UNITED STATES
CONSUMER PRODUCT SAFETY COMMISSION
WASHINGTON, DC 20207

DATE: NOV 19 2004

TO: The Commission
Todd A. Stevenson, Secretary

THRU: John Gibson Mullan, General Counsel JGM

FROM: Lowell F. Martin, Assistant General Counsel L.F.M.

SUBJECT: Petition to Delete Consideration of Toxicity from Test Failure Criteria for Child-Resistant Unit Packaging (PP 03-1)

Attached is a briefing package from the staff concerning a petition submitted by the Healthcare Compliance Packaging Council requesting a change to the Commission's regulatory requirements concerning child-resistant packaging under the Poison Prevention Packaging Act, 15 U.S.C. §§ 1471 - 1476. The staff recommends that the Commission deny the petition (Option III.).

Please indicate your vote on the following options.

I. Grant Petition PP 03-1.

_____ _____
Signature Date

II. Defer decision on Petition PP 03-1.

_____ _____
Signature Date

NOTE: This document has not been reviewed or accepted by the Commission.
Initial mk **Date** 11/22/04

III. Deny Petition PP 03-1.

_____ _____

Signature Date

IV. Take other action (please specify):

_____

_____

_____

_____ _____

Signature Date

Attachment: Briefing Package, Petition PP 03-1: *Petition to Amend Child-Resistance Testing Pass/Fail Criterion for Unit Packaging*, November 19 2004.

BRIEFING PACKAGE

Petition to Amend Child-Resistance Testing Pass/Fail Criterion for Unit Packaging (PP03-1)

For Information Contact
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Briefing Memorandum

EXECUTIVE SUMMARY

Under the current Poison Prevention Packaging Act (PPPA) regulations a test failure for child-resistant unit packaging is defined as access by a child to the number of individual units that constitutes an amount that would cause serious injury or access by a child to more than eight units, whichever is less. The U.S. Consumer Product Safety Commission (CPSC) received a petition from the Healthcare Compliance Packaging Council (HCPC), requesting that consideration of the toxicity of the packaged substance be eliminated from the current regulatory definition. The HCPC's position is that unit packaging is safer than reclosable packaging. The HCPC asserts that the current standards for child-resistance for unit packaging are responsible for the limited use of unit packaging and that removing the toxicity criterion from the definition of failure for child-resistance would result in greater usage of unit packaging.

The numerical criterion was established as an addition to the toxicity criterion, to provide the packaging industry with parameters for the development of child-resistant unit packaging. The original PPPA regulations set the numerical criterion at access to more than five units as a failure but the number of units was changed to eight by the FDA in 1973 (38 FR 12738). In doing so, the FDA made it clear that no impact with respect to protecting children would occur since the toxicity criterion would still prevail to assure that children are protected.

The CPSC staff does not agree with the HCPC's assertions regarding the safety of unit packaging. There are many drugs and other household chemicals that are toxic and would cause serious injury or illness to a child if eight or fewer units were consumed or accessed. These include sulfuric acid, oral hypoglycemic drugs, tricyclic antidepressant drugs, and antipsychotic drugs to name a few. If the change the petitioner requested is adopted, children would have no protection from the most toxic products, that is, those that can result in serious injury or serious illness following access to eight or fewer units. This concern was echoed in the comments from various Poison Control Center Directors, Clinical Toxicology Associations, and the American Academy of Pediatrics.

The CPSC staff does not believe that there is adequate information to demonstrate that changing the definition of failure for unit packaging as the petitioner requests will result in greater use of unit packaging or in fewer child poisonings. The Pharmaceutical Research and Manufacturers of America, a major pharmaceutical trade association, stated that its member companies would not knowingly use packaging that was insufficiently protective for children. Furthermore, child-resistant unit packaging providing the most protective levels of child-resistance is technically feasible, practicable, appropriate, and commercially available.

Based on the foregoing information, the CPSC staff recommends that the Commission deny the petition.

UNITED STATES
CONSUMER PRODUCT SAFETY COMMISSION
WASHINGTON, DC 20207

Memorandum

Date: NOV 19 2004

TO : The Commission
Todd Stevenson, Secretary

THROUGH: John Gibson Mullan, General Counsel
Patricia Semple, Executive Director

FROM: Jacqueline Elder, Assistant Executive Director for Hazard Identification and Reduction
Suzanne Barone, Ph.D., Project Manager for Poison Prevention, Directorate for Health Sciences

SUBJECT : Petition to Amend Child-Resistance Testing Pass/Fail Criterion for Unit Packaging (PP03-1)

This memorandum forwards the staff analysis of information related to petition PP03-1 from the Healthcare Compliance Packaging Council. The staff recommendation to deny the petition is also presented.

BACKGROUND

Petition PP03-1

The U.S. Consumer Product Safety Commission (CPSC) received correspondences dated March 17, 2003 and May 5, 2003 from the Healthcare Compliance Packaging Council (HCPC), requesting two actions under the Poison Prevention Packaging Act (PPPA) (Tab A). First, the HCPC is requesting that consideration of the toxicity of the packaged substance be eliminated from the current definition of test failure for unit packaging. That is, HCPC is requesting that a failure for unit packaging be defined as "any child who opens or gains access to more than 8 individual units during the full 10 minutes of testing." The HCPC refers to this as an "objective standard." Second, the HCPC is requesting that type testing for unit packaging be allowed under the PPPA child-resistance testing protocol.

In a letter dated May 27, 2003, the CPSC's Office of the General Counsel informed the HCPC that the first request was docketed as a petition (PP03-1). The second request was not docketed because the current PPPA regulations do not restrict a company from relying on relevant data generated by other sources or for other products. Therefore, no amendment to the rule is necessary. The discussions in this memorandum are limited to the petitioner's request that consideration of the toxicity of

the substance to be packaged be eliminated from the current definition of test failure for unit packaging.

The HCPC is a trade association comprised of suppliers and producers of unit dose packaging, packaging components, and unit packaging machinery. The group was founded in 1990 to promote the use of unit packaging. The HCPC states that the existing PPPA regulations create a disincentive for pharmaceutical product manufacturers to use unit packaging because of the toxicity component within the child-resistance standard for unit packaging. The HCPC requests that the toxicity criterion be deleted from the determination of child-resistance for unit packaging because they assert that unit packaging is "inherently" safer than reclosable[1] packaging. HCPC offers support for their position that unit packaging is safer with their analysis of ingestion incident data from various CPSC databases.

The HCPC asserts that deleting consideration of toxicity of the product and keeping the portion of the standard that a failure of unit packaging is any child who opens or gains access to more than 8 individual units during the full 10 minutes of testing, will provide child protection because unit packaging will still be difficult for children to open. The HCPC alleges that the results of testing child-resistant and conventional unit packaging that was conducted by the CPSC staff support this assumption.[2] The HCPC also states that the "more than eight" failure criterion without the toxicity consideration has been adopted in Europe.

The current PPPA regulations, the origin and purpose of the "more than eight" restriction, and the issues raised by the petitioner are discussed below.

Poison Prevention Packaging Act Regulations - Child Test Protocols

The PPPA defines "special packaging" as packaging that is designed or constructed to be significantly difficult for children under age 5 to open or obtain a toxic or harmful amount of the substance within a reasonable time (child-resistant), and not difficult for normal adults to use properly (adult-use-effective). The PPPA expressly prohibits the Commission from prescribing specific packaging designs (15 U.S.C. 1472(d)). Whether a package meets the definition of special packaging is based on human performance testing of the packages. The PPPA regulations at 16 CFR § 1700.20 prescribe testing protocols that use child participants to determine child-resistance and adult participants to determine adult-use-effectiveness. The test protocols were developed in the early 1970s and amended in 1995 to further address ease of adult use.

The current child test protocols involve testing sequential panels of 50 children aged 42 to 51 months. The children are tested in pairs. They are given 5 minutes to

[1] The term reclosable will be used in this memorandum to refer specifically to bottle/closure packaging. There are several reclosable unit packages currently available but they will be referred to as unit packaging.
[2] Wilbur, C and S. Barone, "Is Unit Dose Packaging Inherently Child-Resistant?" April 1998.

open a package. If they are not successful, they are given a single visual demonstration. If they have not used their teeth during the first 5 minutes they are told that they can use their teeth if they wish to. The test then continues for an additional 5 minutes.

The PPPA regulations define a test failure for reclosable packaging as any child who opens a package or gains access to its contents. A test failure for unit packaging is a child who opens or gains access to the number of units which constitute the amount that may produce serious personal injury or illness, or a child who opens or gains access to more than 8 units, whichever number is lower, during the full 10 minutes of testing (16 CFR § 1700.20(a)(2)(ii)). The PPPA regulations also state that the calculation of the amount of substance that would produce serious injury or illness is to be based on a 25-pound child. While the terminology is not used in the PPPA regulations, the number of individual units to which access is considered a test failure is commonly referred to as the "F-value."

The PPPA stipulates that special packaging does not mean packaging which all children under 5 years of age cannot open or obtain a toxic or harmful amount within a reasonable time. The standards at 16 CFR § 1700.15(b)(1) and 16 CFR § 1700.20(a)(2)(iii) specify the number of child test failures that are permitted for special packaging. The criteria used to determine whether a package complies with the child-resistant standard are given in Table 1 below. A package is child-resistant if at least 80 percent of 200 children are not able to open the package or access the product during the test. If fewer packages are tested with children, the percentage of children unable to access the package increases statistically.

Table 1[3]
Sequential Testing for Child-resistance

Test Panel	Cumulative # of children	Package Openings					
		First 5 minutes[4]			Full 10 minutes		
		Pass	Continue	Fail	Pass	Continue	Fail
1	50	0-3	4-10	11+	0-5	6-14	15+
2	100	4-10	11-18	19+	6-15	16-24	25+
3	150	11-18	19-25	26+	16-25	26-34	35+
4	200	19-30	-	31+	26-40	-	41+

These criteria are applicable to all package types including unit packaging. Examples of results from testing a reclosable package and a non-reclosable unit dose package (blister) are as follows:

1. A vial-and-cap reclosable package is tested with 50 children. Three children open the package before the demonstration and two children open the package

[3] 16 CFR § 1700.20(a)(2)(iii)
[4] The criteria for the first 5 minutes are not applied to unit packaging since testing for this packaging type is carried out for the full 10 minutes.

after the demonstration for a total of 5 package openings. According to Table 1 this package passes the sequential test and no further testing is necessary.

2. A unit dose blister package is tested with 50 children. The toxicity of the drug in this case is such that access to three units would be considered to be a failure (F=3). The results of testing, presented as the number of children accessing various numbers of units are in Table 2.

Table 2
Example of unit dose packaging testing results for a 50 child test

# of units	0 units	1 unit	2 units	3 units	4 units	5 units	6 units	7 units	8 units	>8 units
# of children accessing this exact # of units	32	10	3	3	-	1	1	-	-	-
# of children accessing at least this # of units		18	8	5	2	2	1	-	-	-

In order to determine the access to the number of units that would be considered a failure or the "F-values," the data are calculated in a cumulative fashion.

In this example, 32 children did not open the package. Eighteen children opened at least one unit (10+3+3+1+1). Eight children opened at least two units (3+3+1+1). Five children opened at least 3 units (3+1+1). Using the Table 1 criteria for the 50 child test this package passes at F=3.

If a more toxic substance were to be packaged in this package, another panel of 50 children would have to be tested to determine if the package would pass at F=2 (eight children accessed at least two units and this requires continued testing per Table 1 criteria). If the substance in this package was so toxic that access to one unit would be considered a test failure, this package would fail to comply with the PPPA. The package fails if F=1 (18 openings is a failure in Table 1).

These two examples demonstrate that a "failure" is access by a child to an amount of substance that may cause serious injury or illness. For a reclosable package, it is assumed that any access to the package constitutes access to a harmful amount and therefore any opening or gaining access is a failure. For a unit package, a failure is access to the amount that may produce serious injury or serious illness to a 25-pound child. It is permissible for a child to access less than that amount. However, for substances that may produce serious personal injury if more than eight units are accessed, the toxicity criteria is superseded by the "more-than-eight" pass/fail criterion.

