3. Article 2—Water Resources Program

No proposed revisions to this article are recommended at this time.

4. Article 3—Project Review Under Section 3.8 of the Compact

(a) The proposed revisions to Article 3 relating to environmental reviews and non-substantial projects are discussed above.

(b) The proposed revision would delete Section 2–3.5.1. The regionalization policy was slightly modified with the adoption of revised Water Quality Regulations in December 1992 (Section 2.30, Basin Regulation—Water Quality). Deleting these requirements eliminates confusion and allows the more recent and flexible policy to control. The revised rule would add (6) in Section 2.1.4 requiring applications to include a discussion of the alternates considered and in Section 2.3.8 (a) ''Exhibits to Accompany Application'', it would revise (8) to include analysis and conclusions of regional water supply and waste water investigations.

(c) The proposed revision would also delete Section 2.3.5.2. This policy was adopted in 1971, Resolution No. 71–3, when the DRBC was involved in four or five nuclear plants and several major expansions or new fossil fuel plants, all by the seven major electric utilities serving the Basin. Planning at that time centered around mega stations of 1000 to 3000 Megawatts and use of multi MGD of water. Future locations of such large single use water demands was essential for any future water resource planning. A consortium of the utilities was formed known as DRBEUG (Delaware River Basin Electric Utilities Group) to address this DRBC requirement. Between 1971 and 1989, periodic siting studies were submitted to DRBC. In 1989 DRBEUG explained that they no longer could present a comprehensive siting study since the regulators were now encouraging NUGs (Non Utility Generators) and they could not in any way appear to represent these non-utility electric generators. Essentially, the major utilities have abandoned plans for any new major stations. New applications for several years now have been non-utility projects and generally no more than 200 MW. After several meetings between DRBEUG and staff, it was concluded that the siting study would no longer serve its intended purpose for DRBC.

(d) The remaining sections are intended to clarify the Commission's procedures with regard to Section 3.8 applications and the review thereof.

5. Article 4—Environmental Impact Statements

The Commission proposes deletion of the existing provisions of Article 4 as discussed above. Article 4 will be reserved for future use.

6. Article 5—Review in Water Quality Cases

The proposed revisions to Article 5 clarify that this article applies to administrative actions and decisions by the Executive Director. The procedures for review, hearing and decisions of objections to the Executive Director's actions and decisions will be pursuant to Article 6. The time for requesting a hearing is extended to thirty days to conform with the thirty day period provided for in Article 6. The remaining proposed changes are to broaden the wasteload allocations section to cover allocations in general (including proposed allocations of toxics) as well as the existing allocation program of carbonaceous oxygen demand.

7. Article 6—Conduct of Hearings

The proposed revisions in this article reflect the practices employed by the Commission in connection with hearings, clarify the application of Article 6 to contested hearings and codify existing practices with regard to such hearings.

8. Articles 7, 8 and 9

No changes to these articles are proposed at this time.

Copies of the full text of the proposed amendments to the Administrative Manual—Rules of Practice and Procedure may be obtained by contacting Susan M. Weisman at the address provided in **FOR FURTHER INFORMATION CONTACT**. Persons wishing to testify are requested to notify the Secretary in advance.

Dated: August 18, 1997.

Delaware River Basin Compact, 75 Stat. 688.

Susan M. Weisman,

Secretary.

[FR Doc. 97–23058 Filed 8–28–97; 8:45 am]

BILLING CODE 6360–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 336, 338, 341, and 348

[Docket No. 97N–0128]

RIN 0910–AA01

Labeling of Diphenhydramine-Containing Drug Products for Over-the-Counter Human Use

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend the tentative final monograph for over-the-counter (OTC) external analgesic drug products, and the final monographs for oral OTC diphenhydramine drug products for antiemetic, antihistamine, antitussive, and nighttime sleep-aid indications. The amendment adds warning statements concerning diphenhydramine toxicity. The proposed warnings advise consumers not to use topical products containing diphenhydramine on chicken pox, poison ivy, sunburn, large areas of the body, blistered or oozing skin, more often than directed, or with any other product containing diphenhydramine, even one taken by mouth, and not to use oral OTC diphenhydramine products with any other product containing diphenhydramine including products used topically. This proposal is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Submit written comments by November 28, 1997. FDA is proposing that any final rule that may issue based on this proposal become effective 12 months after the date of its publication in the **Federal Register**.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Nahid Mokhtari-Rejali, Center for Drug Evaluation and Research (HFD–560), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–2222.

SUPPLEMENTARY INFORMATION:

I. Background

Diphenhydramine hydrochloride is proposed for inclusion in the monograph for OTC external analgesic drug products for topical use as an antihistamine external analgesic.

Diphenhydramine hydrochloride is also included in the OTC drug monograph for oral use as an antiemetic (21 CFR part 336). Both diphenhydramine citrate and diphenhydramine hydrochloride are included in OTC drug monographs for oral use as a nighttime sleep-aid (21 CFR part 338), an antihistamine, or an antitussive (21 CFR part 341). The various OTC advisory review panels that reviewed diphenhydramine for these different uses as part of the OTC drug review did not consider interactions that may occur when a person takes oral diphenhydramine and applies diphenhydramine topically.

In the **Federal Register** of December 4, 1979 (44 FR 69768), the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug products (the Panel) evaluated the safety and effectiveness of diphenhydramine hydrochloride as an antihistamine external analgesic. The Panel acknowledged that diphenhydramine is absorbed through damaged skin and gains access to the blood stream. However, the Panel did not consider systemic toxicity from topical application to be of major importance because of its low degree of toxicity when used orally or parenterally. The Panel was unaware of any instance of systemic toxicity reported from topical use of diphenhydramine. The Panel concluded that the drug was safe at 1- to 2-percent concentrations for the temporary relief of pain and itching due to minor burns, sunburn, minor cuts, abrasions, insect bites, and minor skin irritations. The only warning the Panel recommended was not to use for longer than 7 days except under the advice and supervision of a physician (44 FR 69768 at 69809).

