

**TAB B**



UNITED STATES  
CONSUMER PRODUCT SAFETY COMMISSION  
WASHINGTON, DC 20207

Memorandum

Date: August 2, 2004

TO : Suzanne P. Barone, Ph. D.  
Project Manager, Petition PP 03-1

THROUGH: Susan W. Ahmed, Ph. D. *SW*  
Associate Executive Director  
Directorate of Epidemiology

Russell H. Roegner, Ph. D., Director *RHR*  
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FROM : Michael A. Greene, Ph. D. *MAG*  
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Division of Hazard Analysis

SUBJECT : Accidental Poisoning in Unit Dose and Bottle Formats: Data and Analyses  
related to petition PP 03-1

Attached is an analysis of the data and conclusions in the subject petition.

**Accidental Poisoning in Unit Dose and Bottle Formats:  
Data and Analyses Related to Petition PP 03-1**

**Michael A. Greene, Ph. D.  
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The present regulation defines test failure as more than 8 units or “the number of individual units which constitute the amount that may produce serious personal injury or serious illness...whichever number is lower...”<sup>1</sup> The petition<sup>2</sup> recommends changing the definition of test failure in the child-resistance test for unit dose packages to delete the toxicity requirement (“... the amount that may produce serious personal injury or serious illness...”). The petition argues that the toxicity requirement deters manufacturers of drug products from using unit dose packages. Removing this requirement from the regulation will, according to the petition, provide an incentive for manufacturers to switch products from cap and vial (i.e., bottle) formats to unit dose formats. This is claimed to have the potential to reduce deaths and injuries from accidental poisonings because, according to the petition, unit dose format is “inherently safer” than bottles.

The petition presents several analyses of data in support of the claim that unit dose packaging is safer than bottles.<sup>3</sup> Staff of the Directorate for Epidemiology has reviewed the analyses presented in the petition. From this and other analyses described in this document, we have drawn the following conclusions:

1. Most of the data and analyses in the petition comparing deaths, injuries and serious incidents in bottles and unit dose formats do not demonstrate that unit dose packaging is safer than bottles. The data show fewer such adverse events in unit dose packaging, but this could also have resulted from the smaller number of unit dose drug products on the market.
2. One exception, the data for iron poisoning, provides some limited support to the argument that unit dose format for iron at the present level of child-resistance may be safer than bottles. In a regulation effective in July 1997, the Food and Drug Administration required (a) all compounds containing 30 mg or more of elemental iron per dosage unit to be packaged in unit dose format and (b) a new warning message to be placed on bottles and unit dose packages containing iron tablets or capsules. The data shows that iron poisoning fatalities and injuries had begun to decrease several years before enactment of this regulation and continued decreasing afterwards. Other factors besides the shift to unit dose packaging might have played a role in these decreases. Such factors include the warning, the

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<sup>1</sup> See 16 CFR § 1700.20.

<sup>2</sup> Letter from Peter G. Mayberry, Executive Director, Healthcare Compliance Packaging Council to Todd Stevenson, Secretary, U. S. Consumer Product Safety Commission 3/17/03. Hereafter, “Petition.”

<sup>3</sup> The term “bottle” or “bottles” will be used here as a synonym for cap and vial reclosable packaging.

reduction of dosage units to less than 30 mg to avoid the unit dose packaging requirement and the increased awareness about the danger of iron poisoning in young children.

3. Even if other factors could be ruled out, there is no evidence to suggest that these same decreases would have occurred if the toxicity requirement had been eliminated, as requested in the petition and iron tablets had been in less protective unit-dose packages. There is also no evidence to suggest that similar decreases would be observed with other drug products.
4. By eliminating the toxicity requirement in the definition of a test failure, as is requested in the petition, unit dose packages could be allowed on the market that would be less protective than current unit dose packaging. There is no way to estimate how many, if any, existing unit dose package designs would be so revised, nor is there any way to estimate how many drug products would switch from bottle to unit dose formats. As a result, the only certainty from eliminating the toxicity requirement is lesser protection in unit dose formats for drugs where the toxicity requirement defines test failure at less than eight individual units. If children are able to access a larger number of doses, then it is possible that deaths and injuries from accidental poisonings in unit dose format could increase.

The purpose of this document is to examine the evidence in the petition and other available evidence related to the safety of unit dose and bottles formats. The next section describes an experiment showing that child-resistant features of unit dose packages make a difference in preventing access to drug products as compared with non-child-resistant unit packages. The following sections discuss the analyses of accidental poisonings data that are found in the petition.