History of the "More-Than-Eight" Pass/Fail Criterion for Unit Packaging

The Food and Drug Administration (FDA) administered the PPPA in the early 1970s before the CPSC was formed. The FDA proposed testing procedures for special packaging on July 20, 1971, after consultation and input from an advisory committee (36 FR 13335). This proposal was silent on packaging type.

The FDA received comments in response to the proposal stating that the proposed test protocol did not provide for the testing of unit packaging such as blister packaging. The FDA responded that the proposal was not intended to exclude unit packaging. The FDA modified the test procedure to specifically include references to unit packaging, including the definition of test failure for unit packaging which was:

"A test failure shall be any child who opens the special packaging or gains access to its contents. In the case of unit packaging, however, a test failure shall be any child who opens or gains access to the number of individual units which constitute the amount that may produce serious personal injury or serious illness, or a child who opens or gains access to more than 5 individual units, whichever number is lower, during the full 10 minutes of testing."

There was no additional discussion concerning the five unit level in the *Federal Register* notice. This testing protocol became final 60 days after publication (37 FR 22151).

On January 15, 1973, the FDA proposed to modify the definition of a test failure for unit packaging from five to eight units because five units was "unnecessarily restrictive" and was "tending to stifle initiative" in the packaging industry for developing suitable unit packaging because of the inability of technology at the time to meet the performance level (38 FR 1510). The proposal stated that the level of five units was established to provide the packaging industry with parameters within which to develop unit packaging. The FDA also stated that the results of an evaluation of an estimated attention span of children with respect to opening unit packaging was considered. The FDA stated that the criterion of eight units was chosen following review of data from protocol tests initiated by the FDA and other data from other sources. The FDA stated that, "a change from five to eight units would not compromise safety or reduce the child protection quality of special packaging because the number of individual units constituting the amount that may produce serious personal injury or serious illness will prevail in establishing the test failure when such number is eight or less." This amendment was finalized and became effective on May 15, 1973 and has been in effect since that time (38 FR 12738).

PETITION ISSUES

The petition submitted by the HCPC discusses several issues including the safety of unit packaging relative to other packaging types, international standards for non-reclosable packaging, the protection afforded by unit packaging, and the technical

difficulties of making unit packaging that complies with the existing PPPA standards. The following sections discuss these issues.

Relative Safety of Unit Packaging

The HCPC submission espouses the relative safety of unit packaging over reclosable packaging. The HCPC presents their analysis of various poisoning data sources as evidence that unit packaging is inherently safer than other packaging types. The HCPC requested injury data associated with child poisonings from various databases maintained by CPSC. A discussion of why the CPSC staff believes HCPC's conclusions are not supported by CPSC data is at Tab B.

The data from the CPSC databases do not establish the general safety of unit dose packaging over reclosable packaging for drug products. While the data include fewer ingestion exposures involving unit dose packaging, the analysis by HCPC did not take into account the markets for these two packaging types, the number of units available, or the toxicity of the drug products. The HCPC analysis does not make a distinction between incidents involving child-resistant and conventional (non-child-resistant) packaging either for unit packaging or for reclosable packaging.

The HCPC's specific analysis of the iron poisoning data before and after the FDA required additional standards for iron-containing products shows a decline in the deaths and injuries due to iron poisonings. Based on the toxicity of iron, the FDA required unit packaging of products with 30 mg or more iron per dosage unit, and more stringent warning labels on the packaging in July 1997. The FDA rules clarified that iron-containing products subject to the FDA new packaging requirements were still subject to the child-resistant special packaging requirements in 16 CFR parts 1700, 1701, and 1702 (21 CFR §111.50(a) and 21 CRF § 310.518(a)). Under the pre-existing PPPA regulations, packages of iron-containing drugs and dietary supplements that contain 250 mg or more elemental iron require child-resistant packaging. Therefore, following the FDA rule, iron-containing products with 30 mg iron/dosage unit and at least 250 mg iron/package required child-resistant unit packaging as well as stronger warning labels.

The extent to which the reduction in iron-related deaths and injuries following the FDA's requirements is attributable to the requirement for unit-dose packaging is confounded by several factors and cannot be determined by available data. For example, the CPSC staff is aware of companies that decreased their iron level below 30 mg of iron per dosage unit following the FDA requirement to avoid using unit packaging. The proportion of drugs with reduced iron versus those that were switched from reclosable packages to unit packages is unknown. The relative and interactive influence of other factors which occurred concomitantly with the FDA rule also cannot be determined. These factors include the lower per dose iron levels, the requirement for unit dose packaging, the child-resistance of the unit packaging, the added warning label, and the publicity and public education efforts that followed the peak in child iron ingestion deaths.

The CPSC staff believes that it is not possible to conclude, based on available data, that unit packaging is safer than reclosable packaging. Most of the iron poisonings that were associated with deaths involved preparations with at least 65 mg of elemental iron per dosage unit. Under the existing PPPA requirements for unit packaging which considers the toxicity of the product, the child-resistance level of F=4 is required for the packaging of these products. This is more stringent than the "more than eight unit" standard requested by the petitioner. Thus, should the HCPC proposal be adopted, there would be less protection of children from such products. There are many other household chemical products including sulfuric acid drain openers and a number of other commonly prescribed drugs and drug classes such as oral hypoglycemics, tricyclic antidepressants, and antipsychotics that are more toxic than iron. These products would require child-resistance below the "more than eight unit" level requested by the petitioner in order to prevent serious injury to children. Therefore, the staff believes that eliminating the current child-resistance requirements for unit packaging of very toxic products could result in increased poisonings from drugs and other hazardous household chemicals in unit packaging.

International Standards for Non-reclosable Packaging

Several individual countries, as well as Europe, have child-resistance requirements for non-reclosable packages. The HCPC petition stressed the point that the "more than eight" failure criterion without consideration of toxicity, has been adopted in Europe by the European Committee for Standardization (CEN). A more detailed comparison and discussion of the various international standards is at Tab C. The review of the various standards for child-resistance is limited to the definition of failure for non-reclosable packaging since that is the focus of the HCPC petition.

As explained above, the United States has one standard test method to measure child-resistance that is used for all packaging types and all product types including household chemical products and drugs. This method is set out in the PPPA regulations and has been in place since 1971. The test protocol contains specific requirements for a package failure for unit packaging.

In Canada, the Canadian Standards Association (CSA) has a voluntary standard specific for non-reclosable packaging. The CSA voluntary standard for non-reclosable packages has the same definition of failure as the PPPA standard which is, "a test failure for unit packaging is a child who opens or gains access to the number of units which constitute the amount that may produce serious personal injury or illness or a child who opens or gains access to more than 8 units, whichever number is lower, during the full 10 minutes of testing."

CEN in Europe has adopted standards for non-reclosable packaging. CEN was founded in 1961 by the national standards bodies in the European Economic Community and the European Free Trade Association. CEN has adopted two standard test methods for non-reclosable packaging, one for non-pharmaceutical products (household chemical) and the other for pharmaceutical products. Both of these

standards have the status of a national standard in the member countries. Countries with conflicting standards have to withdraw them.

The definitions of failure in the two standards differ from one another as well as from the definition found in the PPPA regulations and the CSA voluntary standard. The definition of failure for the CEN non-reclosable package standard for non-pharmaceutical products (EN 862) is the child opens the package or gains access to one unit using shortened testing periods of 3 minutes as compared to the 5-minute test periods specified in the PPPA and CSA standards. A revision to increase the time periods is currently under consideration by CEN.

The second standard for non-reclosable packaging for pharmaceuticals was adopted and issued by CEN in November 2003. The definition of failure for CEN non-reclosable packages for pharmaceuticals (EN 14375) is a child who opens or gains access to more than 8 units during the full 10 minutes of testing without consideration of the pharmaceutical product that is packaged. There was not a general agreement in Europe about this standard. EN 14375 passed with a minimal 72 percent approval (71 percent is minimum necessary for adoption). One country stated that it would apply for a revision to make the standard more stringent. The EN 14375 standard expressly acknowledges that toxicity may be addressed in later revisions (EN 14275 4.2.1 NOTE).

Protection Afforded by "More Than Eight" Unit Packaging

The petitioner states that adopting a failure criterion for child-resistant unit packaging of "any child who opens or gains access to more than 8 individual units during the full 10 minutes of testing," will provide child protection because unit packaging will still be more difficult for children to open than non-child-resistant unit packaging. The results of a CPSC staff study which tested child-resistant and conventional unit packaging were cited as the rationale for the petitioner's assertion that children would continue to be protected.

In 1997, the CPSC staff tested a non-child-resistant "conventional" pouch, a non-child-resistant "conventional" blister, and a "child-resistant" blister to measure the ability of children to access unit packaging. The results of this study were presented at an international meeting on product safety.[5] The results demonstrated that "conventional" unit packaging that is not intended to be child-resistant, afforded very little protection since children were able to access many units.

The petitioner, citing the results of the CPSC testing, claims that unit packaging meeting the "any child who opens or gains access to more than 8 individual units during the full 10 minutes of testing" failure criterion will afford more protection than non-child-resistant "conventional" unit packaging and therefore should be considered to be special packaging under the PPPA. However, the unit package with "child-resistant" features

[5] C. Wilbur and Barone, S. "Is Unit Dose packaging Inherently Child-Resistant? Presented at the 6th International Conference on Product Safety Research, Amsterdam, The Netherlands, May 15-16, 1998.

tested by CPSC staff for this study had greater child-resistance (approximately F=4) than a package functioning at the "more than eight" failure criteria level, but less child-resistance than would be necessary for a product that is toxic at less than four units. In this testing, 53 of the 100 children tested opened at least 1 unit. If the substance contained in this package caused serious injury after access to one unit, more than half of the children tested would be in danger.

The CPSC staff disagrees with the HCPC conclusion that a "more than eight" failure criteria for unit packaging protects children from serious injury or illness from handling, using, or ingesting the various products currently regulated under the PPPA. As the FDA originally stated in 1973, the CPSC staff believes that the determination of the amount of packaged product that causes serious injury or serious illness to a child is the most important criterion in assuring that children are protected. The CPSC staff has found no information generated since that time to demonstrate otherwise.

Technical Feasibility, Practicability, and Appropriateness of Unit Dose Packaging

The PPPA requires that before the Commission issues a regulation, the Commission must find that special packaging is technically feasible, practicable, and appropriate. Technically feasible means that the technology is available or can be developed to produce packaging that conforms to standards. Practicable means special packaging is adaptable to modern mass production and assembly line techniques. A package is appropriate if it adequately protects the integrity of the substance and will not interfere with its intended storage or use.

Currently, there are many examples of unit packaging available which meet the existing PPPA regulations. The petitioner does not cite lack of availability of such packaging as the basis of their request. However, both availability and usage of unit packaging meeting the existing standards warrant consideration. A detailed discussion of unit packaging types that meet the current toxicity-based PPPA standards from an F=1 level (the most secure) to F=8 is at Tab D.

Senior-friendly unit packaging is also commercially available in various degrees of child-resistance ranging from F=1 packaging to F=8. The staff concludes that these data demonstrate that special unit packaging in a wide range of child-resistance levels including F=1 is technically feasible, practicable, appropriate and readily available.

RESPONSE TO COMMENTS

The Commission published a *Federal Register* notice soliciting comments on petition PP 03-1 (68 FR 35614). Twenty-eight comments, in addition to an additional comment submitted by the petitioner, were received. A list of the organizations and individuals who commented is at Tab E. Six of the comments supported the petition. Sixteen comments opposed the petition; many specifically objected to relaxing the standard by eliminating the toxicity criterion. Many of the commenters supported the

use of unit packaging in general while opposing the relaxation of the toxicity criteria. Specific issues raised by the comments are discussed below.

Toxicity of Drugs and Other Products

A more detailed assessment of comments related to the toxicity of drug products is at Tab F.

