



UNITED STATES
CONSUMER PRODUCT SAFETY COMMISSION
WASHINGTON, DC 20207

VOTE SHEET

Date: OCT - 9 2002

TO : The Commission
Todd Stevenson, Secretary

FROM : Melissa Hampshire, Acting General Counsel *MHP*
Stephen Lemberg, Assistant General Counsel *SL*
Patricia M. Pollitzer, Attorney *MP*

SUBJECT : Final Rule to Exempt HRT Products from Special Packaging Requirements

Ballot Vote Due OCT 19 2002

The staff recommends that the Commission issue a final rule to exempt hormone replacement therapy ("HRT") products from the special packaging requirements of the PPPA. A draft Federal Register notice is attached at Tab D of the briefing package.

Please indicate your vote on the following options.

I. Approve the draft Federal Register notice without change.

Signature Date

II. Approve the draft Federal Register notice with the following changes (please specify):

Signature Date

NOTE: This document has not been reviewed or accepted by the Commission.
Initial rh Date 10/9/02

CPSA 6 (b)(1) Cleared
No Mfrs/Prvtlbrs etc
Products Identified
Exempted by *[Signature]*
Firms Notified
Comments Processed

III. Do not approve the draft Federal Register notice.

Signature

Date

IV. Take other action (please specify):

Signature

Date

U.S. Consumer Product Safety Commission



Final Rule to Exempt Hormone Replacement Therapy Products from the Special Packaging Requirements of the Poison Prevention Packaging Act

For Information Contact:
Jacqueline Ferrante, Ph.D.
Directorate for Health Sciences
(301) 504-0477

CPSA 6 (b)(1) Cleared
No Mirc./Prohibits or
Products Identified
Excepted by *[Signature]*

NOTE: This document has not been
reviewed or accepted by the Commission.
Initial *rh* Date *10/9/02*

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Executive Summary

On February 19, 2002, the Commission proposed a rule to exempt hormone replacement therapy (HRT) products from the special packaging requirements of the Poison Prevention Packaging Act (PPPA) (67 FR 7319). HRT has been widely used in recent years to relieve menopausal symptoms and prevent osteoporosis. The proposed exemption is based on the low acute toxicity of the sex hormones used in these products. The Commission received one comment in favor of the proposed exemption.

Since the exemption was proposed, a study was published in the Journal of the American Medical Association showing that women using a combination of estrogen and progestin for about 5 years had an increased risk of breast cancer, heart disease, stroke, and blood clots compared to placebo. While this study suggests that HRT may not be indicated for long-term use, physicians may still consider using short-term hormone therapy for menopausal symptoms after evaluating the risks and benefits in individual patients. Therefore, HRT products are expected to remain available.

Under the PPPA, there are four exemptions for sex hormones. Three exemptions specify the hormone (i.e., conjugated estrogens, norethindrone acetate, and medroxyprogesterone acetate) and one exemption is for oral contraceptives with one or more progestogens or estrogens. HRT products contain the same or similar sex hormones as those used in oral contraceptives.

The staff recommends that the Commission issue a rule to exempt HRT products with one or more progestogen or estrogen substances.



United States
CONSUMER PRODUCT SAFETY COMMISSION
Washington, D.C. 20207

OCT - 9 2002

MEMORANDUM

To: The Commission
Todd Stevenson, Secretary

Through: Melissa Hampshire, Acting General Counsel *MH*
Through: Patricia Semple, Executive Director *PS*

From: Jacqueline Elder, ^{je} Acting Assistant Executive Director, Office of
Hazard Identification and Reduction
Jacqueline Ferrante, Ph.D., Pharmacologist, Directorate for Health *JF*
Sciences

Subject: Final rule to exempt hormone replacement therapy (HRT) products
from child-resistant (CR) packaging requirements

I. Introduction

The Commission proposed a rule (67 FR 7319) to exempt hormone replacement therapy (HRT) products from the special packaging requirements of the Poison Prevention Packaging Act (PPPA) on February 19, 2002 (Tab A). The Commission's decision was based on information provided in a staff briefing package dated January 14, 2002.

HRT products contain either estrogen alone or combinations of estrogen and progestogens (also known as progestins). These products have been used to relieve menopausal symptoms and prevent osteoporosis. Since sex hormones have low acute toxicity, the staff recommended in the proposed rule that the Commission exempt HRT products from special packaging. Moreover, a number of sex hormones are already exempt including conjugated estrogens, norethindrone acetate, and medroxyprogesterone acetate, and oral contraceptives with one or more progestins or estrogens.

