serum phosphorus in patients with chronic kidney disease (CKD) who are on dialysis. Genzyme's proposed powder formulation is to be provided in 2.5-gram (0.09-ounce) packets containing 2.40 grams (0.085 oz) SC along with agents intended to improve its taste, color, and texture (Genzyme Corporation, March 6, 2009). Both products contain citrus flavoring and a noncaloric sweetener. They are intended to be mixed with water and taken before meals.

Staff 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. Staff recommended granting the petitions based on the low toxicity of the products and the low likelihood that children under age five[6] would ingest them in significant amounts. The Commission voted to grant the petition, and on February 16, 2011, published a Notice of Proposed Rulemaking (NPR; 76 Federal Register 8942). This memorandum responds to the comments received regarding the rulemaking that are relevant to issues addressed by the Division of Human Factors.

Discussion

Staff received two comments that relate directly to issues discussed in the Human Factors staff memorandum. These are discussed individually below.

Comment: One commenter objected: (1) that the evidence that children are unlikely to accidentally take Welchol® or Renvela® is based on common sense or everyday experience, which may be unreliable; (2) that there is little support for the claims that powder forms are more difficult for children to ingest, and that claims that children would have difficulty opening the packages without spilling them and be unlikely to thoroughly mix the powder are based on little more than common experience; and (3) that the only benefits of the exemptions are increased profits for the manufacturers of the drugs in question. (CPSC-2011-0007-0004).

Response: The commenter offered no evidence or information that contradicts staff's assessment. "Common" or "everyday" experience alone is unreliable as a basis for analysis. However, it should be considered in light of relevant data and literature. As discussed in the staff memo, except in some cases of pica,[7] ingestion of powdered substances is uncommon, and poisoning among children resulting from ingestion of powders in large amounts is rare. The results of staff's review of available poisoning data for both the 1995 petition for exemption of powdered iron supplements and for the current petition[8] supported that conclusion and were consistent with the assessments of Done in 1970 and Writer in 1993[9] that, in general,[10] powders are a low-risk formulation.

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[6] The Poison Prevention Packaging Act of 1970 addresses child-initiated, unintentional poisoning among children younger than five years of age. Incidence in this category peaks around two years of age and declines thereafter.

[7] Pica is a disorder characterized by a pattern of eating non-food materials that can include powder and powder-like substances, such as baking soda and dirt or sand. For example, see http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0002505/ (accessed 5/18/11).

[8] The Commission's Children and Poisoning (CAP) Database, a subset of the National Electronic Injury Surveillance System (NEISS), contains reports of emergency room visits for exposure and potential exposure of children under five years of age to substances that meet code criteria for poisoning, chemical burns, or ingestion. In Human Factors staff's informal review, between 1/1/00 and 12/31/09, approximately 0.23 percent of reports (102 of 43,864) involved substances formulated as powders, including personal care products, cleaners, and drugs such as aspirin powder and vials of powder inhalant used to treat respiratory symptoms. In one instance, it was reported that a child ingested a significant amount of loose powder, which occurred when he poured ¾ of a bottle over his face. In another, the mother described the victim as having his mouth full of powder. Neither required treatment.

[9] These authors were cited in both packages.

This is hardly surprising. As discussed in the briefing package, powder is more difficult to ingest than liquid and solid forms of many medications and household chemicals by virtue of its dryness and granularity. This is true for adults, and more so for children under five because of their level of fine-motor development. For example, preschool children have difficulty holding and manipulating ordinary game cards, and while children may display an adult pencil grip around four years of age, they lack the smooth control and coordination of the fingers, hand, and arm necessary for writing. It is not until nine or ten years that children's fine-motor skills become comparable to those of an adult (cf. Goodson & Bronson, 1985; and Therrell, Brown, Sutterby, & Thornton, 2002). The amount in each packet—less than two-tenths of one ounce for the larger size of Welchol® (CH) and less than one-tenth of one ounce for Renvela® (SC)—is small and would not result in an adverse event even if all of it were ingested. Because of the precision and control required, opening many packets and ingesting the fine powder they contain would be challenging for children under five, particularly for those at the younger end of the distribution most at-risk of ingestion incidents. It is unlikely to occur, as indicated by the lack of incidents involving similar powdered products that are intended for ingestion, such as colestipol and cholestyramine (respectively, Colestid® and Questran®; O'Brien, 2011), which have been exempt since 1979, and powdered iron supplements, which have been exempt since 1995.