### **Experimental Evidence about Child-resistance Features in Unit Dose Packages**

Several years ago, CPSC staff conducted a laboratory experiment that showed that the number of unit doses children could access depended on how the doses were packaged. Staff compared the number of packages children opened in three different unit dose formats in a laboratory during a 10 minute test period. The results were as follows:

- For non-child-resistant unit dose pouch packaging, children were able to open an average of 20 pouches (maximum 54 pouches opened).<sup>4</sup>
- For non-child-resistant blister packaging, children opened an average of 23 blisters (maximum 85).
- With child-resistant (CR) blister packaging, children opened an average of 3 blisters (maximum 8).

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<sup>4</sup> The term "non-child-resistant" used in this document describes unit dose packaging that has not specifically been subject to the child-resistance test protocol of the regulation.

In addition, on average it took children almost twice as much time to open the CR blister package than the conventional blister package. This is an indication of safety for the CR packages because the longer it takes to open a package, the more time available for adult intervention.

The staff report concluded that "...various designs of unit packaging provide substantially different resistance to child access...."<sup>5</sup>

This experimental evidence suggests that child-resistance of unit dose packaging plays a role in the number of doses accessed. But it does not fully explain if unit dose packaging (child-resistant or not) is safer than bottles (also child-resistant or not). Access to the actual dosage is only one of the events in an accidental poisoning. Other factors include safe storage and adult supervision. In particular, there is evidence that a substantial proportion of child poisonings involved packages that had been left open at the time of ingestion.<sup>6</sup> Only data on adverse events including injuries and deaths from accidental poisoning can shed any light on whether one format is inherently safer than another.

### Three Comparative Analyses of Data Included in the Petition

In brief, the analyses comparing unit dose and bottle formats in the petition are as follows:

1. According to CPSC Incident Report data, from 1983 through 2003, 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 6.8 percent involved CR unit dose formats.<sup>7</sup>
2. CPSC Incident Report data recorded 47 fatalities from 1983 through 2003 in which children age 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 of a fatality in the United States after a child removed a drug product from a unit dose package.<sup>8</sup>
3. Between November 5, 2000 and January 14, 2003, 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. During the

<sup>5</sup>Wilbur CJ and Barone S (1998), "Is Unit Dose Packaging Inherently Child-Resistant?" U. S. Consumer Product Safety Commission, Bethesda, MD.

<sup>6</sup>Rogers GB (1996), "The Safety Effects of Child-Resistant Packaging for Oral Prescription Drugs: Two Decades of Experience." *JAMA* 275-21, 1661-1665.

<sup>7</sup>Petition, page 3.

<sup>8</sup>Petition, pages 3-4. The other cases were either non CR or the child-resistance status of the packaging was unknown.

same time period, the maximum number of units ingested was five from packages in unit dose formats and in 17 of the 31 reported incidents one unit or a portion of a single unit was ingested.<sup>9</sup>

The staff analysis produced similar but not identical numbers to those shown above. We believe that the numbers presented in the petition are plausible.<sup>10</sup>

However, none of these analyses in the petition account for other factors that might have produced the differences in incidents between bottles and unit dose packages. The central problem is that there were more drug products distributed in bottles than unit dose over the time period of the comparison. Thus, the greater frequency of incidents and fatalities and the greater number of large dose ingestions could be explained by the larger number of drug products in bottle format. Even if we could control for the different number of drug products in each format, it would also be necessary to adjust for possible differences in toxicity of the drugs in each format. Differences in toxicity could also account for the difference in the number of incidents. Everything else held constant, more toxic drugs should be expected to have more adverse events than less toxic drugs.

As a result of these competing explanations, none of the analyses in the petition can be used to support the proposition that unit dose packaging is inherently safer than cap and vial format.

## Iron Poisonings

### *Background*

In 1992 and 1993, there were five deaths of children 11-18 months old in the Los Angeles area from ingestion of iron. In four of the five cases, prenatal vitamins with elemental iron content of 60 mg per tablet were identified as the toxic agent. The vitamins were in child-resistant packages (i.e., bottles) and had warning labels. In the fifth death, no package was available to determine the strength of the tablets. In four of the five cases, children consumed at least 30 tablets containing iron. In the fifth case, the number of tablets was not known.<sup>11</sup>

According to *Morbidity and Mortality Weekly Report*, for iron poisoning, a fatal dose is typically more than 250 mg/kg but doses as low as 60 mg/kg have resulted in deaths. *MMWR* also issued a number of recommendations to help prevent deaths including (1) iron should be prescribed in limited amounts and dosages, (2) health care

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<sup>9</sup> Petition, page 4.