The agency concurred with the Panel's recommendations in the tentative final monograph for OTC external analgesic drug products, published in the **Federal Register** of February 8, 1983 (48 FR 5852). The agency did not change the Panel's recommended warnings for diphenhydramine, or add any other warnings.

II. Developments After Publication of the External Analgesic Tentative Final Monograph

Since publication of the external analgesic tentative final monograph, the agency has become aware of reports of adverse events (toxic psychosis), especially in children, when diphenhydramine was used topically for relief of pruritus due to chicken pox, poison ivy, and sunburn. Some reports mentioned the concurrent use of topical diphenhydramine with oral diphenhydramine drug products to relieve the itch and rash associated with chicken pox. Chicken pox is not a monograph indication for topical or oral diphenhydramine products.

A. Early Case Reports to FDA

The agency has reviewed case reports of toxic psychosis reported to its Spontaneous Reporting System for the period from 1979 to 1989 (Ref. 1).

In 1979, a 6-year-old boy developed chicken pox and was treated with baking soda baths (8 ounce (oz)/tub) every 2 hours followed by topical application of a lotion containing 1 percent diphenhydramine and calamine every 2 hours. Twelve hours later he developed unusual behavior (talking to imaginary people, playing with imaginary toys, did not recognize parents). On the third day, a doctor saw the child and prescribed diphenhydramine elixir every 4 hours. After 2 doses, the boy became agitated and his strange ideas became worse. He was hospitalized with hallucinations, bizarre inappropriate behavior, and disorientation to time and place. He was afebrile. His pupils were dilated and his face was flushed. Diphenhydramine in calamine and diphenhydramine elixir were suspected of causing the toxic psychosis. The child was given no medication and the following morning he was fully alert and his behavior was normal, without hallucinations or delusions.

In 1980, a physician reported that diphenhydramine from a 1 percent diphenhydramine-calamine lotion was absorbed in high concentrations in two patients who were afebrile in the late stages of chicken pox. The first patient had diphenhydramine lotion painted on the body and sealed with a dryer by his mother. The patient developed hallucinations and delirium. A second patient who had the same lotion applied but not sealed also developed hallucinations. The physician noted that hallucinations and delirium would not be expected in the late stages of this disease.

In 1987, an 8-year-old child was admitted to the hospital for severe psychosis, urinary retention, ataxia, bizarre posturing, and dilated pupils. During the 12 hours before admission, 1 percent diphenhydramine-calamine lotion was applied three different times on the child from head to toe for severe poison ivy contact dermatitis. A toxic drug screen was negative for diphenhydramine but revealed traces of benzodiazepine which the child might have ingested. No other medication was given. The diphenhydramine lotion was removed and the child recovered fully.

In 1989, a pharmacist reported that his 6-year-old son experienced toxic psychoses (hyperactive, jittery, disoriented with visual hallucinations) within 24 hours of application of 1 percent diphenhydramine-calamine lotion to chicken pox lesions. Diphenhydramine elixir was given 2 days before and on the day of the topical application. The child was hospitalized, treated with activated charcoal, and recovered completely within 24 hours, with no further problems.

B. Early Pediatric Literature

Patranella (Ref. 2) reported an incident where a 4-year-old boy became toxic after topical application of 3 oz of 1 percent diphenhydramine-calamine lotion to chicken pox rash. The child was admitted to the hospital because of increasing hyperactivity, irregular eye movements, hallucinations, and intermittently failing to recognize his parents. The rash developed the day before admission, 16 days after exposure to varicella. The child's pupils were 4 millimeters in diameter and reacted sluggishly to light. He was awake, disoriented to person and place, combative, ataxic, and displayed tongue rolling. A urine drug screen revealed the presence of diphenhydramine. The lotion was washed from his skin with water and his mental status returned to normal within 6 to 8 hours. The report noted that diphenhydramine is a histamine (H_1) receptor blocker which can cause central nervous system excitation or sedation. The fatal dose in adults is 20 to 40 milligrams/kilogram (mg/kg). The 4-year-old boy received 50 mg/kg topically over a 6-hour period.

Filloux (Ref. 3) described a 9-year-old boy with chicken pox who had 1 percent diphenhydramine-calamine lotion applied liberally from head to toe, a total of 12 oz in 48 hours, for intense pruritus. Diphenhydramine toxicity resulted with organic psychosis masquerading as varicella encephalitis, a serious neurologic complication of varicella zoster (chicken pox) disease that can result in permanent neurologic sequelae or death. On admission to the emergency room, the boy was markedly agitated, frightened, disoriented, completely confused, having frequent visual and auditory hallucinations, and would assume bizarre postures. Pupils were dilated but reactive. Laboratory results were within normal limits. The serum toxic screen showed a diphenhydramine level of 1.4 micrograms per milliliter (μg/mL), which exceeded the therapeutic level of 0.3 μg/mL. No further diphenhydramine

lotion was applied. Although agitated and hallucinating through the night, the following morning he was calmer, but still confused. His diphenhydramine level had dropped to 0.7 μg/mL. He was lucid by noon and by 4 p.m. his diphenhydramine level was 0.6 μg/mL. He was discharged from the hospital with a normal mental status. Ample evidence in this patient confirmed that transdermal absorption of diphenhydramine resulted in intoxication and organic psychosis. The report advised that appropriate caution was warranted when treating pruritus with topical antihistamine preparations, particularly when substantial epidermal breakdown exists.