Comment: One of the petitioner's assertions is that the vast majority of drugs are not harmful to a small child if ingested in small amounts. Nine commenters (CP03-1-1, 3,4,5,6,14,16,19,20,26) including directors from poison control centers in New Jersey, California, Maryland, Indiana, two toxicology associations (American Academy of Clinical Toxicology and American College of Medical Toxicology), American Academy of Pediatrics, and a European consumer group listed numerous pharmaceutical products that would pose a risk of serious injury or illness to children with the ingestion of fewer than eight units. Many of these commenters are responsible for treating poisoned children. Drugs of concern listed by the commenters include beta-adrenergic antagonists (i.e., timolol, metoprolol, atenolol, propranolol); calcium channel blockers (i.e., nifedipine, verapamil), clonidine; morphine, and the sustained release opiates (i.e., oxycodone); oral hypoglycemics (i.e., sulphonylureas); colchicines; digoxin; Lomotil®; olanzapine, and other antipsychotics; tricyclic antidepressants; bupropion; and isoniazid. The European Association for Consumer Participation in Standardization (ANEC) forwarded a commissioned toxicity assessment of certain solid-dose medications involved in accidental poisonings of children 5 years old and younger that demonstrates the toxicity of these drugs at doses lower than eight units.

Response: The CPSC staff agrees that there are commonly prescribed pharmaceutical products found in many households that would cause serious injury or illness to a child following ingestion of fewer than eight units. Many of the drugs and drug classes identified by the commenters are of concern because of their pharmacological action on the heart and central nervous system. In addition, there are many non-pharmaceutical hazardous household substances currently regulated under the PPPA such as sulfuric acid drain openers that would cause serious injury or illness to a child following access to or ingestion of one unit.

Comment: One commenter, the Consumer Healthcare Product Association, a drug trade association (CP03-1-11) requested that CPSC provide clearer guidance on establishing what constitutes serious personal injury or illness of a 25-pound (11.4 kg) child. The commenter suggested that CPSC work with industry and other stakeholders on the development of guidelines and approaches for determining a toxic dose in children. Another commenter, ANEC (CP03-1-1) forwarded a study that proposed an approach for determining a toxic dose for children (i.e., the dose that would require medical intervention).

Response: The current PPPA regulations require that the determination of the amount of a substance that may produce serious personal injury or serious illness be based on

a 25-pound (11.4 kg) child (16 CFR § 1700.20(a)(2)(ii)). When the FDA finalized the modification of the definition of failure of unit packaging from five to eight units, the FDA acknowledged that variables exist in establishing the amount of substance which would produce serious injury or illness. The 25-pound criterion was put in place to serve as general guidance (38 FR 12738).

The CPSC staff agrees that the determination of the amount of a substance that will cause serious injury or illness to a young child can be difficult especially when data are limited (e.g., for a new drug). The staff reviewed briefly the general approach developed by ANEC (Tab F). The ANEC approach is to derive from various data sources a No Treatment Dose (NTD) to define a safe dose in children less than 5 years of age. This method demonstrates that it may be feasible to develop an approach to determine the toxic dose to children and subsequently determine the number of units that correspond with that dose. The CPSC staff believes that a standardized methodology or approach for establishing a toxic dose in children merits further study, particularly for newer pharmaceutical products for which reliable data on pediatric toxicity has not yet been developed.

Comment: Two commenters (CP03-1-14,17) including the staff of the Environmental Protection Agency (EPA) voiced concern that changes to the definition of failure for unit packaging would affect toxic pesticides regulated by the EPA as well as Federal Hazardous Substances Act (FHSA) regulated household chemical products that are toxic at levels well below an eight unit level.

Response: The PPPA does not cover pesticides directly. However, the Federal Insecticide, Fungicide, and Rodenticide Act defines a pesticide as misbranded if it does not comply with EPA's child-resistant requirements for pesticides. The EPA's requirements for special packaging of pesticides use the testing protocols and definitions in the PPPA.

The packaging standards in the PPPA do not distinguish between drug products and household chemical products. The same test methods and standards are used for packaging that contains any product regulated under the PPPA including household chemicals, cosmetics, and drug products. The CPSC staff has identified no basis for a distinction for packaging based on product type. Toxicity and access to the product are the variables of importance. Several commenters (CP03-1-7, 8, 9, 10, 11) agree that toxicity is the most important criterion.

International Standards on Unit Dose Packaging

Comment: Two commenters, Colin Scaife, the convenor of the CEN working group and American Health Packaging, a member company of the HCPC (CP03-1-15, 22), who agree with the petitioner, state adopting the "more than eight" failure criteria would make the United States consistent with Europe.

Response: The CPSC staff does not agree that eliminating the toxicity requirement would make the PPPA standards consistent with Europe. As the staff indicated in Tab C and discussed above, CEN has two very different standards for non-reclosable packaging. One of the standards defines failure as any access during a shortened test period, while the other standard defines failure as access to more than eight units. The standard that is used depends on the type of product (household chemical or pharmaceutical) and not on the toxicity of the product. The PPPA regulations do not make a distinction based on product type.

The commenters and petitioner specifically refer to EN 14375, the requirements for non-reclosable packaging for pharmaceutical products. The CPSC staff does not recommend that the PPPA standards that have been in effect since the early 1970s be relaxed to harmonize with a newly developed CEN standard that does not have general agreement among the European nations, does not take into account the toxicity of the products to be packaged, and may be amended in the future to address this deficit.

"Objective Standard"

Comment: Several commenters, including companies that make unit packaging and unit packaging components (CP03-1-2, 8, 13, 18, 22, and 25) stated the need for a standard not relying on the calculation of toxicity of products to be unit packaged. They referred to this as an "objective standard." Most of the comments indicated that this is needed because of the difficulty in determining the toxic amount for each regulated oral prescription drug. It was also noted by some commenters that different companies could determine different levels and thus different required F levels for the same drugs.

Response: Presumably, the most reliable toxicity information about drugs, especially new drugs, is generated by the original drug manufacturer as required by the FDA. The CPSC staff understands that the members of the HCPC are not drug manufacturers. Repackagers and some generic drug manufacturers may have limited knowledge about the toxicity of the drugs they make and/or package. This makes it difficult for such entities to determine what level of child-resistance (F-value) needs to be used for those products. However, CPSC staff does not believe that this warrants relaxing the safety of the current PPPA packaging regulations. Manufacturers and repackagers can avoid the calculation of the amount of substance that would cause serious injury to a child by using F=1 packaging. Manufacturers could use F=1 packaging with any product since this most stringent package would be acceptable for drugs of all toxicity levels. As discussed above and in Tab D, packaging meeting the F=1 level is technically feasible, practicable, appropriate, and commercially available.

Alternative Proposals

Comment: Several of the comments (CP-03-1-7, 8, 9, 10) suggested alternatives to the "more than eight" criteria requested by the HCPC. These are to make the failure level one unit instead of more than eight units (option 1) or to eliminate the more than eight restriction thereby making toxicity the only criterion (option 2).

Response: Both of the alternatives proposed by the commenters are consistent with prevention of serious injury and illness as the most important factor for determining child-resistance. Option 1, using a criterion of F=1 can be done voluntarily today as discussed above.

Option 2 is to eliminate the more than eight criterion and to rely solely on toxicity to determine the level of child-resistance required. This proposal may have merit in that less restrictive (above F=8) unit packaging for drugs with low toxicity would be allowed without petitioning the CPSC for exemption. For example, the exemption for oral contraceptives in mnemonic packages (16 CFR § 1700.14(a)(10)(iv)) would not have been necessary since children are unable to access an amount of the hormones that would result in serious injury (even though there are 21 or 28 tablets included). However, the CPSC staff believes that it is premature to pursue this option until more robust guidance for determining the amount of a substance that causes serious injury or illness in a child can be developed. It is also expected that additional resources would be required to enforce the PPPA if such a change were made.

While a number of factors contribute to a manufacturer's decision to use unit packaging, it is possible that option 2 could potentially increase the amount of unit packaging that is used for drugs. However, it does not eliminate the toxicity criterion as the petitioner requests. Another alternative is to make the failure criterion F=1 or the amount that would cause serious injury whichever is greater. Again, it is premature to recommend this option until guidance for defining the level of toxicity is explored and the staff resource requirements assessed.

Miscellaneous Issues

Comment: The HCPC (CP03-1-29) stated that the CPSC should specifically require only F=1 unit packaging for all of the toxic drugs listed by the various commenters. The HCPC stated that this would be permitted under the PPPA because there are several different designs of F=1 unit packaging.

Response: The PPPA expressly forbids the CPSC from prescribing specific packaging designs, product content, package quantity, and most labeling (15 U.S.C. 1472(d)). In 1991, the American Association of Poison Control Centers requested that the CPSC require child-resistant unit dose packaging for iron-containing products. This request was not docketed as a petition because of the statutory prohibition in the PPPA against specifying designs.[6]

Comment: Several commenters (CP03-01-6, 9, 14, 21) questioned the HCPC analysis of the ingestion data and their conclusions that unit packaging is "inherently safer." The commenters listed the limitations of the data that the HCPC did not take into account, including the limited market for unit packaging and the relative toxicity of the OTC drug

[6] Correspondence from Clement D. Erhardt, III, General Counsel to Toby Litovitz, MD and Anthony Manoguerra, Pharm.D., of AAPCC, June 21, 1991.

products commonly found in unit packaging compared to prescription drugs in child-resistant bottles. Several commenters pointed out that the HCPC petition contradicted itself by saying both that unit packaging was safer because of the low number of injuries and that "unit packaging was not widely used in the U.S."

Response: The CPSC staff agrees with many of the commenters' assertions. As described in Tab B and in the section above on Relative Safety of Unit Packaging, the data from the CPSC databases cannot be used to establish the safety of unit dose packaging as compared to reclosable packaging for drug products.

Comment: One commenter, Pharmaceutical Research and Manufacturers of America (CP03-1-23), a trade association that represents pharmaceutical manufacturers, stated that the elimination of the toxicity criterion proposed by the HCPC will not increase the use of unit packaging because drug companies will continue to assess the toxicity of their products and would not take advantage of the petitioner's suggested alternative standard if potential exposure could result in toxicity.

Response: The CPSC staff acknowledges that the choice of packaging for drug products involves factors affecting liability such as prevention of injury and the state of the art, in addition to other factors such as patient compliance, drug stability, and cost.

Comment: One commenter (CP03-1-9) noted that the HCPC was incorrect when they stated that the CPSC requires child-resistant package testing and the submission of toxicity data.

Response: The PPPA does not require pre-market approval of child-resistant packaging. There is no requirement for submission of testing data to the CPSC. However, manufacturers, importers, and distributors must ensure that their products comply with the PPPA and most will test to do so. The HCPC petition states at the top of page 6, "...they must determine the amount that may cause a somewhat undefined serious injury or illness to a small child, submit toxicological data to CPSC, wait for CPSC confirmation of their conclusions as to the number of units that would constitute a failure, and then test the package." This is incorrect. While the PPPA regulations request that data be submitted to the staff (16 CFR § 1700.20(a)(2)(ii)), it is not required.

OPTIONS

The Commission has two options:

1. If the Commission concludes that it is appropriate, the Commission could grant the petition and begin a proceeding to delete the toxicity criterion from the definition of a test failure for unit packaging under the PPPA.

2. If the Commission concludes that deleting the toxicity criterion from the definition of test failure for unit packaging is inappropriate, the Commission could deny the petition.

RECOMMENDATION AND DISCUSSION

The staff recommends that the Commission deny the petition. The petitioner requests that the existing failure criteria for unit packaging be access to more than eight individual units regardless of the toxicity of the product. The CPSC staff believes that by eliminating the consideration of toxicity of the packaged product, the resulting criterion would weaken the existing child-resistance failure criteria for unit packaging resulting in little or no protection of children from the most toxic products on the market.

The CPSC staff does not agree with many of the petitioner's assertions about unit packaging. The CPSC staff does not agree that eliminating the toxicity consideration will result in an "objective standard" as the petitioner claims. The FDA made it clear when they amended the definition of failure from more than five units to more than eight units that no impact with respect to protecting children would be felt since toxicity is the prevailing and major consideration in assuring that children are protected. It is currently possible for manufacturers and repackagers to avoid the calculation of the amount of substance that would cause serious injury to a child and use an "objective standard" that is also protective. Manufacturers could use F=1 packaging with any product since this most stringent package would be acceptable for all toxicity levels. Unit packaging providing the most protective levels of child-resistance is readily commercially available.