<sup>10</sup> To get the same numbers as the analysis in the petition, it is necessary to make the same interpretations of the data. This includes identifying and removing duplicate cases, making assumptions about cases where the dose may appear to have been removed from the original packaging before the child accessed the dose by someone other than the child victim, deciding whether to include liquid drug products in the comparisons and many other issues involving the judgment of the analyst.

<sup>11</sup> *Mortality and Morbidity Weekly* (1993), 42(06) 111-113. February 19, 1993.

providers and others dispensing iron should emphasize the hazard of unintentional consumption by children and (3) adults should be instructed in the proper use of child-resistant packages when they receive them. They also suggested the use of child-resistant individual blister packages and making the tablets less appealing to children by eliminating the use of sugar coating and attractive colors.<sup>12</sup>

On January 20, 1993, the Los Angeles County Department of Health Services issued a warning through the local media to parents and medical practitioners about the potential dangers of iron overdose.<sup>13</sup>

In a regulation effective July 15, 1997, the Food and Drug Administration required all products containing dosage units of 30 milligrams or more of elemental iron to be packaged in unit dose format.<sup>14</sup> Iron is found in food supplements and vitamin capsules in dosages that range from a few milligrams to 65 mg.<sup>15</sup> According to the National Academy of Sciences, only pregnant women require 30 mg of iron per day.<sup>16</sup> Thus, the regulation provided manufacturers with the alternatives to use either unit dose format or to keep the drug products in bottles but to reduce the dosage unit below 30 mg.

The 1997 FDA regulation also required warning statements on these products. The new warning statement was as follows:

**WARNING:** Accidental overdose of iron-containing products is a leading cause of fatal poisoning in children under 6. Keep this product out of reach of children. In case of accidental overdose, call a doctor or poison control center immediately.<sup>17</sup>

Once in unit dose format, these products were subject to provisions of CPSC's Poison Prevention Packaging Act requiring all packages containing at least 250 mg of elemental iron to be child-resistant.<sup>18</sup> For unit dose packaging, a test failure is defined as a child opening a number of doses equivalent to at least 250 mg or opening more than 8 dosage units, whichever is less. For example

- If each dose contains 65 mg of iron, then a test failure is 4 or more doses opened.

<sup>12</sup> *Ibid.*, page 113.

<sup>13</sup> *Loc cit.*

<sup>14</sup> Department of Health and Human Services, Food and Drug Administration, *Federal Register*, 62, No 10, January 15, 1997, pages 2218-2250.

<sup>15</sup> In an informal survey of prenatal vitamins in on-line drug stores in July 2004, we found a number of bottles labeled as "prenatal" and containing doses between 6 and 28 mg. The number of daily recommended doses varied between 1 and 6 generally bringing the total recommended intake in most cases to between 20 and 30 mg per day. We also found iron supplements in unit dose format containing individual doses of 50-60 mg.

<sup>16</sup> *Federal Register*, *op cit.*, page 2242.

<sup>17</sup> *ibid.*, page 2250. An earlier draft of the warning was released on 10/5/94. See "FDA Proposes Safety Measures to Prevent Childhood Iron Poisoning," Press Release ([www.fda.gov/bbs/topics/NEWS/NEW00495.html](http://www.fda.gov/bbs/topics/NEWS/NEW00495.html))

<sup>18</sup> 16 CFR § 1700.14 (a) (12) and (13). Both the CPSC and FDA requirements deal with the quantity of elemental iron.

- If each dose contains 30 mg or less of iron, then a test failure is more than 8 doses.

For bottle formats, opening the bottle is a test failure.

The FDA proposed the unit dose packaging requirements to reduce the number of acute iron poisonings and deaths in children under 6 years of age. The rule followed petitions submitted by various groups and over 100 responses commenting on the original proposal.<sup>19</sup> The FDA estimated that unit dose packaging would reduce deaths by an average of 4.9 per year.<sup>20</sup>

On October 17, 2003, following the decision in *Nutritional Health Alliance v. FDA*,<sup>21</sup> the FDA withdrew the parts of the 1997 rule requiring unit dose packaging for products containing iron.<sup>22</sup> This decision meant that iron in doses of 30 mg or more could be packaged in bottles. These bottles would need to be child-resistant because the *Nutritional Health Alliance* decision did not have any impact on CPSC's regulation. The FDA regulation regarding the warning label was not withdrawn and continues to remain in effect.