As to the benefits of granting the petitions, the commenter ignores the potential benefit to patients who must use these medicines. Poor adherence to medication regimes for chronic health problems is a well-established concern, and inconvenience is negatively associated with behavioral compliance in both health care (*e.g.*, McDonald, Garg, & Hanes, 2002) and safety more generally (*e.g.*, Kalsher & Williams, 2006). Making these drugs easier to use may improve adherence, which could benefit patients with little or no risk to children.

Comment: One commenter maintained that the containers for colesevelam hydrochloride (Welchol®) and sevelamer carbonate (Renvela®) should be "… childproof [because the] drug[s] can potentially be mixed with something to create an adverse reaction." (CPSC-2011-0007-0006).

Response: As discussed in staff's original memo, it is possible that a child under five will try to mix the powder with a liquid in imitation of an adult's use. It is reasonable to assume that children might try to mix the contents of one or more packets with something else, particularly if they have observed adults do so, with these or other substances in packet form. However, the commenter provided no information to indicate what otherwise benign substance, that when mixed with Welchol® or Renvela,® would interact to cause an adverse reaction. Human Factors defers to the Directorate for Health Sciences to advise whether there are such substances.

[10] Products such as caustics that can be dangerous in small amounts are exceptions.

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TAB E: Colesevelam Hydrochloride (Welchol®) and Sevelamer Carbonate (Renvela®) Petitions for Exemption from the Child-Resistant Packaging Requirements of the Poison Prevention Packaging Act – Response to Comments and Small Business Considerations

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

Memorandum

Date: May 20, 2011

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 – Response to Comments and Small Business Considerations

Introduction

In early 2009, Daiichi Sankyo, Inc. (February 24) and Genzyme Corporation (March 6) 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). Because the two petitions are similar (both are prescription drugs currently available in pill form seeking exemption for a new powder formulation), CPSC staff addressed them together.

On February 8, 2011, the Commission voted unanimously to approve publication in the *Federal Register* of the draft notice of proposed rulemaking (NPR) that would exempt the powder formulations of colesevelam hydrochloride (Welchol®) and sevelamer carbonate (Renvela®) from the CR packaging requirements of the PPPA. The NPR was published in the *Federal Register* on February 16, 2011 (Vol. 76, No. 32, pp. 8942–8945).

Issues Raised by Public Comments

CPSC received 27 comments in response to the NPR. Fifteen comments supported the proposed exemptions, while 12 opposed the exemptions for a variety of reasons. Health Sciences and Human Factors staff considered most of the comments, and the responses are reflected in the briefing memo. None resulted in a change to staff's recommendation.

Two comments indirectly respond to the economics memo included as part of the NPR package. Both commenters were concerned that the benefits were not sufficient to balance even the "minor" costs of acute exposure effects cited by CPSC staff. However, both comments focused on a subset of benefits.

As noted by one commenter, the ease of opening the package for those with chronic conditions is indeed an advantage. A second commenter noted that the manufacturers would benefit from using fewer packaging materials. However, neither commenter mentioned another major benefit of the exemption from CR packaging—it could improve patients' adherence to their medication regimen. These advantages of non-CR packaging were balanced against the risks to children from acute exposure to colesevelam hydrochloride (Welchol®) and sevelamer carbonate (Renvela®) in both the economic memo and the full NPR package.