The CPSC staff does not believe that there is adequate information to demonstrate that changing the definition of failure for unit packaging as the petitioner requests will result in greater use of unit packaging. The Pharmaceutical Research and Manufacturers of America, a major pharmaceutical trade association stated that its member companies would not knowingly use packaging that was insufficiently protective for children.

The results of CPSC staff analysis conclude that current CPSC data do not demonstrate conclusively that unit packaging is "safer" than reclosable packaging as the petitioner asserts. The percentage of market share of unit packaging as compared to bottles and closures was not considered in the petitioner's analysis of ingestion data even though the petitioner states that the market share of unit packaging is low. In addition, there are other confounding factors not considered in the petitioner's analysis such as the difference between child-resistant and non-child-resistant packaging. The potential impact of weakening the existing PPPA requirements for unit packaging on the number and severity of poisonings is not known but could result in an increase in poisonings of products in unit packages.

The petitioner focuses on the packaging of drug products because the HCPC member companies make packaging components or packages specifically for pharmaceutical products. The CPSC staff does not believe that the PPPA packaging standards for drug products should be different from packaging standards for other household products. Toxicity of and access to products are the most important variables. Children should be protected equally from toxic drugs and acids, caustics, pesticides, and other household chemical substances with considerable toxicity.

TAB A

PP 03-1

HCPC
HEALTHCARE COMPLIANCE PACKAGING COUNCIL

March 17, 2003

VIA FACSIMILE (301/504-0124) AND FIRST CLASS MAIL

Todd Stevenson
Secretary
U.S. Consumer Product Safety Commission
4330 East West Highway
Bethesda, Maryland 20814-4408

RE: Petition to Alter Portions of the CR/SF Test Protocol

Dear Mr. Secretary:

By this letter, the Healthcare Compliance Packaging Council (HCPC) petitions the U.S. Consumer Product Safety Commission (CPSC) to alter provisions of the Child-Resistant/Senior-Friendly (CR/SF) test protocol codified under Title 16, Code of Federal Regulations, Sections 1700-1750.

Specifically, we petition CPSC to amend 16 CFR 1700.20 (a) (2) (ii) of the CR/SF protocol because it applies a subjective pass/fail criteria which differs from that for other CR-compliant designs, and discourages use of unit dose blister and strip packaging as manufacturers' original packaging[1] with prescription (Rx) and over-the-counter (OTC) drug products.

To make the pass/fail criteria for unit dose formats as objective as those that apply to other CR formats, we petition CPSC to adopt a strict numerical standard for determining failure of unit dose formats used with Rx and OTC drugs.

We also ask CPSC to adopt "type testing" provisions for the protocol such that – once a package has passed protocol – the package "type" will be considered compliant with provisions of 16 CFR 1700-1750 without having to be re-tested. This step would reduce the number of small children who are subjected to protocol testing each year in the United States, provide clear compliance requirements for manufacturers/ packagers, and harmonize U.S. standards with those in use by other nations.

[1] Packaging that is transferred to the consumer in the same packaging that left the manufacturer, without the need for repackaging drugs from bulk formats into individual containers at the pharmacy.

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We are petitioning the CPSC at this time for a number of reasons, three of the primary ones being:

1) A recent decision by the U.S. Court of Appeals for the Second Circuit (*Nutritional Health Alliance v. Food and Drug Administration*) that overturns key provisions of a regulation implemented by the U.S. Food and Drug Administration (FDA) in 1997 that had been extremely successful in protecting small children against accidental poisonings caused by ingestion of iron.

2) Publication of data by CPSC staff in 2002 indicating that CR/SF packaging has achieved only "partial" success in preventing accidental poisonings of small children caused by the ingestion of aspirin products, and recommending that "additional strategies designed to prevent unintentional drug poisonings need to be developed and evaluated."[2]

3) Growing support within numerous public health organizations, learned professionals, and other government agencies[3] for use of unit dose and unit-of-use formats as manufacturers' original packaging to combat medication and dispensing errors that routinely and inherently occur as the result of pharmacy repackaging of drug products from bulk containers to individual containers. While this is an area that, regrettably, is outside CPSC's jurisdiction, we nonetheless request that the Commissioners keep these endorsements in mind when considering our petition.

As we will outline in this petition, unit dose blister and strip packaging is inherently safer than packaging systems with CR features that rely on proper operation by consumers each time the package is accessed (often 30, 60, 90 or more times during the package's "life span"), and inherently require repackaging before being dispensed to consumers. Yet despite the superiority of unit dose formats, these formats are not widely used in the United States as manufacturers' original packaging for Rx drug products, largely due to concerns over compliance with the CPSC protocol.

If the subjective pass/fail criteria were removed from the current protocol, and if CPSC allowed use of "type testing," the disadvantages to greater use of unit dose formats would be removed and, consequently, manufacturers would be better able to adopt these formats. If that were the case, the HCPC asserts that there would be a quantifiable reduction in accidental poisonings of small children due to ingestion of drug products.

By implementing the actions requested in this petition, CPSC would not be mandating use of unit dose formats for any drug product. Nor by any means would CPSC be lowering the bar of public safety. Considering all available data, in fact, the HCPC contends that adoption of the actions called for in this petition would help to significantly improve public safety—in numerous ways.

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[2] The Effectiveness of Child-Resistant Packaging for Aspirin," Gregory B. Rodgers, Ph.D., *Arch Pediatr Adolesc Med.*, 2002; 156:929-933.

[3] Adoption of unit dose and/or unit-of-use formats as manufacturers' original packaging has been endorsed by the: U.S. Department of Veterans' Affairs, U.S. Centers for Disease Control, U.S. Pharmacopoeia Convention, Institutes of Medicine, National Patient Safety Partnership, American Society of Health-System Pharmacists, and National Quality Forum.

I. INTEREST OF THE HCPC

The HCPC is a not-for-profit trade association founded in 1990 to promote the many benefits of unit dose blister and strip packaging. HCPC members include companies involved in the manufacture of pharmaceutical-grade plastic films, aluminum, and paperboard used to produce unit dose blister and strip packaging, as well as manufacturers of machinery used to create unit dose formats. HCPC corporate members also include firms that provide packaging services to pharmaceutical manufacturers on a contract basis, as well as companies that purchase bulk quantities of drug product from pharmaceutical manufacturers and re-package those products into unit dose and other formats for use by hospitals, clinics, and other similar facilities. For a complete list of HCPC members and other information about the Council, please visit our Website at www.unitdose.org.

Over the past 13 years the HCPC has worked to become the recognized authority on matters related to unit dose packaging, including compliance with 16 CFR 1700-1750. As such, the HCPC has been an active participant and supporter of ASTM subcommittee D10.31 on child-resistant packaging, as well as the Poison Prevention Week Council. Our participation in both of these groups dates back more than ten years. In addition, the HCPC participates in the activities of the United States Pharmacopeia's (USP) Committee on Packaging, Storage, and Distribution (PSD), and has been in close contact with the CEN Working Group on child-resistant packaging standards for non-reclosable packaging in Europe (CEN/TC 261/SC 5/WG 27).

The HCPC has also taken it upon itself to obtain data from CPSC through the Freedom of Information Act regarding accidental poisonings of children six years old and younger that involve Rx and OTC drug products from January 1983-January, 2003.

II. UNIT DOSE PACKAGING IS INHERENTLY SAFER THAN CAP-AND-VIAL CLOSURES.

All available data indicate that unit dose formats are far more effective than cap-and-vial closure systems when it comes to preventing accidental ingestion of drug products. This is due to the fact that unit dose formats house each dosage unit in a separate cavity. Unlike any type of closure system – which inherently allows instant access to the entire contents of the package if the CR cap is left loose, removed, or defeated by the child – unit dose formats require that each unit be removed one at a time. This allows more time for children to lose interest, or for adults to intervene, should a child come into contact with a drug product. In addition, unit dose systems, by their design, do not need to be properly re-secured after each use and, therefore, their CR properties are not dependent on repeated proper usage by adult consumers.

As previously noted, the HCPC has conducted an extensive review of data collected by CPSC regarding accidental poisonings of small children who ingested drug products, and our review clearly shows that unit dose formats are rarely involved in these incidents. According to CPSC Incident Report data, from 1983 through 2002, of all incidents reported (*i.e.*, accidental ingestion of pharmaceutical products) in which the type of packaging could be identified, 84.6 percent involved cap-and-vial closure systems, while only 6.8 percent involved CR unit dose formats.

CPSC Incident Report data also record 47 fatalities from 1983 through 2003 in which children aged six years or younger ingested lethal amounts of drug product that had been removed from a closure system.

In 22 of these incidents it is specifically noted that the packaging was a "child resistant" cap-and-vial closure system. There are no reported incidents, however, of a child fatality in the United States after he/she removed drug product from a unit dose package.

We also note that CPSC data indicates that children in real world situations ingest far fewer dosage units when they come in contact with unit dose packages than they do when they gain access to CR cap-and-vial closure systems. As shown by the table below, over the past two years alone, CPSC data recorded 15 incidents in which children ingested more than ten dosage units after defeating a closed CR cap-and-vial system. In eight of these incidents the child ingested 20 or more units, and the maximum number of units ingested was 33.

These data can be contrasted to incidents over the same period of time in which unit dose packaging – CR *and* non-CR – was involved. With unit dose formats the maximum number of units ingested was five, and in 17 of the 31 reported incidents (nearly 55 percent of all such incidents) one unit or only a portion of a single unit was ingested.

Number of Units Ingested: November 5, 2000 – January 14, 2003									
Units Ingested, CR Closures*	12	14	15	18	20	22	24	25	33
Number of Incidents	1	1	6	1	2	1	1	1	1
Units Ingested, Unit Dose**	0.25	0.5	0.75	1.0	1.5	2	3	4	5
Number of Incidents	1	2	1	13	1	6	2	2	3
*Incidents in which more than 10 units were ingested									
**Includes CR and non-CR unit dose formats									

The HCPC recognizes that CPSC data are not comprehensive, but we find the disparity outlined in the above table extremely compelling.

Indeed, FDA recognized the fact that unit dose formats are inherently safer than closure systems in protecting against accidental poisonings of small children when the Agency finalized regulations in 1997 requiring, among other things,[4] that unit dose formats be used for products that contain more than 30 mg of iron. As FDA noted in the preamble to its final regulation:

[4] In addition to the unit dose packaging requirements, FDA's final rule mandated use of one of the two following labels depending on the type of package used with the product: 1) for products packaged in unit dose formats, manufacturers must use the label "WARNING – Keep away from children. Keep in original package until each use. Contains iron, which can harm or cause death to a child. If a child accidentally swallows this product, call a doctor or poison control center immediately"; or 2) for products packaged in other than unit dose formats, manufacturers must use "WARNING – Close tightly and keep away from children. Contains iron, which can harm or cause death to a child. If a child accidentally swallows this product, call a doctor or poison control center immediately."

- "FDA's concern is limiting the possibility that the product will be injurious to health. Unit dose packaging, ***even conventional unit dose packaging***, will help accomplish this goal by limiting the amount of iron that a child can consume in a short period of time."

- "...unit dose packaging, ***even conventional unit dose packaging***, limits pediatric access to product and is not dependent on proper reclosure of the container."
  – *Federal Register*, January 15, 1997, pp. 2227-2231 [Emphasis added]

FDA's wisdom was proven by the success of the regulation. Between 1991 and 1997 there were a total of 48 deaths in which children six years old and younger ingested lethal amounts of iron. But in the five and a half years since the regulation took effect, there has only been one such fatality.

Unfortunately, as described more fully below, FDA's authority to require unit dose packaging was thwarted by the January 21, 2003, U.S. Court of Appeals for the Second Circuit decision in *Nutritional Health Alliance v. Food and Drug Administration*.[5] While CPSC cannot specifically require unit dose packaging under the Poison Prevention Packaging Act, at the very least, it should not create artificial barriers to the use of this widely recognized safer packaging alternative.

III. THE CURRENT REGULATION CREATES A DISINCENTIVE FOR PHARMACEUTICAL MANUFACTURERS AND PACKAGERS TO USE THE SAFER UNIT DOSE PACKAGING.