#### *Changes in Iron Poisoning Deaths and Injuries*

In the petition submitted to CPSC, comparisons were made between the number of deaths and injuries before the 1997 FDA regulation and following its enactment. Most importantly, this comparison gets around the central problem with the other comparisons in the petition, which was that there may have been far more adverse events with bottles than unit dose merely because there were more drug products packaged in bottles. With iron compounds, as long as there were no substantial changes in the amount sold before and after enactment of the FDA regulation, the comparison of the number of adverse events before and after the regulation should be attributable to the regulation.

According to the petition

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...<sup>23</sup>

Staff conducted a similar analysis, essentially finding the same information. The staff analysis in this section went into some greater depth, also comparing injuries as well. Deaths are presented first, injuries are presented next, and finally some implications of the data are discussed.

<sup>19</sup> *Federal Register*, *op. cit.*, page 2218.

<sup>20</sup> *Ibid.*, page 2243.

<sup>21</sup> 318 F.3d 92 (2d Cir. 2003))

<sup>22</sup> *Federal Register*. October 17, 2003.

<sup>23</sup> Petition, page 4.

### Iron Poisoning Deaths

Deaths from iron poisoning for children 0-4 years old are shown in figure 1 below.

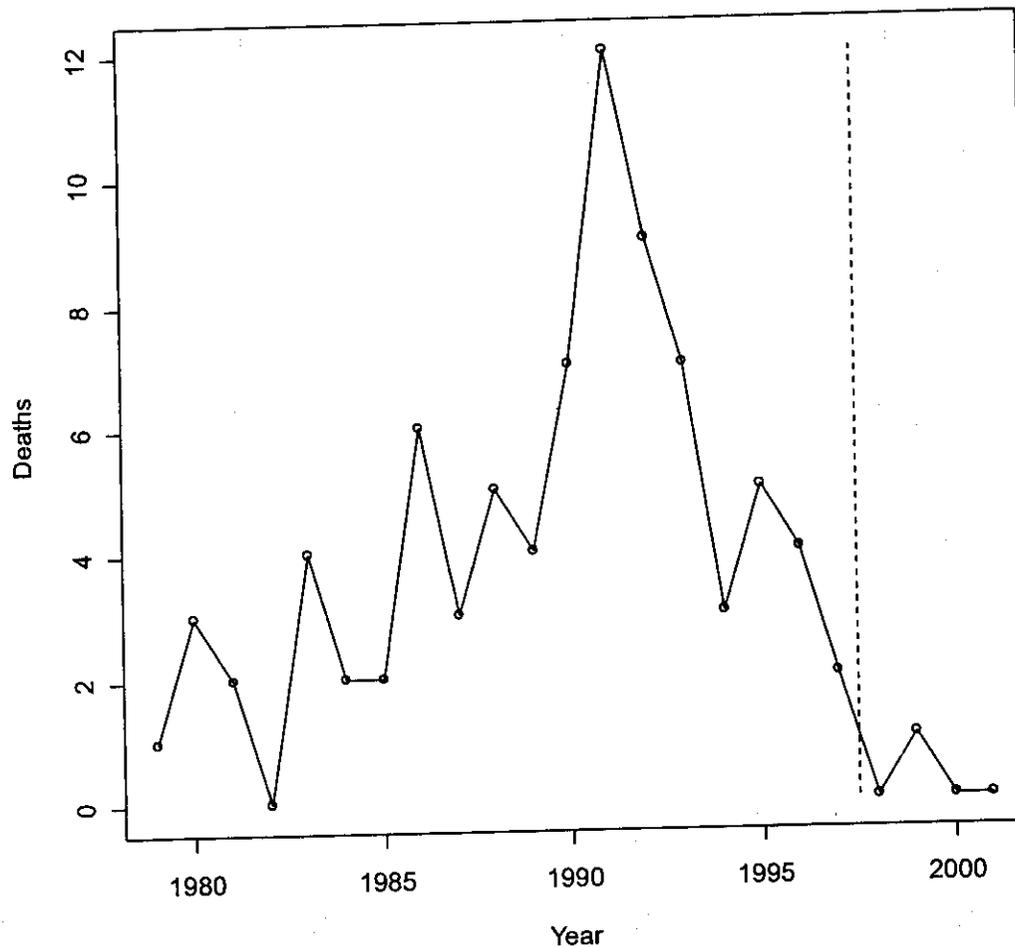


Figure 1. Iron Poisoning Deaths 1979-2001

The solid line in figure 1 uses data from the web site of the Centers for Disease Control and Prevention ([www.cdc.gov](http://www.cdc.gov)) for 1979-2001 (the latest available). For the period from 1979 to 1998, we selected on the E-Code (external cause of death) 858.2, defined as "Accidental Poisoning from Blood Constituent Agents." This code also includes the anti-coagulant warfarin sodium as a blood constituent agent, however, it is believed that in