A. Recent Study

Since the exemption was proposed, a Women's Health Initiative (WHI) study was terminated three years early when it was shown that women treated for a mean 5.2 years with a combination HRT product containing conjugated equine estrogens (0.625 mg/day) and medroxyprogesterone acetate (2.5 mg/day) had an increased relative risk of invasive breast cancer compared to women taking a placebo (WHI

CPSA 6 (b)(1) Cleared

10/9/02
[Signature]

NOTE: This document has not been reviewed or accepted by the Commission.
Initial *rh* Date 10/9/02

Investigators, 2002; Lacey et al., 2002). Other negative observations included an increased risk of heart disease, stroke, and pulmonary embolism. The study also showed that there were beneficial effects including decreases in colorectal cancer and hip fracture.

The WHI study did not address the risks and benefits associated with short-term estrogen/progestin HRT nor did it examine different doses, different estrogens or progestins (e.g., estradiol or norgestimate), or alternative formulations (e.g., transdermal patches).

Given this new information, the American College of Obstetricians and Gynecologists (ACOG) advises women taking combination HRT that the increased risks of breast cancer in the recent study “applied to an entire population of women, not to increased risks for individual women” (ACOG, 2002). Concerning a woman’s short-term use of combined HRT for relief of menopausal symptoms, the ACOG recommends that “this be a personal, individualized decision, made after consultations between a woman and her physician taking into account a woman’s individual benefits and risks from such use.” Thus, HRT may still be used and made available to some women. The risks associated with chronic hormone therapy are not expected in children after a single acute ingestion.

II. Poisoning Data

In the proposed rule, the staff provided acute poisoning data for estrogens, progestins and oral contraceptives involving children under five years old from the American Association of Poison Control Centers (AAPCC) Toxic Exposure Surveillance System (TESS) from 1993 to 1998. During this time period, there were no reported deaths and most of these cases were non-toxic. The staff reviewed available AAPCC poisoning data since that time and found that there were no major outcomes or deaths in any of these hormone categories in 1999 and 2000.

III. Public Comment

Berlex Laboratories Inc. submitted the only comment to the Commission, which supports the proposed exemption (Tab B). Berlex currently markets estrogen replacement therapy (ERT), long-acting contraception, and oral contraception products with plans to market an oral HRT product in the near future. Berlex states that the proposed exemption is “beneficial in terms of cost and efficiency” and provides “drug producers greater flexibility in meeting the needs of the HRT patient population.”

IV. Economic Information

The Directorate for Economic Analysis determined that exempting HRT products from special packaging requirements would not have a significant impact on the environment or on a substantial number of small businesses (Tab C). The exemption allows more packaging options and is expected to reduce the final

product cost because manufacturers can use slightly cheaper packages. Additionally, the Commission's regulations state that rules exempting products from special packaging requirements under the PPPA usually have little or no potential for affecting the environment.

V. Effective Date

This rule would lift the requirements for child-resistant (CR) packaging usually applicable to oral prescription drugs. Thus, the rule would not impose new requirements. Under these circumstances, the staff recommends that the rule become effective upon publication in the Federal Register.

VI. Options

A. The Commission may issue a rule to exempt HRT products from special packaging requirements if it concludes that special packaging is not required to protect children from serious personal injury or illness resulting from handling, using, or ingesting HRT products.

B. The Commission may decline to issue a rule to exempt HRT products from special packaging requirements if the findings cannot be made.

VII. Conclusion and Recommendation

Sex hormones (estrogen and progesterone) have low acute toxicity. While recent studies show that the risks associated with the long-term use of these products may outweigh the benefits, health providers may still use HRT for short-term treatment of menopausal symptoms in some women after careful evaluation. Additionally, therapy with estrogen alone is still an option for women who have had a hysterectomy.

Although a number of currently marketed HRT products do not require CR packaging, others are not exempt because they do not fall under a current exemption for sex hormones (including some natural forms of estrogen such as estradiol). Based on available information, the staff recommends that the Commission issue a rule to exempt HRT products from the special packaging requirements of the PPPA that rely solely upon the activity of one or more progesterone or estrogen substances. A draft Federal Register notice is at Tab D.

VIII. References

ACOG (American College of Obstetricians and Gynecologists) website, www.acog.org, 2002.

WHI (Women's Health Initiative) Investigators, Principal Results from the Women's Health Initiative Randomized Controlled Trial. JAMA, 288(3):321-333, 2002.

Lacey , J., Mink, P., Lubin, J., Sherman, M., Troisi, R. and Hartage, P. JAMA 288 (3):334-341, 2002.

TAB A

stator assembly's inner seal support to a serviceable configuration. This condition, if not corrected, could result in increased fatigue damage of the second stage turbine stator inner seal support, rotating knife seal, and the second and third stage turbine wheels which may result in an uncontained rotor failure and damage to the aircraft.

FAA's Determination of an Unsafe Condition and Proposed Actions

Since an unsafe condition has been identified that is likely to exist or develop on other Honeywell International Inc. TPE331 series turboprop and TSE331-3U turboshaft engines of the same type design, the proposed AD would require replacing the existing second stage turbine stator assemblies, P/N's 894528-1, -2, -3, -5, -6, -10, and -11, with serviceable assemblies.