The HCPC is petitioning CPSC to alter the pass/fail criteria for unit dose formats under 16 CFR 1700.20 (a) (2) (ii) because the current regulation creates a disincentive for pharmaceutical manufacturers and packagers to utilize the safer unit dose packaging formats. The current test protocol provides as follows:

> A test failure shall be any child who opens the special packaging or gains access to its contents. ***In the case of unit packaging, however, a test failure shall be any child who opens or gains access to the number of individual units which constitute the amount that may produce serious personal injury or serious illness***, or a child who opens or gains access to more than 8 individual units, whichever number is lower, during the full 10 minutes of testing. [Emphasis added]

This provision maintains an *objective* pass/fail standard for cap-and-vial closure systems (*i.e.*, if a child removes the cap, the package fails), but establishes a *subjective* standard for unit dose formats in that the manufacturer must determine the quantity of product that constitutes "the amount that may produce serious personal injury or serious illness." Moreover, the only guidance offered under the regulations for making these subjective decisions is the following, inexact, CPSC definition:

> The determination of the amount of a substance that may produce serious personal injury or serious illness shall be based on a 25-pound (11.4 kg) child. Manufacturers or packagers intending to use unit packaging for a substance requiring special packaging are requested to submit such toxicological data to the Commission's Office of Compliance.

In other words, for pharmaceutical manufacturers/packagers that must comply with the CR/SF packaging requirements, there are two general choices when facing protocol testing: 1) use a CR system such as a

[5] This decision has no impact on the labeling requirements contained in FDA's final rule.

closure for which they know exactly how to determine compliance with the protocol; or 2) use a unit dose format for which they must determine the amount that *may* cause a somewhat undefined serious injury or illness to a small child (note that these determinations are often based on limited data, especially with new chemical entities), submit toxicological data to CPSC, wait for CPSC confirmation of their conclusions as to the number of units that would constitute a failure, then test the package. Should the package fail – either in protocol testing or the marketplace – these considerable investments of time and money cannot be recovered.

Faced with such a choice, it is understandable why manufacturers are less inclined to adopt unit dose formats – especially when other packaging options are readily available.

This provision is also widely recognized within pharmaceutical packaging circles as favoring cap-and-vial closures over unit dose formats. In a "stimuli" article released for comment in February 2003 by an Expert Project Team convened by USP's Committee on Packaging, Storage, and Distribution, for instance, the USP Project Team noted that:

> It is important to understand why bottles are the primary means for distributing and dispensing prescription products in the United States. There is a requirement within the US to utilize 'special packaging'...for a prescription product intended for oral administration which is dispensed to a household. The protocol requirements and evaluation criteria are different for reclosable packages (bottles) vs. non-reclosable packages (blister packs and pouches).
>
> Once a reclosable package...has been proven to pass the protocol described in 16 CFR 1700...[it] can be used for any dosage form, irrespective of count...[But], a non-reclosable package...is considered to be specific to the drug product's shape, size, and color as well as the affected blister card's count and overall size. This means it is prudent to test each and every blister package marketed to ensure it meets the requirements described in 16 CFR 1700. Unlike reclosable packages, for non-reclosable packages, one must determine what a harmful dose to a 25-pound child is in order to determine at which point a failure occurs....The determination of harmful dose is not straightforward, as generally, no data exists that directly correlates to this number. Generally, data is reviewed from animal toxicity studies, clinical studies, and other adverse events such as inadvertent overdose information that may be available. The degree to which data is available is [therefore] generally a function of where in the product's life cycle it is....Often times, for a new chemical entity for which there is little information, [the manufacturer] will default to a conservative number. This may translate to a failure if the child gains access to one, two, or three units. It is important to note that when a prescription goes Over-the-Counter (OTC), it is generally half the maximum commercial strength which translates to a failure level that is twice what the prescription strength was.
>
> Recognizing the subjective, costly, and uncertain nature of this process (determination of harmful dose, design, development, and testing of commercial blister packs) it is no surprise that many drug manufacturers opt for utilizing bottles with counts between 30 and 5,000 with either child-resistant or non-child-resistant [caps] as their most used package. Unfortunately, this practice does not facilitate patient compliance and often requires some form of repackaging before the patient receives the product. As described earlier, it is quite likely that the packaging utilized will be inferior to the original package

utilized by the manufacturer. In addition, the act of repackaging itself adds opportunity for problems (e.g., dispensing errors, mislabeling, cross contamination of products) as well as cost.

IV. AMENDING THE REGULATION WOULD RESULT IN A DISCERNABLE REDUCTION IN ACCIDENTAL POISONINGS FROM PHARMACEUTICAL PRODUCTS.

PETITION REQUEST 1: The Definition of test failure for unit dose packaging should be an objective standard, *i.e.*, "any child who opens or gains access to more than 8 individual units during the full 10 minutes of testing."

As demonstrated above, unit dose packaging is inherently safer than cap-and-vial closures because: 1) cap-and-vial closures rely on consumers to properly replace the cap after each use, and many accidental poisonings result from the failure of consumers to do so; and 2) if the CR feature is defeated, the entire contents of a vial is compromised, and children are much more likely to consume a lethal amount of the contents with a cap-and-vial closure than with unit dose packaging. Even though unit dose packaging is demonstrably safer than cap-and vial closures, CPSC's current regulation imposes an economic barrier to the use of unit dose packaging for pharmaceuticals in the United States. We respectfully request that CPSC amend the regulation to remove this economic barrier. Specifically, we request that CPSC remove the subjective criteria in the definition of a test failure of unit dose packaging in 16 CFR 1700.20 (a) (2) (ii), and limit the definition to objective criteria, *i.e.*, "any child who opens or gains access to more than 8 individual units during the full 10 minutes of testing."

Under the Poison Prevention Packaging Act of 1970, Congress defined "special" packaging as:

> ...packaging that is designed or constructed to be significantly difficult for children under five years of age to open or obtain a toxic or harmful amount of the substance contained therein within a reasonable time and not difficult for normal adults to use properly, ***but does not mean packaging which all such children cannot open or obtain a toxic or harmful amount within a reasonable time.*** (15 USC 1471 (4), [Emphasis added]

Moreover, under 15 USC 1472 (d), Congress specifically precluded CPSC from "[prescribing] specific packaging designs, product content, ***package quantity***, or...labeling" [Emphasis added].

Based on these two provisions, CPSC would be well within its statutory authority to alter 16 CFR 1700.20 (a) (2) (ii) so that it is based solely on a numerical standard. The current test protocol inconsistently requires that manufacturers make a determination regarding the amount of drug product that "may" cause serious personal injury or illness to a small child ***only*** when they elect to use unit packaging. If the same rationale were applied consistently, a cap-and-vial closure system, for example, could not be considered "child resistant" unless its contents were limited to a quantity that would not cause serious personal injury or serious illness to a small child – no matter how well the package performed under protocol testing. However, the regulation provides no such parallel requirement for cap-and-vial closures.

Indeed, the requirements contained in 16 CFR 1700.20 (a) (2) (ii) contradict Congressional intent in that the provision establishes a unique pass/fail standard for unit dose formats, and bases pass/fail criteria for

unit dose formats on package quantity (*i.e.*, a unit dose format will fail criteria if a child can open or gain access to more than eight units ***even if ingestion of the entire contents of the package could not be expected to cause serious personal injury or illness***). For these reasons alone, HCPC's request is appropriate, complies with the legislative intent of the PPPA, and is within CPSC's statutory authority to grant.

As to the exact numerical standard that should be adopted by the Commission for determining whether a unit dose format should be considered "child resistant," CPSC data described above suggests that number should remain at eight units. That is, in the course of the existing ten-minute test period, with the existing instructions and provisions, if a child is able to open or gain access to more than eight individual units, a unit dose package should be considered a failure.

To this point, we note that research published by CPSC staff in 1998[6] found that children given unlimited numbers of unit dose packages with no CR feature were able to open, on average, 23 units during the ten-minute protocol. Moreover, 90 percent of the children were able to open more than eight units in these tests.

Based on these findings, it is evident that placing a pass/fail numerical standard of more than eight units for unit dose formats would require unit packaging to be fortified in such a way that would make it far more protective than a unit dose package that has no CR feature at all.

As such, CPSC would clearly be in compliance with Congressional intent that CR packaging be "...significantly difficult for children under five years of age to open or obtain a toxic or harmful amount of the substance contained therein within a reasonable time...but does not mean packaging which all such children cannot open or obtain a toxic or harmful amount within a reasonable time."

With regard to products that could cause serious personal injury or serious illness to a small child should he/she ingest fewer than eight units, CPSC data described above suggests that protocol testing is not reflective of real world situations, and that a numerical standard of no more than eight dosage units under protocol conditions translates to packaging that, in real world situations, meets the standard established by Congress under 15 USC 1471 (4), and is safer than cap-and-vial closures that meet the current standard. As noted above, CPSC's own data shows that children ingest very few dosage units when they gain access to unit dose formats (even those that have no CR feature).

Moreover, the well-documented success of FDA's iron regulations in preventing accidental poisonings further supports movement toward an objective standard for unit dose packaging.

We also note that CR standards for non-reclosable packaging that have been adopted in Great Britain, and are currently under consideration throughout the entire European Union, set failure criteria at more than eight units. These decisions were not made arbitrarily, nor were they made in a vacuum. Rather, these standards are based on nearly three decades of data and experience with the U.S. protocol, and in consultation with ASTM and other bodies in the United States. We urge CPSC, therefore, to consider the precedent set by these other nations, as well as the opportunity to harmonize CR packaging standards for non-reclosable formats on a more global basis.

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[6] "Is Unit Dose Packaging Inherently Child-Resistant?" Charles J. Wilbur, M.S. and Suzanne Barone, Ph.D.

PETITION REQUEST 2: Allow Type Testing for Unit dose Packaging Under the Protocol.

The HCPC's second request under this petition is that CPSC allow a package type that has successfully passed protocol testing to be used for other products without additional testing – a.k.a., "type testing." This request is based on the fact that the current regulation allows *de facto* type testing for cap-and-vial closures, but not for unit dose formats, thereby creating further disincentive for the use of the safer unit dose packaging. The regulation allows *de facto* type testing for cap-and-vial closures in that, once the closure passes the protocol, it may be used for any drug product. Unit dose packaging, however, must be tested under the protocol for each particular product to be packaged in a particular unit dose format.

There is precedent for this request in CPSC's handling of CR/SF packaging requirements for investigational substances dispensed for home use in clinical trials. We also note that type testing has been adopted by standards-setting bodies in Germany and Great Britain, and is included in the draft protocol currently being circulated by the European standards-setting body, CEN.

With regard to packaging for investigational substances, CPSC released correspondence to industry in 1999 and 2000 in which the Commission noted it would exercise its enforcement discretion in allowing type testing, as long as investigational substances dispensed for home use during clinical trials were packaged in a format that has at least one feature described in ASTM D-3475. ASTM D-3475 is basically a list of recognized CR features such as peel/push, push/turn, notch/tear, etc. that, in many cases, have been in use for decades.

By allowing use of ASTM D-3475, manufacturers need not put packages through protocol testing to ensure that they are compliant with PPPA requirements if they have already been proven to meet those requirements, and have not been altered in any way.

While the HCPC recognizes the special circumstances related to packaging for clinical trials, we also note that protocol testing is an expensive, time-consuming process that utilizes small children. Indeed, it is the HCPC's understanding that tens of thousands of children are subjected to protocol testing each year, and this is due, in part, to regulatory silence as to how often a package must be tested.

This issue was well articulated in the summer 2000 edition of *Child Resistant Packaging Update* published by Perritt Laboratories, in which the author states:

> It is widely accepted that, when changes are made to a packaging system that has been qualified as child-resistant, the newly modified packaging system should be tested to ensure that it is still child-resistant. However, if there are no *known* changes to your child-resistant packaging system, how long should you rely on the original test data? When does data become "too old"? ...Current consensus around the industry indicates that five years in the longest period that protocol data should be used. This matches the recent statements from CPSC staff indicating they do not consider data older than five years to be reliable.