Tomlinson, Helfaer, and Wiedermann (Ref. 4) described a case of diphenhydramine toxicity mimicking varicella encephalitis. Physical examination disclosed evidence of diphenhydramine toxicity related to systemic absorption of a topical preparation. The patient, a 5-year-old girl, developed chicken pox rash 4 days before admission to the hospital. Her mother had applied 1 percent diphenhydramine-calamine lotion repeatedly over most of the child's body during this 4-day-period, but gave no other medications. The day before admission the child appeared agitated, did not sleep, had an unsteady gait, and had trembling of the extremities. Later, she developed visual hallucinations and her speech became unintelligible. Upon admission to the hospital, she was disoriented, agitated, and grasping at imaginary objects in the air. Neurologic examination revealed dilated pupils, flushed face, and ataxia. A urine toxicity screen was positive only for diphenhydramine. The child's status improved quickly after the diphenhydramine lotion was removed. No other therapy was given and she was discharged on the fourth day. A followup examination done 2 weeks later was normal.

Although initially believed to have varicella encephalitis, the child's symptoms (ataxia, hallucinations, mydriasis, and flushing of the face) were more suggestive of an anticholinergic reaction. Tests confirmed diphenhydramine toxicity rather than varicella encephalitis. The report concurred with one manufacturer's recommendations that diphenhydramine not be used in skin disorders, such as varicella, where extensive systemic absorption of topical preparations may occur. The report suggested that families of children with chicken pox be warned to be cautious in the use of this drug product.

Schunk and Svendsen (Ref. 5) reported on three children (ages 4, 5, and 7) with chicken pox who developed toxic encephalopathy from having been treated with both oral and topical diphenhydramine. All displayed some of the symptoms common to diphenhydramine toxicity: Dilated pupils, flushed face, agitation, confusion, hallucinations, and ataxic gait. The plasma diphenhydramine level was 1.5 μg/mL in the 4-year-old and 0.96 μg/mL in the 5-year-old. After discontinuing the diphenhydramine, all children displayed normal mental status.

This report advised that physicians should be alerted to the possibility of diphenhydramine toxicity when confronted with a child with varicella and acute mental status changes. Further, both families and physicians should be advised against combined use of topical and oral diphenhydramine-containing preparations.

Woodward and Baldassano (Ref. 6) described a case of diphenhydramine intoxication from the combined effects of oral diphenhydramine elixir and topical diphenhydramine-calamine lotion in a 5-year-old boy who developed chicken pox 3 days before being taken to the emergency room. He had been treated with 6 or 7 teaspoons of oral diphenhydramine (12.5 mg/5 mL) for a total dosage of 75 to 87 mg (over 36 hours). His mother also had applied 1 percent diphenhydramine-calamine lotion liberally over his body in a 12-hour period, 24 hours prior to presentation in the emergency department. The boy's behavior was bizarre; he was talking to and seeing objects and people that were not present. The boy had the classic symptoms of diphenhydramine toxicity, including hallucinations, tachycardia, and dilated pupils. A toxic screen showed both acetaminophen and diphenhydramine (1.94/μg/L approximately 14 hours after the last oral dose). All diphenhydramine was discontinued, and the child returned to normal the next day. Varicella encephalitis was ruled out. The report stated that children more often show excitation with overdosage of antihistamines than the usual sedative effect seen in adults.

The article further stated that data on percutaneous absorption of diphenhydramine are limited. The recommended oral dose is 5 mg/kg/24 hours and three to four applications of topical diphenhydramine lotion per day. The child had a total of 3.6 mg/kg/36 hours, or less, of oral diphenhydramine, less than half the daily recommended dosage, and a larger amount of lotion over a 12-hour period. Therefore, absorption of the lotion appears to have been a primary factor in the adverse reaction. The report noted that toxicity from oral use is more common than toxicity from topical use of diphenhydramine. Fatalities have been reported in both children and adults from oral overdosage. However, no deaths have been reported from topical diphenhydramine use alone. The report advised that physicians and patients need to be aware of this potential toxicity.

C. More Recent Case Reports

Between 1987 and 1990, a major manufacturer of OTC diphenhydramine drug products received four adverse event reports that described toxic psychoses in seven children (Ref. 7). Apparently the drug products were being misused, contrary to labeling, and were being applied to large areas of the body where there was broken skin, possibly causing increased systemic absorption. Based on these seven cases, the manufacturer voluntarily revised the label warnings for its topical products containing diphenhydramine. In 1989, the manufacturer added to the following products a warning not to use on chicken pox and measles unless supervised by a doctor: A cream and lotion product containing 1 percent diphenhydramine and 8 percent calamine, and a cream and spray product containing 1 percent diphenhydramine and 0.1 percent zinc acetate. In 1990, the manufacturer added to these products a second warning not to use any other drugs containing diphenhydramine while using the topical products. This warning was added based on reports that the topical diphenhydramine drug products were being used with oral diphenhydramine drug products to relieve the itch and rash associated with chicken pox and measles, possibly resulting in toxic serum diphenhydramine levels. In April 1993, the manufacturer reformulated its lotion and cream products containing 1 percent diphenhydramine and 8 percent calamine to replace the diphenhydramine with 1 percent pramoxine hydrochloride.