Based on the evidence presented in the NPR, there is little risk of acute ingestion with either drug, and the health effects that might result are "mild to moderate gastrointestinal discomfort."[11] Further, there have only been two cases involving possible acute ingestion of these drugs and no cases with the powder forms of cholestyramine and colestipol (two bile acid sequestrants with similar chemical profiles), which are already exempt from CR packaging requirements.

Small Business Considerations

Staff concluded in the NPR that the CR packaging exemption for colesevelam hydrochloride (Welchol®) and sevelamer carbonate (Renvela®) would not have any significant economic effect on a substantial number of small entities. Staff reached this conclusion, in part, because the affected firms are requesting the exemption and because both firms are large.

Staff did not receive any comments in response to the NPR regarding the impact of the exemption on small firms. Therefore, staff believes that the exemption of the powder formulations of colesevelam hydrochloride (Welchol®) and sevelamer carbonate (Renvela®) from the CR packaging requirements of the PPPA will not have a significant economic impact on a substantial number of small entities.

[11] Memorandum from Adrienne R. Layton, Ph.D., Directorate for Health Sciences dated March 15, 2010, Subject: Toxicity Review of Colesevelam Hydrochloride (Welchol®) and Sevelamer Carbonate (Renvela®).

TAB F: Draft Final Rule

DRAFT 7-5-11

[Billing Code 6355-01-P]

CONSUMER PRODUCT SAFETY COMMISSION

16 CFR Part 1700

CPSC Docket No. CPSC-2011-0007

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

AGENCY: Consumer Product Safety Commission.

ACTION: Final rule.

SUMMARY: The Consumer Product Safety Commission ("CPSC," "Commission," or "we") is amending 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 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 also available as a powder formulation and is indicated for the control of elevated serum phosphorus in chronic kidney disease patients on dialysis. The rule exempts 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: The rule becomes effective on [**insert date of publication in the FEDERAL REGISTER**].

FOR FURTHER INFORMATION CONTACT: John Boja, Office of Compliance, Consumer Product Safety Commission, Bethesda, MD 20814-4408; telephone (301) 504-7300; jboja@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.

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®. The product, in tablet form, would continue to be in CR packaging.

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

Renvela® 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 the FDA approved 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. Proposed Rule

On February 16, 2011, we published a notice of proposed rulemaking ("NPR") proposing to exempt from special packaging the powder forms of colesevelam hydrochloride (Welchol®) and sevelamer carbonate (Renvela®). 76 FR 8942. As explained in the preamble to the proposed rule, we considered the two exemption petitions together because Welchol® and Renvela® have similar chemical structures, biological properties, and powder formulations.

C. Toxicity and Human Experience Data

1. Summary of Data from Proposed Rule

As noted in the preamble to the proposed rule (76 FR at 8943), the systemic toxicity of colesevelam hydrochloride and sevelamer carbonate is limited because they are not absorbed from the gastrointestinal (GI) tract. There is no data indicating that either drug is acutely toxic. Acute toxicity is the type of toxicity that is 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.

If a child were to ingest accidentally Welchol® or 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.

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

As discussed in the preamble to the proposed rule (76 FR at 8944), we 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"). We 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. We also searched Poisindex,® Pub Med, and Google for Welchol,® Renvela,® colestipol, and cholestyramine, and found no relevant incidents of acute poisoning in humans.

Before publication of the proposed rule, and as noted therein, we 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.

The FDA gave us 151 distinct incidents of adverse events associated with Welchol® reported through the Medwatch system. We 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.®

We also received reports from the FDA of 40 distinct incidents of adverse events associated with Renvela®. We 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 treatment with Renvela®. One of the five incidents involved intestinal obstruction and perforation, which the patient's physician thought were possibly related to the patient's treatment with 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 Renvela.®

2. Updated Injury Data

We updated the injury data since publication of the proposed rule. We searched the IPII, NEISS, and death certificate databases from 2000 through 2010, for incidents associated with Welchol,® Renvela,® and related drugs (*i.e.*, cholestyramine (Questran®) and colestipol (Colestid®)). We did not identify any incidents related to Renvela,® cholestyramine, or colestipol, and identifed only one new Welchol®-related case. This incident occurred in July 2010, when a 19-month-old boy was found in his crib with an open Tylenol® bottle. The bottle was previously used for carrying Welchol® and other drugs. It was not clear from the report if any Welchol® tablets were in the bottle when the child accessed it. The child was taken to the emergency department, held overnight for observation, and then released the next day.