Economic Effect

There are approximately 4,700 engines of the affected design in the worldwide fleet. The FAA estimates that 2,350 engines installed on aircraft of U.S. registry would be affected by this proposed AD, that it would take approximately 4.0 work hours per engine to do the proposed actions, and that the average labor rate is \$60 per work hour. Required replacement parts would cost approximately \$8,000 per engine. Based on these figures, the total cost of the proposed AD on U.S. operators is estimated to be \$14,958,000.

This proposed rule does not have federalism implications, as defined in Executive Order 13132, because it would not have a substantial direct effect on the States, on the relationship between the national government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the FAA has not consulted with state authorities prior to publication of this proposed rule.

For the reasons discussed above, I certify that this proposed regulation (1) is not a "significant regulatory action" under Executive Order 12866; (2) is not a "significant rule" under the DOT Regulatory Policies and Procedures (44 FR 11034, February 26, 1979); and (3) if promulgated, will not have a significant economic impact, positive or negative, on a substantial number of small entities under the criteria of the Regulatory Flexibility Act. A copy of the draft regulatory evaluation prepared for this action is contained in the Rules Docket. A copy of it may be obtained by contacting the Rules Docket at the location provided under the caption ADDRESSES.

List of Subjects in 14 CFR Part 39

Air transportation, Aircraft, Aviation safety, Safety.

The Proposed Amendment

Accordingly, pursuant to the authority delegated to me by the Administrator, the Federal Aviation Administration proposes to amend part 39 of the Federal Aviation Regulations (14 CFR part 39) as follows:

PART 39—AIRWORTHINESS DIRECTIVES

1. The authority citation for part 39 continues to read as follows:

Authority: 49 U.S.C. 106(g), 40113, 44701.

§ 39.13 [Amended]

2. Section 39.13 is amended by adding the following new airworthiness directive:

Honeywell International Inc.: Docket No. 99-NE-53-AD.

Applicability: This airworthiness directive (AD) is applicable to Honeywell International Inc. (formerly AlliedSignal Inc., Garrett Engine Division, Garrett Turbine Engine Company, and AiResearch Manufacturing Company of Arizona) Model TPE331-1, -2, -2UA, -3U, -3UW, -5, -5A, -5AB, -5B, -6, and -6A series turboprop and TSE331-3U Model turboshaft engines with second stage turbine stator assemblies, part numbers (P/N's) 894528-1, -2, -3, -5, -6, -10, and -11. These engines are installed on, but not limited to Ayres S-2R series; Beech 18 and 45 series and model JRB-6, 3N, 3NM, 3TM, and B100 airplanes; Construcciones Aeronauticas, S.A. (CASA) C-212; De Havilland DH104 series 7AXC (Dove); Dornier 228 series; Fairchild SA226 series (Swearingen Merlin and Metro series); Grumman American G-164 series; Mitsubishi MU-2 and MU-2B series; Pilatus PC-6 series (Fairchild Porter and Peacemaker); Prop-Jets, Inc. Model 400; Rockwell Commander S2-R; Schweizer G-164 series; Shorts Brothers and Harland, Ltd. SC7 (Skyvan); and Twin Commander 680 and 690 series (Jetprop Commander) airplanes; and Sikorsky S-55 series (Helitec Corp. S55T) helicopters.

Note 1: This AD applies to each engine identified in the preceding applicability provision, regardless of whether it has been modified, altered, or repaired in the area subject to the requirements of this AD. For engines that have been modified, altered, or repaired so that the performance of the requirements of this AD is affected, the owner/operator must request approval for an alternative method of compliance in accordance with paragraph (c) of this AD. The request should include an assessment of the effect of the modification, alteration, or repair on the unsafe condition addressed by this AD; and, if the unsafe condition has not been eliminated, the request should include specific proposed actions to address it.

Compliance: Compliance with this AD is required as indicated, unless already done. To reduce fatigue damage of the second stage turbine stator inner seal support,

rotating knife seal, and the second and third stage turbine wheels which may result in an uncontained rotor failure and damage to the aircraft, do the following:

(a) Replace second stage turbine stator assemblies, P/N's 894528-1, -2, -3, -5, -6, -10, and -11, with a new or reworked second stage turbine stator assembly at the next removal of the second stage turbine stator assembly from the engine or at the next turbine section inspection, but do not exceed 3,100 engine operating hours since last turbine section inspection. Information for replacing second stage turbine stator assemblies is available in Honeywell International Inc. Alert Service Bulletin (ASB) TPE331-A72-2082 dated May 16, 2001. Information for reworking second stage turbine stator assemblies is available in Honeywell International Inc. SB TPE331-72-2085RWK dated May 16, 2001.