Summaries of the adverse event reports received by the manufacturer follow:

The first report involved a 7-year-old boy who developed chicken pox. Oral hydroxyzine hydrochloride (one dose at 6:30 p.m.) was prescribed. The child's mother applied 5 to 10 mL of 1 percent diphenhydramine-calamine lotion three times to the child's abdomen and chest between 7:45 and 11:30 p.m. Around 12

a.m., the child became confused, irritable, and began hallucinating. When hospitalized, his diphenhydramine level at 5:40 a.m. was 73 nanograms per mL (ng/mL) (the normal level is 25 to 40 ng/mL). The diphenhydramine-calamine lotion was removed from the skin and the child recovered uneventfully the next day.

The second report involved four children, ages 4 to 6 years, who developed chicken pox. Typically, the mothers applied 1 percent diphenhydramine-calamine lotion over an extensive area of the body three to four times daily. In one case, the child was concurrently receiving diphenhydramine syrup. In all cases, within 24 to 48 hours, the children became irritable, delirious, and began hallucinating. The children were treated in an emergency room by washing the diphenhydramine lotion from their bodies, and they responded within 24 to 36 hours.

The third report concerned a 9-year-old boy with a mild sunburn without broken or blistered skin. An hour after his mother liberally applied one-half of a 45-gram tube of 1 percent diphenhydramine-calamine cream to the boy's trunk and limbs, he developed increased tiredness and became confused and disoriented. He convulsed, with widespread muscular twitching and ''rolling of the eyes'' 1½ to 2 hours after the cream had been applied. He was taken to the hospital and a chemical toxicology screen revealed a diphenhydramine level of 60 ng/mL. The child was treated with activated charcoal and intravenous fluids. Approximately 32 hours later, the diphenhydramine level was 16 ng/mL; the child recovered uneventfully and was discharged the following day.

The fourth report described an 8-year-old boy with a history of allergies and asthma who developed extensive chicken pox. One percent diphenhydramine-calamine lotion was applied all over the body every 4 to 5 hours for approximately 48 hours. The child complained of blurred vision and ''not being able to see clearly'' on the second day after ''breaking out.'' He received acetaminophen every 4 to 5 hours for fever. About 2 to 3 a.m., the child awoke with hallucinations of flying insects. A dose of acetaminophen and a teaspoon of diphenhydramine elixir were given, and additional diphenhydramine-calamine lotion was applied. Afterwards, the boy's body was twitching, he was restless and unable to sit still or sleep. On the advice of the local emergency room's personnel, the child was placed in a cool tub of water to lower his temperature (103 to 104 °F). Although his temperature was reduced, the boy continued to hallucinate. After another application of diphenhydramine-calamine lotion, the child was taken to the hospital around 7 a.m., still hallucinating. Neurological tests and a test for Reye's syndrome were negative, and the child was sent home. Another dose of diphenhydramine-calamine lotion was applied at 11 a.m. and after 1 to 2 hours the child began to bump into a hallway wall and was unable to sit still. The last dose of diphenhydramine lotion was applied mid-afternoon. A few hours later, the boy fell asleep for 4 hours, awoke vomiting, and had difficulty breathing. After these problems subsided, the child recovered uneventfully.

In the last 6 years, FDA has received several additional reports of toxic psychoses as a result of topical application of diphenhydramine. One doctor reported two cases in children who had symptoms of delirium from absorption of diphenhydramine from a 1 percent diphenhydramine-calamine product applied to their bodies (Ref. 8). One child had a blood level of 0.31 µg/mL while the other child's blood level was drawn much later and was not indicative of a toxic level. The doctor expressed concern about the potential side effects of the diphenhydramine in this product.

Chan and Wallender (Ref. 9) reported three cases of diphenhydramine toxicity. Two of the cases were included in earlier articles discussed previously. The third case described a 2-year-old boy who developed chicken pox lesions over his body. He was given an unknown amount of diphenhydramine elixir every 3 to 4 hours, and a 1 percent diphenhydramine-calamine in a lotion and/or spray was applied topically to most of his body surface. The child became increasingly irritable and displayed inappropriate behavior. The parents contacted the emergency room and were instructed to bathe the child to remove the diphenhydramine lotion. However, the child continued to have inappropriate behavior and visual hallucinations, and was brought to the emergency room 4 hours later. Vital signs were temperature 37.1 °C (rectally), heart rate 124 beats per minute, and respiration 36 breaths per minute. Chicken pox lesions covered his body and, although he had brief periods of inappropriate behavior, he was able to follow simple commands. The serum diphenhydramine concentration was 1.5 µg/mL. Based on laboratory reports, diphenhydramine concentrations greater than 0.1 µg/mL are potentially toxic. After 2 hours of observation, the boy was dismissed. He was alert and playful without evidence of toxicity during a follow-up examination later that morning.

The report noted that the topical diphenhydramine products used in treating the patients discussed in the article had a label warning against use in chicken pox unless supervised by a physician. According to the authors, cases described in the article demonstrated three important points. First, absorption of topically applied diphenhydramine in patients with chicken pox and possibly other skin disorders with extensive disruption of the skin barrier can occur, resulting in serious systemic toxicity. Second, the use of topically applied diphenhydramine products in this patient population should be discouraged. Finally, pharmacists should educate the public as well as health professionals regarding the potential toxicity of these easily accessible diphenhydramine-containing nonprescription medications.

McGann et al. (Ref. 10) reported a case of a 19-month-old girl who developed chicken pox 5 days before being brought to the clinic. The girl had been treated with acetaminophen for fever, colloidal oatmeal baths, 1 percent diphenhydramine-calamine lotion applied to her entire body three or four times a day, and syrup given in varying doses totaling approximately 50 mg of diphenhydramine. Two hours later, the child began behaving strangely and rolling her eyes back into her head.