Additionally, we searched Poisindex® (a comprehensive database which identifies the toxicity of commercial, biological, and pharmaceutical products), and the medical literature for updated information on colesevelam hydrochloride and sevelamer carbonate colestipol, and cholestyramine. We found no incidents of acute poisoning in humans through this search.

3. Powder Formulations Generally

We 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. It would be difficult for children under 5 years old to eat large amounts of powder quickly without aspirating or coughing. It also would be difficult for children to mix powder thoroughly 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.

As noted in the preamble to the proposed rule (76 FR at 8944), 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 children in this age group are still developing, and such children are likely to spill most of the powder.

D. Response to Comments on the Proposed Rule

We published a notice of proposed rulemaking in the *Federal Register* on February 16, 2011, to exempt colesevelam hydrochloride (Welchol®) and sevelamer carbonate (Renvela®) from the special packaging requirements of the PPPA. 76 FR 8942. The proposed rule would amend our existing regulations at 16 CFR § 1700.14 by adding a new paragraph (a)(10)(xxii) to exempt coleselam hydrochloride in powder form in packages containing not more than 3.75 grams of the drug. The proposed rule also

would create a new paragraph (a)(10)(xxiii) to exempt sevelamer carbonate in powder form in packages containing not more than 2.4 grams of the drug. We received 27 comments, with 15 supporting the proposed rule. In general, the comments did not address the codified text; instead, they focused on issues relating to the drugs themselves. The comments are available at http://www.regulations.gov/#!docketDetail;rpp=50;po=0;D=CPSC-2011-0007. This section summarizes the issues raised by the comments and provides responses to those issues. Each summarized issue is identified below as a single comment, and the word "Comment," in parentheses, will appear before the summary description of all comments on that issue, and the word "Response," in parentheses, will appear before our response to the issue. We also have numbered each summarized issue as a separate comment to help distinguish between the different issues raised by the commenters and summarized by us. They are listed in no particular order.

1. Concern about Possible Harm to Children

(Comment 1) - Some commenters were concerned about what they felt was a lack of data, and they thought that these drugs could be harmful to children (*e.g.*, cause bowel obstruction, electrolyte/serum glucose imbalance, and death), particularly if ingested in large amounts. One commenter also questioned the use of adverse effect data from adults and animals in predicting toxicity from accidental poisoning in children.

(Response 1) - We typically consider all available data in toxicity assessments, with human data taking precedence over animal data. While limited data are available on the acute toxicity of Welchol® and Renvela® in children, the adverse effects reported are similar to those in adults. Because these drugs are not absorbed systemically, acute

adverse effects typically are limited to the GI tract and are unlikely to be serious. An extension of these effects would be expected in an overdose scenario. Notably, intestinal obstruction has only been observed during therapeutic use of these drugs in patients whose health has been compromised otherwise (*e.g.*, low birth weight, chronic kidney disease, and adhesions). Cases have been documented in infants and one child following treatment with a similar drug, cholestyramine. In addition, a 45-year-old male developed an intestinal obstruction, perforation, and an abdominal fistula (abnormal opening in the stomach or bowel, which allows the contents to leak) after several months of treatment with Renvela.® Intestinal obstruction has occurred very rarely after treatment with Welchol.® In fact, Welchol® has a greater specificity for bile acids than cholestyramine and colestipol and has been suggested to have greater gastrointestinal tolerance than the other two drugs.