young children most of these fatalities in this E-Code are iron poisoning related.<sup>24</sup> In 1999, the system for coding the cause of death was revised. Data from 1999 and later uses the code T45.4 which only includes iron compounds.<sup>25</sup> The vertical dashed line marks mid-year 1997 when the FDA regulation took effect. The data are for children age 0-4 years, rather than 0-6 as found in the petition because the child-resistance test is conducted with children up to 51 months.

Figure 1 shows that between 1979 and 1991 deaths rose from 1-3 annually to a peak of 12. Between 1994 and 1996 deaths varied between 3 and 5, declining to 2 in 1997 and to one between 1998 and 2001.

### *Emergency Department Treated Injuries*

Staff also obtained similar findings for emergency department treated injuries for iron poisoning. Data from the Children and Poisoning System (CAP), a subset of the National Electronic Injury Surveillance System (NEISS) are shown below in figure 2.<sup>26</sup> Between 1994 and 1997 there were between 2,105 and 3,127 estimated emergency department visits associated with iron poisoning, averaging 2,565 annually. Between 1998 and 2003, the annual average dropped to 946. Like the deaths in figure 1, emergency department treated injuries in the mid 1990's were trending downward. The largest decrease in injuries occurred in 1998, the first complete year under the new FDA regulation on iron, where the number of injuries dropped from the previous year's total of 2,105 to 704.

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<sup>24</sup> See Morris, CC (2000), "Pediatric Iron Poisonings in the United States," *Southern Medical Journal*, 93,4, 352-358 for the explanation about warfarin sodium.

<sup>25</sup> The CDC data shows the 1999 death with the code X44, defined as "Accidental poisoning by and exposure to other and unspecified drugs, medicaments and biological substances." The death certificate lists the immediate cause of death as "Complications of Acute Iron Intoxication."

<sup>26</sup> Data were adjusted for the change in sample frame in 1997. Sample weights were taken from the NEISS system.