When brought to the clinic, the child was awake but did not interact with the examiner. She was moderately agitated and frightened; would not respond to commands; had a wide-eyed stare; had widely dilated pupils that were sluggishly reactive to light; occasionally made grimacing, tongue-chewing, and lip-smacking motions; staggered when walking; and retained urine. Her serum diphenhydramine level was 1,948 ng/mL. The girl was bathed to remove the diphenhydramine, then admitted to the hospital for hydration, cardiac monitoring, bladder catheterization for urine retention, and observation. After 48 hours, she had returned to normal and was discharged from the hospital.

The report cautioned parents to refrain from using topical diphenhydramine to avoid a serious life-threatening drug toxicity, and noted that the drug label specifically warns against use for chicken pox and measles, except under the supervision of a physician. The agency notes that the labeling directions proposed in § 348.50(d) of the tentative final monograph for OTC external analgesic

drug products (48 FR 5852 at 5869) state that a doctor should be consulted for children under 2 years of age. The report did not indicate whether a doctor had prescribed the drug.

III. The Agency's Tentative Conclusions and Proposal

The case reports described a number of adverse events resulting from topical application of diphenhydramine to large areas of the body, often where there was broken skin and, in some cases, concurrent use of topical and oral diphenhydramine products. The diphenhydramine products were used to relieve pain and itching due to chicken pox (most cases), poison ivy (1 case), and sunburn (1 case). The age range of the patients with reactions was 19 months to 9 years. The symptoms determined to be most suggestive of diphenhydramine toxicity included dilated pupils, flushed face, hallucinations, ataxic gait, and urinary retention. As the Panel noted (44 FR 69768 at 69809), diphenhydramine is absorbed through damaged skin, and the case reports confirmed that transdermal absorption occurs. In some cases, high serum concentrations confirmed diphenhydramine toxicity. Symptoms gradually disappeared when diphenhydramine was removed from the body by bathing and oral administration of diphenhydramine was discontinued. Most patients returned to normal in about 48 hours after the drug was withdrawn. No deaths have been reported from topical diphenhydramine use alone.

The authors of many of these reports have indicated the need to inform health professionals and consumers about the situations when topical diphenhydramine should not be used, especially in conjunction with oral diphenhydramine. This is especially true in patients with chicken pox and possibly other skin disorders with extensive disruption of the skin barrier, which can result in serious systemic toxicity if absorption of diphenhydramine occurs. As noted in section II.C. of this document, a major manufacturer of OTC diphenhydramine drug products voluntarily added warning information to the labeling of its topical products.

The agency believes there is underreporting of adverse reactions for topical diphenhydramine drug products. There is currently no adverse event reporting requirement for topical diphenhydramine products included in an OTC drug monograph. In addition, the agency is concerned that consumers, primarily parents, may use these topical products casually because they consider them to be innocuous. Because the exact extent of the problem is not known, and there is a potentially large exposure of the general population to this ingredient, the agency has determined that additional warnings are needed to avoid the possibility of serious adverse reactions. A sufficient number of significant serious neuropsychiatric events have already occurred (especially in children) to propose a change in the labeled warnings for both topical and oral diphenhydramine products. In this document, the agency is proposing to require the following additional warning for topical products containing diphenhydramine: ''Do Not Use'' (these three words in bold print) ''on chicken pox, poison ivy, sunburn, large areas of the body, broken, blistered, or oozing skin, more often than directed, or with any other product containing diphenhydramine, even one taken by mouth.''

The agency notes that one manufacturer includes ''not to use on measles'' in the warning that it voluntarily added to its topical diphenhydramine products. However, because none of the case reports were associated with measles lesions, the agency has not specifically listed measles in the warning. The agency invites interested persons to submit any available information related to any adverse events associated with the topical application of diphenhydramine to measles.

Manufacturers may use bullet points or other identifying marks to emphasize the subparts of this warning. The format of this warning might look something like the following:

Do Not Use (these words in bold print):

- on chicken pox, poison ivy, sunburn
- on large areas of the body
- on broken, blistered, or oozing skin
- more often than directed
- with any other product containing diphenhydramine, even one taken by mouth

The agency is proposing this warning in new § 348.50(c)(10) under the heading *For products containing diphenhydramine hydrochloride identified in § 348.10(c)(1).* For these products, this warning shall be the first statement under the heading ''Warnings:''

In addition, in §§ 336.50, 338.50, 341.72, and 341.74 the agency is proposing an additional warning for oral drug products that contain diphenhydramine. The warning states: ''Do Not Use'' (these three words in bold print) ''with any other product containing diphenhydramine, including one applied topically.'' The agency believes that this warning statement will help reduce the toxicity that may occur from the inadvertent concurrent use of several products containing diphenhydramine. The agency points out that its recent final rule/enforcement policy that provides for diphenhydramine citrate or diphenhydramine hydrochloride to be labeled for concurrent antihistamine and antitussive use should also help reduce the toxicity that may occur from the concurrent administration of more than one oral product containing diphenhydramine. (See the **Federal Register** of April 9, 1996 (61 FR 15700).)

Manufacturers of OTC topical and oral diphenhydramine drug products are encouraged to implement this labeling addition voluntarily as soon as possible after publication of this proposal, subject to the possibility that FDA may change the wording of the warning statement as a result of comments filed in response to this proposal. Because FDA is encouraging the voluntary use of the proposed additional warning statement at this time, the agency advises that manufacturers will be given ample time after publication of a final rule to use up any labeling voluntarily implemented in conformance with this proposal.

IV. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

(1) Drug Experience Reports No. 801101–034–00101, 80051000100501, 8706110020071, 89081500100012, 89081500100011, OTC Vol. 06DTFM, Docket No. 78N–0301, Dockets Management Branch.