(b) After the effective date of this AD, do not install any second stage turbine stator assembly/P/N's 894528-1, -2, -3, -5, -6, -10, and -11.

Alternative Methods of Compliance

(c) An alternative method of compliance or adjustment of the compliance time that provides an acceptable level of safety may be used if approved by the Manager, Los Angeles Aircraft Certification Office (LAACO). Operators must submit their request through an appropriate FAA Principal Maintenance Inspector, who may add comments and then send it to the Manager, LAACO.

Note 2: Information concerning the existence of approved alternative methods of compliance with this airworthiness directive, if any, may be obtained from the LAACO.

Special Flight Permits

(d) Special flight permits may be issued in accordance §§ 21.197 and 21.199 of the Federal Aviation Regulations (14 CFR 21.197 and 21.199) to operate the aircraft to a location where the requirements of this AD can be done.

Issued in Burlington, Massachusetts, on February 12, 2002.

Francis A. Favara,

Acting Manager, Engine and Propeller Directorate, Aircraft Certification Service.

[FR Doc. 02-3877 Filed 2-15-02; 8:45 am]

BILLING CODE 4910-13-U

CONSUMER PRODUCT SAFETY COMMISSION

16 CFR Part 1700

Poison Prevention Packaging Requirements; Proposed Exemption of Hormone Replacement Therapy Products

AGENCY: Consumer Product Safety Commission.

ACTION: Proposed rule.

SUMMARY: The Commission is proposing to amend its child-resistant packaging

requirements to exempt hormone replacement therapy ("HRT") products containing one or more progestogen or estrogen substances. Current exemptions cover some HRT products, but not others. This proposal would uniformly exempt all HRT products that rely solely on the activity of one or more progestogen or estrogen substances from child resistant packaging requirements.

DATES: Comments on the proposal should be submitted no later than May 6, 2002.

ADDRESSES: Comments should be mailed to the Office of the Secretary, Consumer Product Safety Commission, Washington, DC 20207, or delivered to the Office of the Secretary, Consumer Product Safety Commission, Room 502, 4330 East-West Highway, Bethesda, Maryland 20814-4408, telephone (301) 504-0800. Comments may also be filed by telefacsimile to (301) 504-0127 or by email to cpsc-os@cpsc.gov. Comments should be captioned "Proposed HRT exemption."

FOR FURTHER INFORMATION CONTACT:

Jacqueline Ferrante, Ph.D., Division of Health Sciences, Directorate for Epidemiology and Health Sciences, Consumer Product Safety Commission, Washington, DC 20207; telephone (301) 504-0477 ext. 1199.

SUPPLEMENTARY INFORMATION:

A. Background

The Poison Prevention Packaging Act of 1970 ("PPPA"), 15 U.S.C. 1471-1476, provides the Commission with authority to establish standards for the special packaging of household substances, such as drugs, when child resistant 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, the Commission requires that oral prescription drugs be in child resistant ("CR") packaging. 16 CFR 1700.14(a)(10).

The Commission's regulations allow exemptions from this requirement for substances with low acute toxicity. Currently, there are four PPPA exemptions for sex hormones: (1) Oral contraceptives in mnemonic packages containing one or more progestogen or estrogen substances; (2) conjugated estrogen tablets in mnemonic packages; (3) norethindrone acetate tablets in mnemonic packaging; and (4) medroxyprogesterone acetate tablets. 16 CFR 1700.14(a)(10)(iv), (xvii), (xviii) and (xix). Some HRT products fall within these exemptions, but because of the way these exemptions are written, other

HRT products currently require CR packaging. The proposed exemption would cover all HRT products that rely solely on the activity of one or more progestogen or estrogen substances.

B. HRT Products

HRT is used to replace the estrogen and progesterone that normally decline following menopause (the cessation of menstruation). Generally, women experience a range of symptoms with some reporting minimal discomfort, while others have more severe effects. Hot flashes are the most frequent symptom and often begin several years before other menopausal symptoms. Additionally, menopause accelerates bone depletion that commonly occurs with aging, leading to osteoporosis.

HRT relieves a number of menopausal symptoms (e.g., hot flashes and vaginitis) and helps to prevent osteoporosis. HRT consists of using estrogen alone or various combinations of estrogens and progestins. The latter regimen is similar to that for oral contraceptive products except the goal of therapy is to replace declining hormone levels rather than to prevent pregnancy.

Because the life expectancy of women in the United States is increasing, it is estimated that 40 million women will go through menopause in the next 20 years. Therefore, the pharmaceutical industry is developing new prescription products specifically designed and marketed for HRT post-menopausal women. Some of these products may not be covered under current PPPA regulations although their toxicity is as low as those products currently exempt.