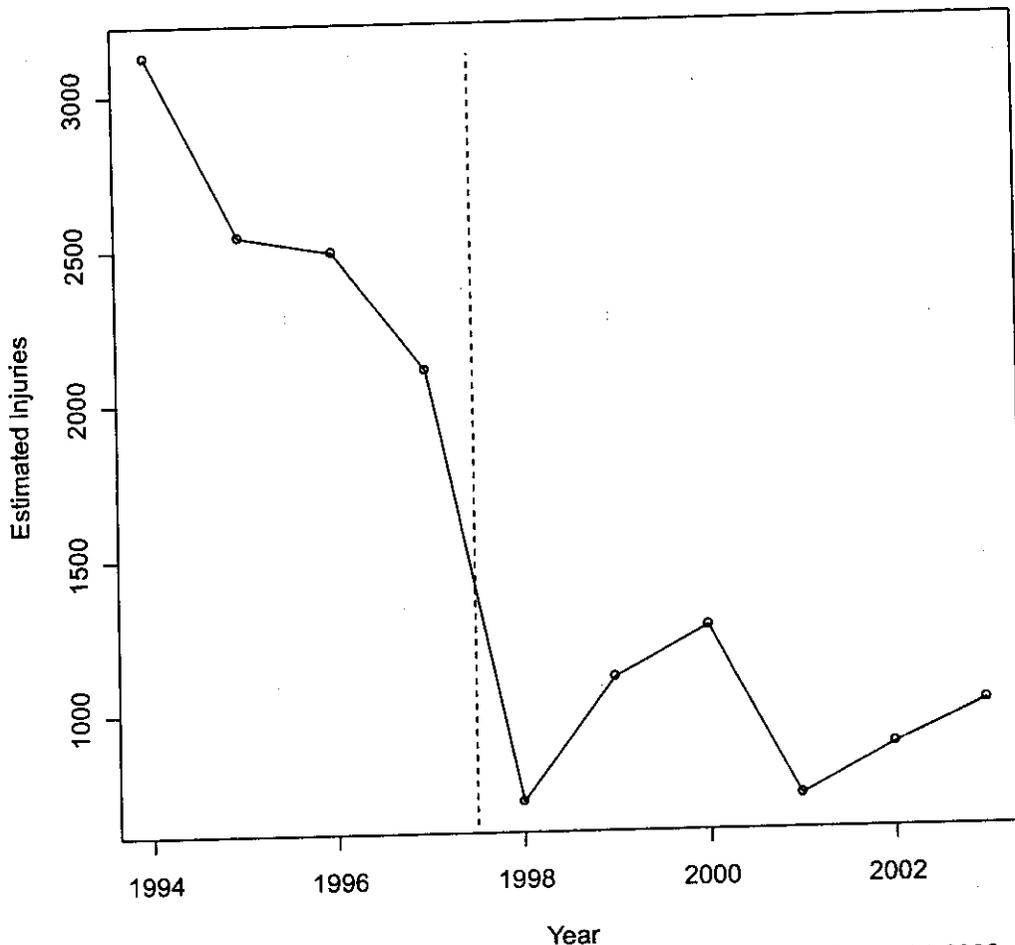


Figure 2. Emergency Department Treated Iron Poisoning Injuries 1994-2003

Why did both deaths and injuries decline from the mid '90s on? One explanation that we can rule out was that *all* emergency department visits for accidental poisonings for children 0-4 years old were declining and iron poisoning was just following that trend. To examine this issue, table 1 compares emergency department visits for iron poisonings with emergency department visits for poisoning from all drug products. Table 1 shows that while emergency department visits for poisonings from all drugs decreased in 1998-2003 from 1994-1997 levels, iron related poisonings dropped faster. In 1994-1997, iron related-poisonings accounted for an average of 6.5% of the poisonings, while in 1998-2003 iron accounted for 2.8% of the poisonings. On average, iron poisonings-related visits dropped by 63% while visits for accidental poisonings from all drugs decreased by 14%.

Table 1  
 Estimated Emergency Department Treated Injuries for Children 0-4 Years Old  
 Associated with Iron Preparations or Other Drugs 1994-2003

| Year              | Estimated<br>Poisoning Injuries<br>from Iron<br>Preparations | Estimated<br>Poisoning from<br>All Drugs | Percent of Total<br>Poisonings from<br>Iron Preparations |
|-------------------|--|--|--|
| 1998-2003 Average | 946  | 33,963                                   | 2.8%   |
| 2003              | 1,009  | 37,850                                   | 2.7%   |
| 2002              | 877  | 38,728                                   | 2.3%   |
| 2001              | 715  | 31,974                                   | 2.2%   |
| 2000              | 1,263  | 31,576                                   | 4.0%   |
| 1999              | 1,106  | 31,455                                   | 3.5%   |
| 1998              | 704  | 32,193                                   | 2.2%   |
| 1994-1997 Average | 2,565  | 39,608                                   | 6.5%   |
| 1997              | 2,105  | 37,539                                   | 5.6%   |
| 1996              | 2,488  | 39,261                                   | 6.3%   |
| 1995              | 2,541  | 41,729                                   | 6.1%   |
| 1994              | 3,127  | 39,901                                   | 7.8%   |

Notes: Iron preparations were identified in the Children and Poisoning System (CAP). CAP is a subset of the National Electronic Injury System with a more detailed description of drug products. Data from all drugs (column 3 in the table) were from the National Electronic Injury Surveillance System (NEISS) using the following product codes: 1914 veterinary medicines, 1916 iron preparations, 1923 aspirin or aspirin compounds, 1928 antihistamines, 1929 drugs or medications not specified, 1930 aspirin substitutes and 1931 tablets or capsule drugs (excluding aspirin, aspirin substitutes, iron preparations and antihistamines).