(2) Patranella, P., ''Diphenhydramine Toxicity Due to Topical Application of Caladryl,'' *Clinical Pediatrics*, 3:163, 1986.

(3) Filloux, F., ''Toxic Encephalopathy Caused by Topically Applied Diphenhydramine,'' *The Journal of Pediatrics*, 108:1018–1020, 1986.

(4) Tomlinson, G., M. Helfaer, and B. Wiedermann, ''Diphenhydramine Toxicity Mimicking Varicella Encephalitis,'' *The Pediatric Infectious Disease Journal*, 6:220–221, 1987.

(5) Schunk, J. E., and D. Svendsen, ''Diphenhydramine Toxicity from Combined Oral and Topical Use,'' *The Pediatric Forum*, 142:1020–1021, 1988.

(6) Woodward, G. A., and R. N. Baldassano, ''Topical Diphenhydramine Toxicity in a Five-Year Old with Varicella,'' *Pediatric Emergency Care*, 4:18–20, 1988.

(7) Letter dated December 14, 1993, from R. G. Kohler, Warner Lambert Co. to W. E. Gilbertson, FDA, in OTC Vol. 06DTFM, Docket No. 78N–0301, Dockets Management Branch.

(8) Drug Experience Report No. 698132, OTC Vol. 06DTFM, Docket No. 78N–0301, Dockets Management Branch.

(9) Chan, C. Y. J., and K. A. Wallander, ''Diphenhydramine Toxicity in Three Children with Varicella-Zoster Infection,'' *The Annals of Pharmacology*, 25:130–132, 1991.

(10) McGann, K. P. et al., ''Diphenhydramine Toxicity in a Child with Varicella,'' A Case Report, *The Journal of Family Practice*, 35:210–214, 1992.

V. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Under the Regulatory Flexibility Act, if a rule has a significant economic impact on a substantial number of small entities, an agency must analyze regulatory options that would minimize any significant economic impact of a rule on small entities.

Title II of the Unfunded Mandates Reform Act (21 U.S.C. 1501 *et seq.*) requires that agencies prepare a written statement and economic analysis before proposing any rule that may result in an expenditure in any 1 year by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million (adjusted annually for inflation).

The agency believes that this proposed rule is consistent with the principles set out in the Executive Order and in these two statutes. The purpose of this proposed rule is to add warning statements to the labeling of oral and topical OTC drug products that contain diphenhydramine. These warning statements concern diphenhydramine toxicity and are intended to help ensure the safe and effective use of all OTC drug products that contain this ingredient. Potential benefits include reduced toxicity when consumers use these products.

This proposed rule amends the final monographs for oral OTC diphenhydramine drug products for antiemetic, antihistamine, antitussive, and nighttime sleep-aid indications and will require some relabeling of these products to add the new warning statement. The proposed rule also amends the tentative final monograph for OTC external analgesic drug products and will require some relabeling to add the new warning statement to products containing diphenhydramine. The agency's drug listing system identifies approximately 100 manufacturers and 300 marketers of over 800 oral OTC diphenhydramine drug products, and 10 manufacturers and 50 marketers of over 100 topical OTC diphenhydramine drug products. It is likely that there are some additional marketers and products that are not currently included in the agency's system. However, after adjusting for overlap among the oral and external counts, the agency estimates that there are a total of 100 manufacturers and 300 marketers of about 1,000 affected stock keeping units (SKU) (individual products, packages, and sizes).

The agency has been informed that relabeling costs of this type generally average about $2,000 to $3,000 per SKU. Assuming that there are about 1,000 affected OTC SKU's in the marketplace, total one-time costs of relabeling would be $2 to $3 million. The agency believes that actual costs would be lower for several reasons. First, most of the label changes will be made by private label manufacturers that tend to use relatively simple and less expensive labeling. Second, for oral OTC diphenhydramine drug products, the agency is proposing a 12-month implementation period that would allow many manufacturers to coordinate this change with routinely scheduled label printing and/or revisions. Similarly, labeling changes for external OTC diphenhydramine drug products would not be required until that monograph is issued and becomes final. Thus, the relabeling costs for a warning statement on these products would be mitigated or eliminated. In addition, because the new warning statement involves only a single sentence, supplementary labeling (e.g., stick on labeling) could be used for those oral products not undergoing a new labeling printing within this 1-year period.

The proposed rule would not require any new reporting and recordkeeping activities. Therefore, no additional professional skills are needed. There are no other Federal rules that duplicate, overlap, or conflict with the proposed rule. The agency does not believe that there are any significant alternatives to the proposed rule that would adequately provide for the safe and effective OTC use of drug products that contain diphenhydramine.

This proposed rule may have a significant economic impact on some small entities. The labeling of many of the affected products is prepared by private label manufacturers for small marketers. Census data provide aggregate industry statistics on the total number of manufacturers for Standardized Industrial Classification Code 2834 Pharmaceutical Preparations by establishment size, but do not distinguish between manufacturers of prescription and OTC drug products. According to the U.S. Small Business Administration (SBA) designations for this industry, over 92 percent of the roughly 700 establishments and over 87 percent of the 650 firms are small. (Because census size categories do not correspond to the SBA designation of 750 employees, these figures are based on 500 employees.)

An analysis of IMS Co. listings for manufacturers of OTC drug products found that from 46 to 69 percent of the 400 listed firms are small using the SBA definition of 750 employees. The agency's drug listing system indicates that about 300 marketers will need to relabel, and that this relabeling will be prepared by about 100 entities, most of which are private label manufacturers. Thus, the agency believes that most of the manufacturers affected by this proposed rule would be small.