Sex hormone products contain various estrogens and progestins. Some are natural hormones (e.g., estradiol) and others are semi-synthetic or synthetic (e.g., norgestimate). Synthetic hormones are usually developed to alter bioavailability (e.g., enhance oral absorption) or to reduce side effects. Since available HRT products contain similar estrogen/progestin combinations, it is reasonable and consistent to exempt them like oral contraceptives.

C. Toxicity Data

Human toxic doses for estrogens or progestins have not been defined. Exposure summaries in the *Poisindex*® for estrogens, progestins, and oral contraceptives state that acute toxicity is unlikely following overdosage. Gastrointestinal effects (e.g., nausea, vomiting, abdominal cramps) may occur after an acute overdose, but typically no treatment is necessary.

There is little information in the medical literature concerning acute overdosage of progestins or estrogens. One case showed that a single dose of 160 mg estradiol valerate (80 tablets/2 mg each), ingested by a 19-year-old woman in a suicide attempt, produced little toxicity. The woman slept easily during the night of the ingestion and the next evening presented in the emergency clinic in generally good condition with nausea and a headache.

Poisoning data from the American Association of Poison Control Centers ("AAPCC") Toxic Exposure Surveillance System ("TESS"), corroborate the lack of acute toxicity associated with sex hormones. The staff reviewed data showing acute exposures in children less than five years old to estrogens, progestins, and oral contraceptives from 1993 to 1998. There were no deaths and most of the exposures were non-toxic. There was one major outcome out of 37,645 exposures to oral contraceptives, but no details are readily available relating to this case. It is possible that this oral contraceptive formulation contained iron or that the child was exposed to a second substance or product.

D. Impact on Small Business

The Commission's Directorate for Economic Analysis prepared a preliminary assessment of the impact of a rule to exempt HRT products from special packaging requirements. The staff reports that it does not know the universe of companies that would be affected by the proposed exemption or how many companies would be small businesses. However, the exemption is not likely to have a significant impact on a substantial number of companies, regardless of size. The exemption would actually increase the packaging options for manufacturers because it would allow them to package the affected HRT products in non-CR packages. Although the cost to manufacturers of CR packaging is small—usually only a few cents per package—the exemption would allow manufacturers to use slightly cheaper packages and thus reduce the final cost of the HRT products.

Based on this assessment, the Commission preliminarily concludes that the proposed amendment exempting HRT products 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, the Commission has assessed the possible environmental effects associated with the proposed PPPA amendment.

The Commission's 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. (3) 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(z). 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 non-identical 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 HRT products from special packaging requirements would preempt non-identical state or local special packaging standards for those products.

The Commission has also evaluated the proposed rule in light of the principles stated in Executive Order 13132 concerning federalism, even though that Order does not apply to independent regulatory agencies such as

CPSC. The Commission does not expect that the proposed rule will have any substantial direct effects on the States, the relationship between the national government and the States, or the distribution of power and responsibilities among various levels of government.

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: Pub. L. 91-601, secs. 1-9, 84 Stat. 1670-74, 15 U.S.C. 1471-76. Secs 1700.1 and 1700.14 also issued under Pub. L. 92-573, sec. 30(a), 88 Stat. 1231, 15 U.S.C. 2079(a).

2. Section 1700.14 is amended by adding new paragraph (a)(10)(xxi) to read as follows (although unchanged, the introductory texts of paragraph (a) and paragraph (10) are included below for context):

§ 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:

* * * * *

(xxi) *Hormone Replacement Therapy Products* that rely solely upon the activity of one or more progestogen or estrogen substances.

* * * * *

Dated: February 12, 2002.

Todd Stevenson,
Secretary, Consumer Product Safety Commission.

List of Relevant Documents

1. Briefing memorandum from Jacqueline Ferrante, Ph.D., Directorate for Health Sciences, to the Commission, "Proposed Rule to Exempt HRT Products from the Special Packaging Requirements of the PPPA," January 14, 2002.

2. Memorandum from Robert Franklin, Directorate for Economic Analysis, to Jacqueline Ferrante, Ph.D., Project Manager, "Small Business and Environmental Considerations Related to Exempting HRT Products from PPPA Requirements," December 20, 2001.

[FR Doc. 02-3995 Filed 2-15-02; 8:45 am]
BILLING CODE 6355-01-P

DEPARTMENT OF TRANSPORTATION

Coast Guard

33 CFR Part 165

[COTP Los Angeles-Long Beach 02-003]

RIN 2115-AA97

Safety Zone; Long Beach, CA

AGENCY: Coast Guard, DOT.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Coast Guard proposes to establish a temporary safety zone in the navigable waters of Long Beach, California for the National Water Ski Racing Association (NWSRA) Water Ski Race from 8 a.m. to 5 p.m. on March 23 and 24, 2002. This safety zone is necessary to provide for the safety of the crew and participants of the race and to protect the participating vessels. Persons and vessels are prohibited from entering into or transiting through this safety zone unless authorized by the Captain of the Port or his designated representative.