The HCPC has long contended that use of children for protocol testing is, at best, a necessary evil. As the HCPC sees it, protocol testing puts small children in a situation where they are encouraged to open packaging designed to contain substances which, under any rational condition, should be avoided at all costs. Moreover, CPSC's protocol specifically requires adults who administer these tests to tell children it is acceptable to use their teeth if they cannot get the test package open after five minutes of trying.

While the HCPC is not aware of any incidents whereby a child who has been through protocol has repeated the test, unsupervised, at home, the potential for such a tragedy is real. Considering the large number of children subjected to protocol each year – and the fact that children are specifically told that they can use their teeth in the course of the test – the HCPC further notes the possibility that small children can be cut, chip their teeth, injure their gums/tongues, or sustain other types of injuries during protocol testing.

While CPSC recognizes the value of using children to determine if a package is truly child resistant, the Commission must weigh that value against the potential risk faced by children used in these tests, particularly when tens of thousands of children are subjected to protocol testing each year. This is especially true when the protocol is being run on packages that have already proven to be compliant.

To the HCPC's knowledge, every other country in the world that has adopted child-resistant packaging standards allows use of type testing as it: 1) reduces the need to use small children in protocol testing; 2) clarifies manufacturers' obligations; and 3) ensures "practicability" (a requirement laid out by Congress under the PPPA).

Recognizing the highly unlikely possibility that CPSC will abandon the practice of using small children during protocol testing, we urge the Commission, at the very least, to alter the protocol so the number of children used in these tests is minimized. This goal will be met by allowing use of type testing.

V. THE DECISION IN *NUTRITIONAL HEALTH ALLIANCE v. FDA* WARRANTS RECONSIDERATION OF THE TEST PROTOCOL.

As noted above, between 1991 and 1997 there were a total of 48 deaths in which children six years old and younger ingested lethal amounts of iron. But in the five and a half years since FDA amended its regulations to require unit dose packaging for iron along with labeling changes, there has only been one such fatality. Despite this success, however, FDA's packaging requirements for iron were overturned in a decision handed down January 21, 2003 by the U.S. Court of Appeals for the Second Circuit in *Nutritional Health Alliance v. Food and Drug Administration* on the ground that FDA lacks authority to impose these types of packaging requirements. As the Court's decision states:

> We conclude that the provisions of the [Food, Drug and Cosmetics Act] relied upon by the FDA unambiguously fail to provide the FDA with authority to regulate packaging for poison prevention purposes. The provisions that the FDA relies upon are plainly limited to delegation of authority to the FDA to regulate conditions under which a drug or dietary supplement product may be adulterated precisely to prevent the manufacture and distribution of adulterated products. The risk of accidental poisoning that the FDA sought to address through its unit dose packaging regulations is unrelated to adulteration under any reasonable interpretation of the term.

Short of a successful appeal by FDA to the Supreme Court or Congressional intervention, this decision means that the packaging regulations in place during the six years that nearly 50 children died due to iron poisoning – *i.e.*, CPSC's protocol requirements that create a disincentive for the use of unit dose packaging – will be the only packaging protection that remains in place.

If this is the case, the HCPC sadly predicts it is only a matter of time before these types of fatalities begin to climb again.

Since CPSC is precluded from mandating one type of CR/SF packaging over another under the Poison Prevention Packaging Act of 1970 (PPPA)[7], the very least the Commission could do in the face of this judicial decision is remove the obstacles to safer packaging contained in the current protocol.

VI. CONCLUSION

As a final consideration, the HCPC notes that unit dose packaging was a growing technology in Europe, but a nascent industry in the United States at the time Congress enacted the PPPA in 1970 and when FDA promulgated the implementing regulations in 1973. Accordingly, there was no input from the unit dose packaging industry for FDA to consider when it promulgated the test protocol, because there was no such industry in the United States at that time.

Shortly after the HCPC was formed in 1990, we were able to discuss the decision making process behind the pass/fail criteria that came to be codified under 16 CFR 1700.20 (a) (2) (ii) with a former FDA official who participated in drafting the regulation, and we learned that there was no industry input whatsoever reflected in this provision. We were told, in fact, that 16 CFR 1700.20 (a) (2) (ii) was drafted by FDA personnel who had no data, evidence, stakeholder input, or anything other than the PPPA language itself to guide them.

On the many occasions that we have raised our concerns about the protocol with CPSC staff in the intervening years, however, we have been told that these issues should have been raised during development of 16 CFR 1700-1750. The implication being that it is somehow "too late now" to alter protocol requirements. The regulation, however, placed restrictions on the unit dose industry before it had a voice to speak, thereby denying it the due process to which it is entitled. It is clear through the legislative history of the PPPA that Congress recognized the evolutionary process of package design, and the need for a means of defining CR based on the realization that new formats would continue to be developed. FDA made reference to this realization in the preamble to its implementation regulations as well.

Certainly, when the test protocol was implemented in 1973, FDA had no way of knowing the relative safety benefits of unit dose packaging *vis-à-vis* cap-and-vial closures. Had FDA had a crystal ball at the time, it would not have included in the regulation the disincentives for manufacturers and packagers to utilize unit dose technologies. With the benefit of 30 years of experience (including CPSC data) that demonstrates the consumer safety advantages of unit dose packaging, the time is now ripe for the Commission to consider the improvements to protocol testing we are suggesting with this petition.

---

[7] Interestingly, in FDA's brief filed in this case, the Agency asserts that unit dose packaging is "not a specific package design which CPSC is prohibited from requiring under the Poison Act" (pp. 56-58). As FDA explains in its brief: "The Poison Act prohibits CPSC from requiring any specific package design....[but] FDA, in its rulemaking, made clear it did not intend to require a specific type of unit dose packaging design, such as "blister" packaging, because, based upon studies, 'other types of conventional unit dose packaging provide a comparable length of time for children to open as that required by conventional blister packaging'....As FDA announced, 'several types of packaging can satisfy the definition of "unit dose packaging," including blister-type packaging, pouches, and dispensers that deliver one dosage at a time....A blister pack and a single dose dispenser are clearly two very different designs even though both of these designs fall under the definition of unit dose packaging.'" (copy attached)

The current test protocol creates a disincentive for the use of a safer packaging alternative, *i.e.*, unit dose packaging. Adoption of the proposed changes would reduce the number of fatalities among children from accidental poisoning. Accordingly, we urge the Commission to adopt the requested changes as soon as possible.

Sincerely,

Peter G. Mayberry
Executive Director

Enclosure: As above

cc/w/enclosure: Chairman Harold D. Stratton, Jr.
Commissioner Thomas H. Moore
Commissioner Mary Sheila Gall

United States Court of Appeals

For the Second Circuit

Docket No. 01-6011

NUTRITIONAL HEALTH ALLIANCE,

Plaintiff-Appellant,

— against —

FOOD AND DRUG ADMINISTRATION and DONNA SHALALA, in her official capacity as Secretary, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES,

Defendants-Appellees.

On Appeal From The United States District Court
For The Eastern District of New York

BRIEF FOR DEFENDANTS-APPELLEES

PRELIMINARY STATEMENT

Plaintiff-appellant Nutritional Health Alliance ("NHA"), an association of manufacturers and distributors of iron-containing dietary supplements, appeals from a judgment entered on November 15, 2000 by the United States District Court for the Eastern District of New York (Johnson, J.). That judgment (1) denies NHA's motion for summary judgment seeking to enjoin enforcement of regulations promulgated in 1997 by defendant-appellee Food and Drug Administration ("FDA"), and (2) grants the

cannot be used to construe the 1938 and 1962 statutes contrary to their plain meanings.

In sum, the plain meaning of the Poison Act, the CPSC's construction of the Poison Act, and standard rules of construction all show that the Poison Act does not deprive the FDA of the authority it has under the plain language of the adulterated food and drug provisions to issue poison prevention packaging regulations. Therefore, the unit-dose packaging regulations are valid.

POINT III

UNIT-DOSE PACKAGING IS NOT A SPECIFIC PACKAGE DESIGN WHICH THE CPSC IS PROHIBITED FROM REQUIRING UNDER THE POISON ACT.

The Poison Act prohibits the CPSC from requiring any specific package design. 15 U.S.C. § 1472(d). NHA argues that unit-dose packaging is such a specific package design. Br. at 56. Even if NHA were correct in so arguing that fact would not assist NHA in this litigation. The unit-dose packaging regulations were promulgated by the FDA under the Food & Drug Act, not the Poison Act, and the Food & Drug Act contains no limitation which is analogous to 15 U.S.C. § 1472(d). In any event, NHA is wrong. Unit-dose packaging is not a specific package design.

FDA, in its rulemaking, made clear that it did not intend to require a specific type of unit-dose packaging design, such as "blister" packaging, because, based upon studies, "other types of

conventional unit-dose packaging provide a comparable length of time for children to open as that required by conventional blister packaging." 59 Fed. Reg. at 51049. As the FDA announced, "several types of packaging can satisfy the definition of 'unit-dose packaging', including blister-type packaging, pouches, and dispensers that deliver one dosage unit at a time ... [and] future advances in package design will result in other types of packaging that will also meet this definition." 62 Fed. Reg. at 2230. A blister pack and a single dose dispenser are clearly two very different designs even though both of these designs fall under the definition of unit-dose packaging.

NHA's reference in its brief, Br. 56, to the CPSC's regulations confirms, rather than refutes, that unit-dose packaging comes in different designs. The CPSC's statement quoted by NHA, to wit, "[t]hese designs include ... unit-dose strip and blister packaging", NHAP 140 (emphasis added), shows that strip and blister packaging constitute two different designs for unit-dose packaging. Indeed, at NHAP 215, the CPSC refers during a rulemaking in which it is announcing final regulations to a "type IVA foil [single-use] pouch with internal (hidden) tear notch" as one single use "package design," while referring to three other types of single-use packaging, to wit, another pouch type and two blister-types, as other single use "package design[s]." Thus, the CPSC construes unit-dose packaging as not constituting a specific design under 15

U.S.C. § 1472(d). Under Chevron and Brown & Williamson, this Court must defer to the CPSC's construction.

CONCLUSION

Basic rules of statutory construction support the decision below. The rule requiring that the Food & Drug Act must be construed liberally to protect the public health supports FDA's efforts to prevent serious injuries to and deaths of thousands of children under six. The district court's judgment should in all respects be affirmed.

Dated: Brooklyn, New York
June 5, 2001

Respectfully submitted,

ALAN VINEGRAD,
United States Attorney,
Eastern District of New York.

DEBORAH B. ZWANY,
CHARLES S. KLEINBERG,
Assistant United States Attorneys,
(Of Counsel).

cv1-99.wpd

KAM:CSK:ec
CV1-113.wpd

UNITED STATES COURT OF APPEALS
FOR THE SECOND CIRCUIT

- X

NUTRITIONAL HEALTH ALLIANCE,

Plaintiff-Appellant,

Docket No. 01-6011

- against -

FOOD AND DRUG ADMINISTRATION and DONNA SHALALA, in her official capacity as Secretary, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES,

Defendants-Appellees.

- X

STATEMENT PURSUANT TO FEDERAL RULE OF APPELLATE PROCEDURE 32(a)(7)(C)

This is to certify that this brief, exclusive of the table of contents, table of authorities, and this statement, uses a monospaced/proportional typeface and is 13,784 words long.

Dated: Brooklyn, New York
June 5, 2001

ALAN VINEGRAD
United States Attorney
Eastern District of New York
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By: _____
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HCPC
HEALTHCARE COMPLIANCE PACKAGING COUNCIL

FAX COVER SHEET

To: Todd Stevenson (Secretary)

Company: U.S Consumer Product Safety Commission

Fax #: 301/504/0127

Number of Pages Including Cover Sheet: 18

From: Peter G. Mayberry, Executive Director

Date: March 17, 2003

Message: Enclosed is a Petition to Alter Portions of the CR/SF Test Protocol

252 N. Washington Street, Suite A
Falls Church, Virginia 22046
Phone: 703/538-4030
Fax: 703/538-6305
E-Mail: pgmayberry@aol.com

HCPC
HEALTHCARE COMPLIANCE PACKAGING COUNCIL

FAX COVER SHEET

To: Stephen Lemberg

Company: U.S. Consumer Product Safety Commission (Office of the General Council)

Fax #: 301/504-0403

Number of Pages Including Cover Sheet: 13

From: Peter G. Mayberry, Executive Director

Date: May 5, 2003

Re: In response to your letter dated April 25, 2003.