Because this regulation would affect the information content of all OTC drug products that contain diphenhydramine, firms that manufacture or relabel these OTC drug products will need to change the information panel for each affected SKU. Some of these costs of doing so will be mitigated because the agency is allowing up to 1 year for oral products so that the required labeling revision may be made in the normal course of business. Labeling changes for topical products may be coordinated with the final monograph for OTC external analgesic drug products. Among the steps the agency is taking to minimize the impact on small entities are: (1) To provide enough time for implementation to enable entities to use up existing labeling stock, and (2) to provide for the use of supplementary labeling (e.g., stick on labeling) if necessary. The agency believes that these actions provide substantial flexibility and reductions in cost for small entities.

The agency considered but rejected several labeling alternatives: (1) Voluntary relabeling, (2) a longer implementation period, and (3) an exemption from coverage for small entities. The agency does not consider any of these approaches acceptable because they do not assure that consumers will have the most recent needed information for safe and effective use of OTC diphenhydramine drug products at the earliest possible time.

This analysis shows that this proposed rule is not economically significant under Executive Order 12866 and that the agency has undertaken important steps to reduce the burden to small entities. Nevertheless, some entities, especially those private label manufacturers that provide labeling for a number of the affected products, may incur significant impacts. Thus, this economic analysis, together with other relevant sections of this document, serves as the agency's initial regulatory flexibility analysis, as required under the Regulatory Flexibility Act. Finally, this analysis shows that the Unfunded Mandates Act does not apply to the proposed rule because it would not result in an expenditure in any 1 year by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million.

The agency invites public comment regarding any economic impact that this rulemaking would have on manufacturers of OTC oral and topical drug products containing diphenhydramine hydrochloride. Comments regarding the economic impact of this rulemaking on such manufacturers should be accompanied by appropriate documentation. The agency is providing a period of 90 days from the date of publication of this proposed rulemaking in the **Federal Register** for comments on this subject to be developed and submitted. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

VI. Paperwork Reduction Act of 1995

FDA tentatively concludes that the labeling requirements proposed in this document for oral and topical OTC drug products are not subject to review by the Office of Management and Budget because they do not constitute a ''collection of information'' under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501 *et seq.*). Rather, the proposed warning statements are a ''public disclosure of information originally supplied by the Federal government to the recipient for the purpose of disclosure to the public'' (5 CFR 1320.3(c)(2)).

VII. Environmental Impact

The agency has determined under 21 CFR 25.24(c)(6) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VIII. Request for Comments

Interested persons may, on or before November 28, 1997, submit written comments on the proposed regulations to the Dockets Management Branch (address above). Written comments on the agency's economic impact determination may be submitted on or before November 28, 1997. Three copies of all comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects in 21 CFR Parts 336, 338, 341, 348

Labeling, Over-the-counter drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR parts 336, 338, and 341, and 21 CFR part 348 (as proposed in the **Federal Register** of February 8, 1983 (48 FR 5852)) be amended as follows:

PART 336—ANTIEMETIC DRUG PRODUCTS FOR OVER–THE–COUNTER HUMAN USE

1. The authority citation for 21 CFR part 336 continues to read as follows:

Authority: Secs. 201, 501, 502, 503, 505, 510, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 371).

2. Section 336.50 is amended by adding new paragraph (c)(8) to read as follows:

§ 336.50 Labeling of antiemetic drug products.

* * * * *

(c) * * *

(8) *For products containing diphenhydramine hydrochloride identified in § 336.10(c).* ''Do Not Use'' (these three words in bold print) ''with any other product containing diphenhydramine, including one applied topically.''

* * * * *

PART 338—NIGHTTIME SLEEP–AID DRUG PRODUCTS FOR OVER–THE–COUNTER HUMAN USE

3. The authority citation for 21 CFR part 338 continues to read as follows:

Authority: Secs. 201, 501, 502, 503, 505, 510, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 371).

4. Section 338.50 is amended by adding new paragraph (c)(5) to read as follows:

§ 338.50 Labeling of nighttime sleep-aid drug products.

* * * * *

(c) * * *

(5) ''Do Not Use'' (these three words in bold print) ''with any other product containing diphenhydramine, including one applied topically.''

* * * * *

PART 341—COLD, COUGH, ALLERGY, BRONCHODILATOR, AND ANTIASTHMATIC DRUG PRODUCTS FOR OVER–THE–COUNTER HUMAN USE

5. The authority citation for 21 CFR part 341 continues to read as follows:

Authority: Secs. 201, 501, 502, 503, 505, 510, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 371).

6. Section 341.72 is amended by adding new paragraphs (c)(6)(iv) and (c)(7) to read as follows:

§ 341.72 Labeling of antihistamine drug products.

* * * * *

(c) * * *

(6) * * *

(iv) *For products containing diphenhydramine citrate or diphenhydramine hydrochloride identified in § 341.12(f) and (g).* ''Do Not Use'' (these three words in bold print) ''with any other product containing diphenhydramine, including one applied topically.''

(7) *For products containing diphenhydramine citrate or diphenhydramine hydrochloride identified in § 341.12(f) and (g).* ''Do Not Use:'' (these three words in bold print) ''with any other product containing diphenhydramine, including one applied topically.''

* * * * *

7. Section 341.74 is amended by adding new paragraphs (c)(4)(viii)(C) and (c)(4)(ix)(C) to read as follows:

§ 341.74 Labeling of antitussive drug products.

* * * * *

(c) * * *

(4) * * *

(viii) * * *

(C) ''Do Not Use'' (these three words in bold print) ''with any other product containing diphenhydramine, including one applied topically.''