DATES: Comments and related material must reach the Coast Guard on or before March 6, 2002.

ADDRESSES: You may mail comments and related material to U.S. Coast Guard Marine Safety Office/Group Los Angeles-Long Beach, 1001 S. Seaside Avenue, Building 20, San Pedro, California, 90731. U.S. Coast Guard Marine Safety Office/Group Los Angeles-Long Beach maintains the public docket for this rulemaking. Comments and material received from the public, as well as documents indicated in this preamble as being available in the docket, will become part of this docket and will be available for

TAB B



United States
CONSUMER PRODUCT SAFETY COMMISSION
Washington, D.C. 20207

MEMORANDUM

DATE: May 7, 2002

TO : HS

Through: Todd A. Stevenson, Secretary, OS

FROM : Martha A. Kosh, OS

SUBJECT: Proposed Rule to Exempt Hormone Replacement Therapy (HRT) Products from the Special Packaging Requirements of the Poison Prevention Packaging Act

ATTACHED ARE COMMENTS ON THE CP 02-1

<u>COMMENT</u>	<u>DATE</u>	<u>SIGNED BY</u>	<u>AFFILIATION</u>
CP 02-1	4/17/02	Michael Doroshuk Manager, Drug Regulatory Affairs	Berlex Drug Development & Technology 340 Changebridge Rd. P.O. Box 1000 Montiville, NJ 07045

2nd Day UPS

April 17, 2002

Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 487-2000

U.S. Consumer Product Safety Commission - Office of the Secretary - Room 502
4330 East-West Highway
Bethesda, Maryland 20814-4408
Attention: Jacqueline Ferrante, Ph.D. Room 600-08

Dear Dr. Ferrante:

Re: Proposed Rule to Exempt Hormone Replacement Therapy (HRT) Products from the Special Packaging Requirements of the Poison Prevention Packaging Act

Reference is made to the Federal Register notice dated February 19, 2002 (Volume 67, Number 33, page 7319 ff.), proposing to exempt all HRT products that rely solely on the activity of one or more progestogen or estrogen substances from child resistant (CR) packaging requirements.

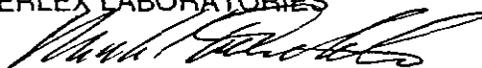
Berlex Laboratories, Inc. ("Berlex"), a subsidiary of Schering AG, Germany, is a leading supplier of hormones to the U.S. market. Berlex has a major US presence in the area of female healthcare, with products for estrogen replacement therapy (ERT), long-acting contraception, and oral contraception. Berlex plans to enter the oral HRT market soon and finds the consistency of packaging for our oral contraception and oral HRT products, as proposed, to be beneficial in terms of costs and efficiency.

Berlex strongly supports the proposed amendment. As noted in the Federal Register announcement, progestogens and estrogens are generally considered to be of low acute toxicity, and the same types of substances are used in oral contraceptives which are already exempt from CR packaging requirements. Therefore, the exemption should be extended to HRT products. In addition, this exemption will give drug producers greater flexibility in meeting the needs of the HRT patient population.

If you have questions or if we can be of further assistance, please contact the undersigned at (973) 487-2184, FAX (973) 487-2016, or email: michael_doroshuk@berlex.com.

Sincerely,

BERLEX LABORATORIES



Michael Doroshuk
Manager, Drug Regulatory Affairs

TAB C



UNITED STATES
CONSUMER PRODUCT SAFETY COMMISSION
WASHINGTON, DC 20207

Memorandum

Date: September 9, 2002

TO : Jacqueline Ferrante
Directorate for Health Sciences

THROUGH: Warren Prunella, AED, Directorate for Economic Analysis *WPP*

FROM : Robert Franklin *RF*
Economist
Directorate for Economic Analysis

SUBJECT : Small Business and Environmental Considerations Related to Exempting HRT Products from PPPA Requirements.

Earlier this year the U.S. Consumer Product Safety Commission (CPSC) issued a notice of proposed rulemaking (NPR) that would exempt hormone replacement therapy (HRT) products from the requirements of the Poison Prevention Packaging Act (PPPA). The notice was published in the Federal Register on 19 February 2002 (67 Federal Register 33). Despite the low acute toxicity of HRT products, they are available only by prescription and so must be in child-resistant packaging unless they are specifically exempted from those requirements. The exemption would apply to HRT products, used for the treatment of menopausal symptoms, that contain one or more progestogen or estrogen substances. The Commission has previously granted exemptions from special packaging requirements for other products that contain the same or similar sex hormones as HRT products, such as oral contraceptives packaged in mnemonic packages. The Commission has also exempted certain specific sex hormones (i.e., conjugated estrogens, norethindrone acetate, and medroxyprogesterone acetate) from some special packaging requirements. The proposed rule would provide a more generic and consistent exemption for HRT products that are generally considered to have low acute toxicity.