Message: Please deliver to Mr. Lemberg A.S.A.P

252 N. Washington Street, Suite A
Falls Church, Virginia 22046
Phone: 703/538-4030
Fax: 703/538-6305
E-Mail: pgmayberry@aol.com

HCPC
HEALTHCARE COMPLIANCE PACKAGING COUNCIL

May 5, 2003

VIA FACSIMILE: 301/504-0403

Stephen Lemberg
Assistant General Counsel
Office of the General Counsel
U.S. Consumer Product Safety Commission
Washington, D.C. 20207

Dear Mr. Lemberg:

Thank you for your letter of April 25, 2003 asking for additional information on two issues raised by the Healthcare Compliance Packaging Council's petition of March 17. Specifically, you have asked for clarification on the following points:

1) "...the HCPC requests that the Commission eliminate the first criterion related to the toxicity of the substance to be packaged and allow a unit dose packaging failure to consist solely of a child gaining access to more than eight individual doses. Because such a change seems to decouple the definition of a child resistance test failure from consideration of the toxicity of a particular substance to be packaged it may not be allowable under the PPPA."

   On this point you further note that the HCPC's request for a numerical pass/fail criteria for unit dose formats could be precluded "...because of the apparent requirement of the PPPA that the Commission consider the toxicity of the specific substance at issue in establishing a special packaging requirement."

2) "The current CPSC regulation does not require a company to test, or preclude a company from relying on test data generated by the package manufacturer or from testing of similar packaging. Thus, the second change requested by the HCPC would seem to be unnecessary."

Following are the HCPC's detailed responses to the points raised in your letter of April 25, 2003:

252 N. Washington Street
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(P) 703/538-4030
(F) 703/538-6305
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www.unitdose.org

I. The PPPA, Toxicity, and 16 CFR 1700.20

With regard to toxicity issues, the PPPA requires CPSC to consider toxicity in determining whether a particular substance requires special packaging. But the PPPA does not require the subjective, zero-tolerance standard that 16 CFR 1700.20 applies solely to unit-dose packaging. The PPPA not only permits the action sought in HCPC's petition, but Congress specifically anticipated it. Indeed, Congress directed the Commission to set a standard that would make the packaging "...significantly difficult for children under five years of age to open or obtain a toxic or harmful amount of the substance contained therein within a reasonable time and not difficult for normal adults to use properly, ***but does not mean packaging which all such children cannot open or obtain a toxic or harmful amount within a reasonable time.***" (Emphasis added).

The implication that removing the subjective element of the test protocol for unit-dose packaging will somehow reduce the level of consumer safety is contradicted by the evidence – including CPSC's own data – outlined in HCPC's petition. To the contrary, removing the subjective element of the test protocol for unit dose closures will enhance consumer safety by making its more practicable for drug manufacturers to utilize this safer type of CR packaging.

Moreover, while it is clear that the PPPA grants CPSC authority to determine which household substances must be shipped from the manufacturer in special packaging, the Act does not specify that this determination be based on the *amount* of product that a child ingests. On the contrary, the only time the PPPA speaks to the issue of quantity is in Section 1472 (d) when Congress specified that:

> Nothing in this Act shall authorize the Commission to prescribe specific packaging designs, ***product content, package quantity***, or, with the exception of authority granted in section 1473(a)(2) of this title, labeling. (Emphasis added)

Indeed it is counter intuitive – and not in keeping with the legislative intent of the PPPA – to say that a unit dose format is not child resistant if children can gain access to a single unit (should that be the amount an individual manufacturer – not CPSC, not even another manufacturer of a product with the same active ingredient – determines to be capable of causing serious personal injury or serious illness to a small child), but then allow 30, 60, 90, 500, or 1,000 dosage units of the same product to be dispensed into households in a format that allows children instant access to the entire contents of the package should the CR cap not be properly replaced, or replaced at all, each and every time the product is accessed by an adult. It is simply incongruous for CPSC to maintain a subjective and discriminatory zero-tolerance standard for unit dose packaging, while allowing the exact same substances to be packaged in cap-and-vial closures, which CPSC knows through its own data allows children to access much greater quantities of the substances because the cap is often left off, or not properly replaced, by consumers.

Also, as noted in our petition, the provision that we have asked to be altered does not relate to toxicity *per se*. Rather, it places unique requirements on manufacturers who wish to use one type of packaging (unit formats) instead of another. Specifically, as outlined in our petition, we are seeking to change a provision contained under 16 CFR 1700.20 that uniquely requires manufacturers who wish to use unit formats to: 1) determine the number of individual units that "...may produce serious injury or serious illness," then 2) fortify the package to a point where children cannot open or gain access to this amount of product during protocol testing.

This "serious personal injury or serious illness" standard that applies solely to unit dose formats is far more vague, subjective, and stringent than the pass/fail standard which applies to other packaging formats, and ignores CPSC's responsibility under the PPPA to require special packaging *only* for substances which "the degree or nature of the hazard to children...by reason of its packaging, is such that special packaging is required to protect children from serious personal injury or serious illness result from handling, using, or ingesting such substance."

HCPC recognizes that the Commission cannot as a practical matter offer definitive guidance regarding the exact number of individual units that could be expected to cause serious personal injury or serious illness to a small child for each Rx, OTC-switched, and OTC drug product required to be shipped in special packaging. Yet, the current test protocol puts the onus on drug manufacturers to do so ***only when they elect to use unit dose formats.*** Because of product liability and other cost concerns, this system has led drug manufacturers to follow the path of least resistance – i.e., opting for less safe cap-and-vial closures.

Absent definitive guidance from CPSC, therefore, the objective pass/fail criteria requested by the HCPC's petition is warranted.

II. The Necessity/Benefits of Type Testing

In your letter of April 25, you questioned the necessity of the HCPC's petition request for type testing. Specifically, you noted that "The current CPSC regulation does not require a company to test, or preclude a company from relying on test data generated by the package manufacturer or from testing of similar packaging."

CPSC regulations do require that certain household substances – including virtually all Rx and OTC-switched drug products, as well as a number of OTC drug products – be packaged in formats that comply with 16 CFR 1700-1750, and the only way for a manufacturer to ensure that their packaging does comply is through protocol testing. This is especially true with unit formats due to the subjective pass/fail criteria contained under 16 CFR 1700.20.

Although CPSC regulations may not *require* protocol testing, CPSC certainly has the legal authority, and the enforcement capabilities, to ensure that non-complying packages are kept off the market.

Similarly, although CPSC regulations do not preclude a company from relying on test data generated by the packaging manufacturer is not reflective of standard industry practice, the practical reality is that the objective standard for cap-and-vial closures has led to a general acceptance of type testing for that type of CR packaging. Conversely, the subjective standard of 16 CFR 1700.20 makes it impractical for manufacturers to utilize type testing for unit-dose packaging.

This point was well articulated during a roundtable discussion published in the June 2001 edition of *Pharmaceutical & Medical Packaging News*[1] in which a panel of packaging professionals was asked whether they would rely on protocol test data from a vendor who had developed a unit-dose package format, put it through the CPSC protocol, and offered it for sale to drug manufacturers as being compliant with 16 CFR 1700-1750. In response to this scenario, the following answers were given:

> John Bitner (Manager of Packaging Design and Development, Pharmacia): "Vendor testing doesn't do us much good. We still have to test our packages. When a vendor comes to us with a child-resistant package that's passed with a given tablet, test protocol, and regimen, we still have to test it."
>
> Arthur Jaeger (Director of Packaging Development, Merck & Company, Inc.): "Supplier test results provide very useful information whenever we are developing new packages. However, the ultimate responsibility for ensuring package performance in the marketplace rests with the manufacturer."
>
> Bruce Cohen (Director, Packaging Technology, GlaxoSmithKline): "In some cases, we have found that even when using the same bottle with different closure suppliers and the same liners, we get different results [from those provided by the vendor]."

Clearly, these industry professionals would not allow their products to be released into the market without conducting a protocol test first, no matter what is actually required under current CPSC regulations. What the HCPC is asking for, therefore, is some means of ensuring that packaging which has successfully passed protocol not have to be re-tested. Perhaps this does not need a formal alteration of existing regulations. It may, in fact, be achieved through: 1) a policy statement from the Commission; 2) publication of a list of acceptable formats by the Commission; and/or 3) indication from the Commission that enforcement discretion will be exercised if packaging is used that has successfully passed CPSC's protocol.

---

[1] Copy attached

Please also note that the primary purpose of the HCPC's petition request for type testing is to minimize the number of small children who are subjected to protocol testing annually. To the HCPC, this goal alone makes our request necessary – especially considering that thousands of children are subjected to protocol testing each year, often to evaluate packages with CR features that have been on the market for decades.

It is my hope that this is a thorough and adequate response to the issues you raised in your letter. Please feel free to contact me should you have any questions or need additional information.

Thank you.

Sincerely,

Peter G. Mayberry
Executive Director

Enclosure

How important is child-resistant packaging to you when you select packaging materials?

Cohen: Certainly for solid-dose formulations, child-resistant packaging is part of the decision. It really depends upon the toxicity level of the product and how the package is going to be presented to the marketplace. If the product is going to be a unit of dispense, then we have to take into consideration everything that's required for child resistance for that particular drug. If it has optional pack or line extensions that make it a pharmacy dispensing pack, then child resistance falls away at that point.

Is child-resistant packaging an issue that first comes up in clinical trials?

Cohen: When we get into the end of Phase II and the beginning of Phase III clinicals, we want to narrow down the packs that marketing has in mind for the product. We try to use the final marketed pack for Phase III, if it's a package that we can get at that point. If not, child-resistant packaging probably wouldn't show up until the launch.

Bitner: We try to get materials into ICH stability testing that we perceive will be useful for child-resistant packaging, even though we have additional development time beyond ICH.

Vega Feliciano: One of the things we consider is cost. We need to be very aware of cost in the over-the-counter (OTC) market because our margins are smaller.

Mayberry: When a product goes from prescription to OTC status, it doesn't necessarily have to be packaged in a child-resistant format. CPSC evaluates each of those drugs case by case. But last year CPSC proposed a rule that would automatically require a child-resistant format for what it refers to as OTC-switched drugs. It accepted public comment on that proposal through November, and now it's deciding what to do based on those comments.

Did anyone here file any comments with the CPSC?

Mayberry: HCPC and the Consumer Healthcare Products Association both did. There were two other comments as well—one from a group of students in Florida and another comment from a private citizen.

Does anyone else here have any reaction to that CPSC proposal?

Cohen: The proposal would put more pressure on both the manufacturers of the components as well as the manufacturers of the drug to reduce costs as products move to OTC status.

special

"What we are trying to accomplish with the child-resistant package is to make it as intuitive as possible. And it's hard to make a blister intuitive at a high toxicity level."

John Bitner
manager of package design and development, Pharmacia (Skokie, IL)

Would it delay OTC product launches?

Jaeger: If products will be packaged in bottles, the proposal is probably not a big deal. However, if you start going into flexibles, you've got other issues: what the toxicity levels are, what the opening features look like, which patients will use the package, and how difficult will the package be to open.

What packages are best at meeting child-resistance requirements?

Bitner: It depends upon the toxicity of the product, the market we're aiming for, and the regimen of the medication. If you're looking at a regimen of three tablets a day, for instance, for a chronic condition, then it's going to be very difficult to get that product into a blister. It would be much better off in a bottle.

Mayberry: There's a quirk in the regulation regarding toxicity and blisters. Under the protocol, if you're using a bottle, it's a failure if the child gets the top off, regardless of the quantity. There could be 100 tablets in the bottle. When you use unit-dose packaging, such as a blister, there is an eight-pill standard, so if during the test children open or gain access to eight tablets in the blister or to an amount that would cause serious illness or serious injury, then that's considered a failure. But CPSC doesn't define what the serious illness or serious injury is, so it's up to the manufacturers to determine the toxicity level. Such a consideration needs to be made for blisters but not for bottles.