(ix) * * *

(C) ''Do Not Use'' (these three words in bold print) ''with any other product

containing diphenhydramine, including one applied topically.''

* * * * *

PART 348—EXTERNAL ANALGESIC DRUG PRODUCTS FOR OVER–THE–COUNTER HUMAN USE

8. The authority citation for 21 CFR part 348 continues to read as follows:

Authority: Secs. 201, 501, 502, 503, 505, 510, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 371).

9. Section 348.50 (as proposed at 48 FR 5852, February 8, 1983) is amended by adding new paragraph (c)(10) to read as follows:

§ 348.50 Labeling of external analgesic drug products.

* * * * *

(c) * * *

(10) *For products containing diphenhydramine hydrochloride identified in § 348.10(c)(1).* The following statement shall appear as the first warning statement under the heading ''Warnings:'' ''Do Not Use:'' (these three words in bold print) ''on chicken pox, poison ivy, sunburn, large areas of the body, broken, blistered, or oozing skin, more often than directed, or with any other product containing diphenhydramine, even one taken by mouth.''

* * * * *

Dated: August 22, 1997.

William B. Schultz,

Deputy Commissioner for Policy.

[FR Doc. 97–22983 Filed 8–28–97; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF JUSTICE

Civil Division; Radiation Exposure Compensation Act: Evidentiary Requirements; Definitions and Number of Claims Filed

28 CFR Part 79

[A.G. Order No. 2111–97]

RIN 1105–AA49

AGENCY: Civil Division, Department of Justice.

ACTION: Notice of reopening of comment period for proposed rule.

SUMMARY: On May 23, 1997, the United States Department of Justice (DOJ) published a proposed rule amending the existing regulations implementing the Radiation Exposure Compensation Act. This proposed rule may be found at 62 FR 28393, May 23, 1997. The original 60 day comment period expired on July 22, 1997.

Several individuals have requested additional time to submit comments regarding the proposed changes. To ensure that the public has ample opportunity to fully review and comment on the proposed amendments, we are now extending the comment period and will accept comments for an additional 30 days after publication of this notice.

DATES: Written comments must be submitted on or before September 29, 1997.

ADDRESSES: Please submit written comments to Gerard W. Fischer, Assistant Director, U.S. Department of Justice, Civil Division, P.O. Box 146, Ben Franklin Station, Washington, D.C. 20044–0146.

FOR FURTHER INFORMATION CONTACT: Gerard W. Fischer (Assistant Director), (202) 616–4090 and Lori Beg (Attorney), (202) 616–4377.

Dated: August 25, 1997.

Janet Reno,

Attorney General.

[FR Doc. 97–23015 Filed 8–28–97; 8:45 am]

BILLING CODE 4410–12–M

DEPARTMENT OF TRANSPORTATION

Coast Guard

33 CFR Parts 148–150

[CGD 97–050]

Deepwater Ports

AGENCY: Coast Guard, DOT.

ACTION: Advanced notice of proposed rulemaking; request for comments.

SUMMARY: The Coast Guard, in an effort to continually update its regulations and in response to recent legislation, plans to revise the Deepwater Port regulations. The Coast Guard solicits comments from the public and industry on the questions listed in this request.

DATES: Comments must reach the Coast Guard on or before October 14, 1997.

ADDRESSES: You may mail comments to the Executive Secretary, Marine Safety Council (G–LRA) (CGD 97–050), U.S. Coast Guard, 2100 Second Street SW., Washington, DC 20593–0001, or deliver them to room 3406 at the same address between 9:30 a.m. and 2 p.m., Monday through Friday, except Federal holidays. The telephone number is (202) 267–1477.

The Executive Secretary maintains the public docket for this rulemaking. Comments and documents as indicated in this preamble, will become part of this docket and will be available for inspection or copying at room 3406, U.S. Coast Guard Headquarters, between 9:30 a.m. and 2 p.m., Monday through Friday, except Federal holidays.

FOR FURTHER INFORMATION CONTACT: LT Diane Foster, Office of Operating and Environmental Standards (G–MSO–2), Room 1210, U.S. Coast Guard Headquarters, 2100 Second Street SW., Washington, DC 20593, telephone (202) 267–1181.

SUPPLEMENTARY INFORMATION:

Request for Information

The Coast Guard encourages interested persons to participate in this request by submitting written data, views, or arguments. Persons submitting comments should include their names and addresses, identify this notice (CGD 97–050) and the specific section or question of this document to which each comment or question applies, and give the reason for each comment. Please submit two copies of all comments and attachments in an unbound format, no larger than 8½ by 11 inches, suitable for copying and electronic filing. Persons wanting acknowledgement of receipt of comments should enclose stamped, self-addressed postcards or envelopes. The Coast Guard will consider all comments received during the comment period.

The Coast Guard plans no public meeting. Persons may request a public meeting by writing to the Marine Safety Council at the address under **ADDRESSES**. The request should include the reasons why a meeting would be beneficial. If it is determined that the opportunity for oral presentations will aid this rulemaking, the Coast Guard will hold a public meeting at a time and place announced by a later notice in the **Federal Register**.

Background and Purpose

The Coast Guard Authorization Act of 1996 prescribes changes to the regulations developed in accordance with the Deepwater Port Act of 1974, and contained in 33 CFR Parts 148 to 150. The changes include:

1. Removing from the regulations and placing in the license conditions, those requirements necessary to carry out the provisions of the Deepwater Port Act;

2. Removing from the regulations and license conditions, those things which can be stated in an approved operations manual. Basic standards and conditions, however, will continue to be addressed in the regulations.

The Deepwater Port regulations were written in the 1970's when there were