Small Business Considerations

A preliminary regulatory flexibility analysis was published with the proposed rule. The analysis stated that although the Commission did not know the universe of companies that would be affected by the proposed rule, it did not believe that the proposed exemption would have a significant adverse economic impact on a substantial number of companies. The exemption would increase the packaging options of manufacturers because it would allow them to package the affected HRT products in non-CR packages. The cost to manufacturers of child-resistant packaging is small, usually only a few cents per package, thus any cost savings is likely to be small. However, because the exemption will allow manufacturers to avoid the use of the slightly more expensive CR packages, it is expected to reduce the final cost of the HRT products.

The Commission received only one comment in response to the NPR. The commenter, a manufacturer of HRT products concurred with the preliminary regulatory flexibility analysis. The commenter stated that the proposed rule exempting HRT products from the requirements of the PPPA would “be beneficial in terms of costs and efficiency.”

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, the staff assessed the possible environmental effects that may be associated with an exemption from CR packaging requirements for HRT products.

The Commission’s regulations at 16 CFR Sec. 1021.5(c)(3) state that rules exempting products from special packaging requirements under the PPPA normally have little or no potential for affecting the human environment. There is no reason to suspect that this exemption would be any different. The staff does not believe that this exemption will have any significant impact on the human environment.

TAB D

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CONSUMER PRODUCT SAFETY COMMISSION

16 CFR Part 1700

Poison Prevention Packaging Requirements;

Exemption of Hormone Replacement Therapy Products

AGENCY: Consumer Product Safety Commission.

ACTION: Final rule.

SUMMARY: The Commission is amending its child-resistant packaging requirements to exempt hormone replacement therapy ("HRT") products containing one or more progestogen or estrogen substances. Current exemptions cover some HRT products, but not others. This rule would uniformly exempt from child resistant packaging requirements all HRT products that rely solely on the activity of one or more progestogen or estrogen substances.

DATES: The rule is effective _____ [insert date of publication in the **FEDERAL REGISTER**], and applies to products packaged on or after that date.

FOR FURTHER INFORMATION CONTACT: Geri Smith, Office of Compliance and Enforcement, Consumer Product Safety Commission, Washington, D.C. 20207; telephone (301) 504-0608 ext. 1160.

SUPPLEMENTARY INFORMATION:

A. Background

The Poison Prevention Packaging Act of 1970 ("PPPA"), 15 U.S.C. 1471-1476, authorizes the Commission to issue standards for the special packaging of household substances, such as drugs, when (1) child resistant packaging is necessary to protect children from serious personal injury or illness due to the substance and (2) the special packaging is technically feasible, practicable, and appropriate for the substance. Accordingly, a Commission rule requires that oral prescription drugs be in child resistant ("CR") packaging. 16 CFR 1700.14(a)(10).

The Commission's regulations allow exemptions from this requirement for substances that have low acute toxicity. 16 CFR 1702.1(b) and 1702.7. Current regulations provide four PPPA exemptions for sex hormones: (1) oral contraceptives in mnemonic packages containing one or more progestogen or estrogen substances; (2) conjugated estrogen tablets in mnemonic packages; (3) norethindrone acetate tablets in mnemonic packaging; and (4) medroxyprogesterone acetate tablets. 16 CFR 1700.14(a)(10)(iv), (xvii), (xviii) and (xix). Some HRT products fall within these exemptions, but because of the way these exemptions are written, other HRT products currently require CR packaging.

On February 19, 2002, the Commission published a notice of proposed rulemaking (“NPR”) proposing to exempt from the special packaging requirements HRT products containing one or more progestogen or estrogen substances. 67 FR 7319. This rule will make the exemption of HRT products more uniform by exempting all HRT products that rely solely on the activity of one or more progestogen or estrogen substances.

B. HRT Products

HRT is used to replace the estrogen and progesterone that normally decline following menopause (the cessation of menstruation). Women may experience a range of menopausal symptoms. Additionally, menopause accelerates bone depletion that commonly occurs with aging, leading to osteoporosis.

HRT has been used to relieve a number of menopausal symptoms and help to prevent osteoporosis. HRT consists of using estrogen alone or various combinations of estrogens and progestins, similar to oral contraceptives. Some are natural hormones (e.g., estradiol) and others are semi-synthetic or synthetic (e.g., norgestimate). Since available HRT products contain estrogen/progestin combinations similar to oral contraceptives, it is reasonable and consistent to exempt them similarly.