Vega Feliciano: I don't think that it's a matter of liking one better than the other, it's a matter of what is best for your product. Some products are more suitable for blisters; some products are more suitable for bottles. There are even some products that will require a pouch because of some specific characteristic.

Jaeger: Most market research shows that, given the choice, a lot of patients seem to prefer bottles—not because they're better or worse, but because they understand them. They've seen push-and-turn caps for so long that they can use them without thinking. However, the bottle is not always appropriate.

Lang: It also depends upon what market you're trying to get into, like OTC decongestants. Everything on the shelf is in blisters.

Bitner: What we're trying to accomplish with the child-resistant package is to make it as intuitive as possible. And it's hard to make a blister intuitive at a high toxicity level. When a failure means that children can access just one tablet, a blister becomes a very difficult package to present, especially to arthritis patients or the elderly.

Cohen: On occasion we've sized the blister with the toxicity level in mind to include as few tablets as possible but still meet patient requirements. For instance, we have one product that has three tablets in a blister pack and that is the sale item. That particular regimen of three might serve a patient for a day and a half or two days, depending on their needs. But because of the toxicity levels, if a child were to get into all three, it wouldn't be harmed.

Jaeger: The access level permitted for an individual product being packaged makes a big difference. If a product has a high allowable access level, you've got a lot more options. You can go with something that's child resistant but not nearly as unfriendly to a lot of patients, especially elderly patients.

Cohen: There's a popular pack out on the market for an antibiotic that marketing wants us to use. But that particular product's toxicity level is nowhere near what's presented in the package, so therefore the package is not child resistant. It's a nice blister pack, and everybody talks about it, but we can't necessarily put every product in it because of the higher toxicity levels.

"Let's be more aggressive about teaching people how to properly use a child-resistant package. We need to teach the consumer that no package is 100% safe."

Rafael Vega Feliciano
senior package engineer, Wyeth-Ayerst Pharmaceuticals, packaging services group (Philadelphia)

special

"When comparing blisters to bottles, it is evident that children access more units when circumventing a child-resistant closure on a bottle."

Peter Mayberry
executive director, Healthcare Compliance Packaging Council (Falls Church, VA)

Mayberry: In the United Kingdom, there's effort to establish a child-resistant packaging standard for nonreclosable packaging. The draft standard was similar to the U.S. standard, and they got more than 300 complaint letters. An overwhelming majority of the complaints focused on the issue of determining toxicity. Based on that, the United Kingdom is leaning more toward a numerical amount rather than an amount determined by toxicity testing.

Cohen: But what if five is your toxicity limit? Then manufacturers are not going to use a blister with a count of eight unless they're looking for trouble.

Mayberry: There are products that are highly toxic, so you need to put them in a count of one, two, or three pills. Then there are others where a package of 30 is not likely going to cause a problem. But the vast majority is in a gray area.

Cohen: At some point, we need to have some standard test, like an ASTM method. We could put blisters through it to ensure that they meet a minimum requirement and are therefore deemed child resistant, rather than spend all the time and effort that all of us do in looking at a group of children who varies by location and ability. If you go to one test lab, test your pack, and get a failure, and then you go to a second test lab, test the same pack, and get a pass, where does that lead you? To a third test somewhere else to try to get another pass. What makes one better than the other? They're very subjective. We need some type of reproducible, mechanical, electronic, standard test.

Mayberry: John and I are both on the ASTM subcommittee D10.31 regarding child-resistant packaging, and just earlier this month at a meeting in Phoenix, it was apparent that ASTM doesn't want to look at specific aspects of the child-resistant packaging testing protocol because ASTM members doubt that CPSC will change it.

Bitner: We've got a protocol that's worked for 30 years. We've cut the number of pharmaceutical-related deaths dramatically to one to two per year.

Mayberry: Yes, but there are data that show there are still thousands of poisonings every year supposedly involving child-resistant closures for bottles or vials. There have been more than 5 million calls to poison prevention centers over the past 17 years involving children 6 years old and younger who ingested prescription or OTC drugs, as documented by the American Association of Poison Control Centers.

Bitner: Those calls may be more prevalent because of education. Patients know that some of these medications can be poisonous and they know who to call now. There are also more poison prevention centers in the country.

Mayberry: We asked CPSC for all its data from 1983 through October of 2000 regarding accidental exposures to prescription drugs or OTC drug products by children 6 years old or younger. What we got back were reams of data. There were hundreds of instances where children were sent to the hospital because they supposedly got these products out of child-resistant bottles, and there were 365 deaths over that period of time. Yet, there were 33 documented cases involving blisters in which children accessed drugs, and of those there were only two—two in 17 years—where child-resistant blisters were involved.

Bitner: Or documented to be involved.

Mayberry: But when comparing blisters to bottles, it is evident that children access more units when circumventing a child-resistant closure. There were 11 instances where children gained access to between 41 and 50 tabs. There are 5 instances where children gained access to between 61 and 75 tabs.

Jaeger: Today there are more once-a-day products with higher concentrations and higher potencies. So there are a lot of products where accessing just one or two tablets may be a problem.

How do you feel about child-resistant blisters currently on the market?

Cohen: It depends upon your toxicity level and what your marketing folks want. We use peel-and-push blisters for most of our child-resistant blister packages. We've had to put some of our blisters into a chipboard card in order to increase the complexity and reduce the number of child openings.

Bitner: Most are extremely difficult for a senior or a debilitated patient to operate. But if you make them too easy, children are just going to rip them apart, easily accessing the medication.

Jaeger: There aren't all that many different types of child-resistant packaging materials to choose from. I'm not talking about suppliers. If it's a blister material, one side needs to be backed with polyester. If it's a pouch, you need

an adequate thickness of polyester on the outside, and the rest depends on die-cutting configuration, graphics, and opening instructions.

Bitner: You bring up a good point regarding the number of vendors. There aren't that many vendors out there with the capability, the intelligence, the resources, the mentality, and the interest to develop programs for us.

Mayberry: Some vendors have gone to the trouble of designing a more intuitive package and putting it through the child-resistant testing protocol themselves to ensure that it'll pass the protocol. They then make it available for licensing, and then no one picks it up. Fortunately, there is one intuitive package that requires cognitive ability over physical strength that has passed the protocol and won HCPC's Compliance Package of the Year Award for 2000.

"We need a standard test, like an ASTM method, that we could put blisters through to ensure that they meet a minimum requirement and can be deemed child resistant."

D. Bruce Cohen
director, packaging technology, GlaxoSmithKline (Research Triangle Park, N.C.)

Bitner: Vendor testing doesn't do us much good. We still have to test our packages. When a vendor comes to us with a child-resistant package that's passed with a given tablet, test protocol, and regimen, we still have to test it.

Jaeger: Supplier test results provide very useful information whenever we are developing new packages. However, the ultimate responsibility for ensuring package performance in the marketplace rests with the manufacturer.

Cohen: In some cases, we have found that even when using the same bottle with different closure suppliers and the same liner, we get different results.

Bitner: As end-users, we know what

special

"Protocol testing certainly meets the regulation, but it does not always give you all the information you need to ensure your package will be well received in the marketplace."

Arthur Jaeger
director of packaging development, Merck & Company, Inc. (West Point, PA)

we want to accomplish, but the vendor still has the greatest converting technology and the understanding of how those materials react, as well as firsthand knowledge of new developments.

Do you need more vendor support?

Bitner: Once we have a concept and engineering designs, we'll do the testing—it's our market, it's our protocol, it's our focus group. But we need more experts to show how to convert materials and how to make our concepts reality.

What are you doing to meet the needs of patients who suffer from conditions that make it difficult to open complex packages?

Bitner: At Pharmacia, we consult a panel of what we call patient partners, who are patients suffering from arthritis. Most are registered with the Arthritis Foundation and doctors, so half a dozen of them can represent hundreds of patients across the country. We run different designs by them and design packages according to their feedback. Before we go to protocol testing, we do some screening and some preliminary tests with 70- to 80-year-old people and patients with arthritis.

Jaeger: More than just CPSC protocol testing is needed. Protocol testing certainly meets the regulation, but it does not always give you the information you need to ensure your package will be well received in the marketplace.

Bitner: If a vendor comes to us and says it passed the CPSC protocol, that's not all that is necessary. We can pass the protocol with any number of different packages. But that doesn't necessarily mean that a patient or consumer is going to use that package in the home.

Lang: You also need to put clear, concise instructions regarding opening features on the package in short bullet points so seniors know how to open it.

Are you leery of using a blister?

Mayberry: Manufacturers don't want to market products that aren't going to be popularly received, and a blister is likely going to be more difficult to open than a bottle, unless tremendous forethought is given to its design.

How do you properly balance child resistance with senior friendliness?

Mayberry: CPSC's response is you need better packages. John mentioned earlier that you can engineer packaging that does not rely on strength as much as on cognitive ability.

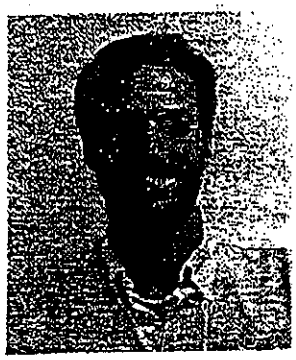
Jaeger: I've heard some companies say they've resorted to instructing patients to use scissors to open packages. But you shouldn't need a tool to open the package.

Cohen: We have several packs on the market that require scissors to open, and I have no complaints that I'm aware of, as opposed to the blister packs we have that frustrate seniors.

Mayberry: Are the scissors-only packages pouches?

Cohen: A couple of them are. One pouch features a tear notch that is an open, unsealed circle within the package that you have to fold over.

Bitner: Scissors are brutal to an arthritis patient, and you certainly don't want a hemophiliac patient using scissors. We have a fantastically successful pouch that has wider heat-seal areas with big, fold-over areas where the notch is positioned on the crease so you can't miss it. A target and arrows point the child to an area that is laser scored and cut. Ninety-nine percent of the kids went right for that score and tore the opening feature off in the first five seconds of the test, disarming the package. Trying to do that same thing with a blister is more challenging.



"You need to put clear, concise opening instructions regarding opening features on the package in short bullet points so seniors know how to open it."

Ken Lang
engineering, strategic improvement department, OTC drugs, Bristol Myers Squibb (Mt. Vernon, IN)

Are there any innovations that you think should become standard, like using squeeze-and-turn closures instead of push-and-turn ones?

Bitner: Squeeze-and-turn designs are one of the most discouraging developments in the last 30 years. They are not senior friendly. Arthritis patients have a lot of trouble with that type of motion.

Cohen: We've looked into squeeze-and-turn closures for a number of reasons, including the fact that they eliminate the torque requirements for opening. They also represent a reduction in price, and there are fewer components that will end up in the trash. But as John said, people who have difficulty squeezing because of limitations in their hands or wrists find that they can open the push-and-turn closures with the palm of their hand and the top of a table. There is a new proposed cap with a one-piece, push-and-turn mechanism that may be a better compromise—it requires the same force and the same procedure that most people are used to, but it is a little less strenuous.

Mayberry: For the first five years of HCPC's existence, I never heard about anything novel with blisters—it was all peel-and-push or notch-and-tear. But over the past five years, there has been an attempt to design better blisters both child resistant and senior friendly.

What else could make your job easier?

Bitner: We need a more formal universal program of national education about poisons. Poisonings occur because of ignorance. FDA responded in a surprising and disappointing way to iron tablets, mandating for the first time in history that iron tablets above a certain level have to be in blisters because they're dangerous to children. This was based on a false assumption that blisters are inherently child resistant. If all parties concerned had made it better known that iron can present a poisonous situation, iron wouldn't have been left out for children to get into.

Mayberry: The protocol gives consumers a false sense of security. In the data that we got from CPSC there were seven instances in which children were given drug products in a bottle with a child-resistant closure as a rattle or toy because an adult believed that it was childproof.

Vega Feliciano: CPSC could do a better job educating people on how to use the package and why it's important to put it away even though it's considered child resistant. Let's be aggressive about teaching people to properly use a child-resistant package. We need to teach the consumer that no package is 100% safe.