Based on all available information, an imbalance of electrolytes or glucose control is unlikely to occur following an acute exposure to Welchol® or Renvela.® No unexpected laboratory tests were seen following chronic administration of 3.75 grams g/day of Welchol® to pediatric subjects with heterozygous familial hypercholesteremia or 15 g/day of Renvela® to normal volunteers. Chronic administration of Welchol® decreased fasting glucose levels 3.9-15.9 mg/dl. Because a blood glucose goal is 100-180 mg/dl for children, it is unlikely that acute administration of Welchol® would cause hypoglycemia (*i.e.*, low blood sugar) in a child (less than 60 mg/dl).

Moreover, as discussed in section C of this preamble, there are no available poisoning data showing that these drugs cause serious toxicity following an acute exposure.

2. Questions about Powder Form

(Comment 2) - Some commenters argued that: (1) the powder may present a choking hazard to children; and (2) there is little support for claims that the powders are more difficult for children to ingest, access from the packet without spilling, and mix thoroughly in a liquid.

(Response 2) - The low acute toxicity of Welchol® and Renvela® is a key factor for the exemptions. Additionally, CPSC's Human Factors staff considered relevant data and medical literature to conclude that powders generally present a low risk because they are more difficult to ingest, particularly in large quantities. Generally, with the exception of caustics, the primary exposure risk associated with powders is aspiration. Notably, any potential choking hazard with these drugs could also occur with any non-pharmaceutical powder formulation available in the household, such as soaps, baby powder, drink mixes, and food products.

We maintain that a child would have difficulty opening the packet of either of these drugs and mixing the powder with a liquid because of the lack of precision and control required. Moreover, there are no available poisoning data with these or similar drugs (colestipol or cholestyramine) to indicate otherwise.

3. Mixing with Other Substances

(Comment 3) - One commenter stated that he believes that "the drug can potentially be mixed with something to create an adverse reaction."

(Response 3) - The commenter provided no evidence to suggest that this is a likely event, and no information or examples of a substance that would cause an adverse reaction when mixed with Welchol® or Renvela®. Although it is possible that a child

might mix the powder with a liquid in imitation of an adult, it is highly unlikely that a child would do so repeatedly because a small child can drink only a limited amount of liquid at one time. In addition, the consistency of incompletely mixed powder is likely to deter repetition.

4. Benefits of the Exemptions

(Comment 4) - Some commenters asserted that benefits from the CR exemptions are limited: increased profits for the manufacturers of the drugs; and ease of opening the package.

(Response 4) - Exempting from CR requirements the powder forms of Welchol® and Renvela® may increase patient compliance. Poor adherence to medication regimens for chronic health issues is a well-established concern. Easier access to these drugs could benefit patients with minimal or no risk to children.

E. Effective Date

This rule exempts two drugs that otherwise would be subject to CR packaging requirements under the PPPA. Because the rule grants an exemption, it is not subject to the usual requirement under the Administrative Procedure Act ("APA") that a rule must be published 30 days before it takes effect. 5 U.S.C. 553(d)(1). Therefore, it is appropriate for the rule to become effective upon publication in the **Federal Register**.

F. Regulatory Flexibility Act Certification

Under the Regulatory Flexibility Act ("RFA"), 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 RFA 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.

As noted in the preamble to the proposed rule (76 FR at 8945), the Commission's Directorate for Economic Analysis prepared a preliminary assessment of the impact of a rule to exempt powder formulations of Welchol® and Renvela® from special packaging requirements. Based on this assessment, we preliminarily concluded that the proposed amendment exempting powder formulations of Welchol® and Renvela® from special packaging requirements would not have a significant impact on a substantial number of small businesses or other small entities. We received no comments on this assessment or any additional information. Therefore, we conclude that 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.

G. 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. As discussed in the preamble to the proposed rule, 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 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.

H. Executive Orders

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

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 rule exempting powder formulations of Welchol® and Renvela® from special packaging requirements preempts nonidentical state or local special packaging standards for the substances.

List of Subjects in 16 CFR Part 1700

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

For the reasons given above, the Commission amends 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:

* * * * *

(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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