Recently, studies have raised questions about the health effects of HRT. A Women’s Health Initiative study indicated that women treated for about 5 years with a combination of

estrogen and progestin had an increased risk of breast cancer, heart disease, stroke and blood clots compared to placebo. While this study suggests that HRT may not be indicated for long term use, it did not examine different doses, different estrogen or progestins or alternative formulations. It is likely that physicians may consider prescribing short term hormone therapy for menopausal symptoms after evaluating the risks and benefits for individual patients. Because the acute toxicity of HRT is low and its use is likely to continue even with the questions raised about its long term use, the Commission believes that a rule uniformly exempting HRT products from CR packaging requirements is appropriate.

C. Toxicity Data

Human toxic doses for estrogens or progestins have not been defined. Exposure summaries in the Poisindex® for estrogens, progestins, and oral contraceptives state that acute toxicity is unlikely following overdosage. Gastrointestinal effects (e.g., nausea, vomiting, abdominal cramps) may occur after an acute overdose, but typically no treatment is necessary.

The medical literature provides little information concerning acute overdosage of progestins or estrogens. One case mentioned in the NPR showed that a single dose of 160 mg estradiol valerate (80 tablets/2 mg each), ingested by a 19-year-old woman in a suicide attempt, produced little toxicity. The woman slept easily during the night of the ingestion and the next evening presented in the emergency clinic in generally good condition with nausea and a headache.

For the NPR, the staff reviewed poisoning data from the American Association of Poison Control Centers (“AAPCC”) Toxic Exposure Surveillance System (“TESS”) showing acute exposures in children less than five years old to estrogens, progestins, and oral contraceptives from 1993 to 1998. There were no deaths and most of the exposures were non-toxic.

For this final rule, the staff reviewed available AAPCC data since the NPR was published, and found no major outcomes or deaths in any of the hormone categories in 1999 and 2000 (the most recent data available).

D. Public Comment on the NPR

The Commission received one comment in response to the NPR. It came from Berlex Laboratories, which wrote that it currently markets estrogen replacement therapy, long-acting contraception, and oral contraception products and plans to market an oral HRT product in the near future. Berlex states that the proposed exemption is “beneficial in terms of cost and efficiency” and provides “drug producers greater flexibility in meeting the needs of the HRT patient population.”

E. Effective Date

With this rule, the Commission issues an exemption from the child-resistant packaging requirements generally applicable to oral prescription drugs. Thus, the rule imposes no new requirements, but lifts requirements currently in existence for some HRT products (some HRT products are already exempt from CR packaging requirements). Under these circumstances the Commission believes it is appropriate for the rule to become effective on the date it is published in the Federal Register.

F. Impact on Small Business

As discussed in the NPR, the Commission preliminarily concluded that the proposed amendment exempting HRT products from special packaging requirements would not have a significant impact on a substantial number of small businesses or other small entities. This conclusion was based on the fact that the exemption would actually increase the packaging options for manufacturers because it would allow them to package the affected HRT products in non-CR packages. Thus, the exemption is not likely to have a significant impact on a substantial number of companies, regardless of size.

G. Environmental Considerations

In the NPR, the Commission also discussed possible impact on the environment as required by the National Environmental Policy Act, and in accordance with the Council on Environmental Quality regulations and CPSC procedures for environmental review. The

Commission found that, 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 non-identical 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).

Accordingly, with the exceptions noted above, the rule exempting HRT products from special packaging requirements would preempt non-identical state or local special packaging standards for those products.

The Commission has also evaluated the rule in light of the principles stated in Executive Order 13132 concerning federalism, even though that Order does not apply to independent regulatory agencies such as CPSC. The Commission does not expect that the rule will have any substantial direct effects on the States, the relationship between the national government and the States, or the distribution of power and responsibilities among various levels of government.

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: Pub. L. 91-601, secs. 1-9, 84 Stat. 1670-74, 15 U.S.C. 1471-76. Secs 1700.1 and 1700.14 also issued under Pub. L. 92-573, sec. 30(a), 88 Stat. 1231. 15 U.S.C. 2079(a).

2. Section 1700.14 is amended by adding new paragraph (a)(10)(xxi) to read as follows (although unchanged, the introductory texts of paragraph (a) and paragraph (10) are included below for context):

§ 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:

* * * * *

(xxi) Hormone Replacement Therapy Products that rely solely upon the activity of one or more progestogen or estrogen substances.

Dated: _____

Todd Stevenson, Secretary
Consumer Product Safety Commission

List of Relevant Documents

1. Briefing memorandum from Jacqueline Ferrante, Ph.D., Directorate for Health Sciences, to the Commission, "Final Rule to Exempt Hormone Replacement Therapy Products from the Special Packaging Requirements of the Poison Prevention Packaging Act," _____, 2002.
2. Memorandum from Robert Franklin, Directorate for Economic Analysis, to Jacqueline Ferrante, Ph.D., Project Manager, "Small Business and Environmental Considerations Related to Exempting HRT Products from PPPA Requirements," _____, 2002.