Recall that the FDA regulation required unit dose packaging for the high dosage prenatal vitamins, while the low dosage children's vitamins and other such products could remain in bottles. The CAP System (see notes following table 1) allows further decomposition of emergency department visits for iron poisoning into four categories as follows: (1) children's vitamins, (2) prenatal vitamins, (3) liquids and (4) unable to be classified. One would expect that the largest decrease in emergency department visits would be for poisonings associated with prenatal vitamins. Unfortunately, too many cases could not be classified by dosage, so that it was not possible to determine if poisoning for the high dosage prenatal vitamins decreased faster than other categories. The data are shown in the appendix.

### *Analysis of Iron Poisoning data*

In summary, the data show that there were decreases in deaths and injuries from iron poisoning during the mid to late 1990s. The downward trend began before the enactment of the FDA regulation in July 1997 and continued after the regulation. The fact that the trend began before the regulation was enacted could be explained by the earlier governmental actions (examples were the FDA October 1994 press release on warning labels or the 1993 article on poisonings in the Los Angeles area and subsequent publicity). In general some impact should be expected before a regulation is enacted, perhaps as a result of the publicity and possibly advance compliance, and some effect should occur after enactment as new products take some time to penetrate the marketplace.

We believe that the sharp decrease in injuries in the first complete year of the regulation and the continued low levels of deaths and injuries in later years provides evidence that the FDA regulation was effective in reducing iron poisonings. Another researcher came to the same conclusion about the regulation.<sup>27</sup> However, it is important to understand that the regulation involved three factors not just the unit dose packaging requirement. The other two factors were (1) an incentive to reduce dosage sizes for products in bottles because the unit dose requirement did not apply to dosage units under 30 mg and (2) the new labeling requirement that included the stronger warning. The data does not allow separating the contribution of each of these factors.

### **Conclusion**

The main arguments in the petition are as follows:

1. Unit dose format is inherently safer than bottle format, regardless of the child-resistance of unit dose format.
2. The toxicity requirement of the child-resistance test deters drug manufacturers from adopting that format.
3. Dropping the toxicity requirement will result in manufacturers switching to unit dose from bottles, ultimately resulting in decreasing fatalities and injuries from accidental poisoning of children.

The analysis in this paper has been limited to the first argument.

As discussed above, the petition's comparative analyses of twenty years of adverse events from bottle and unit dose formats were not convincing that unit dose is

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<sup>27</sup> Morris CC (2000), "Recent Trends in Pediatric Iron Poisonings," Correspondence. *Southern Medical Journal*, page 1229. He wrote that "...it [was] hard to avoid the [after the fact] ...conclusion that unit-dose packaging requirements are responsible for the recent declines in pediatric iron poisonings and fatalities."

inherently safer than bottle format. This was primarily because there were many more drug products dispensed in bottle formats during the time period being compared. However, the iron poisoning data in the petition and in the analysis in this paper, we believe, overcomes this problem by contrasting deaths and injuries before and after enactment of the 1997 FDA regulation on unit dose.

While it appears that the trend of decreasing fatalities and deaths began before enactment of the FDA regulation, it also appears that the data provides evidence that the FDA regulation was effective in reducing adverse events from accidental ingestion of iron products. At the present time, it is impossible to separate the effect of the unit dose requirement in the regulation from other factors such as possible reduction of the dosage size in bottles, increased publicity about deaths and injuries and the new warning labels. It may be possible to conduct such an analysis in the future as a result of the *Nutritional Health Alliance* decision invalidating only the unit dose requirement. Whether an analysis can or cannot be conducted depends on whether high dosage iron products continue to be packaged voluntarily in unit dose formats or whether manufacturers switch back to bottles.

Even if an analysis could be conducted and if it could rule out publicity and warnings, it would still be difficult to generalize from one drug product to others. Whether injuries and deaths would decrease in other drug products that would shift from bottle to unit dose format is still an open question.

As a final issue, it should be noted that iron products that did change to unit dose format under the FDA regulation, had to comply with CPSC's toxicity requirement in the child-resistance test. Prenatal vitamins at 65 mg of iron would be in packages where a test failure would be 4 or more doses opened. The evidence from a CPSC staff experiment indicates that the amount of child-resistance makes a difference in the number of doses that children can access. It is possible that eliminating the toxicity requirement from the requirements for unit dose packaging could lead to decreasing the child-resistance of new or existing unit dose packages that would then result in an increase in accidental poisonings from unit dose packages.

Appendix

Table A.1  
 Estimated Emergency Department Treated Injuries for Children 0-4 Years Old  
 Associated with Iron Preparations by Type of Preparations

|                   | All Iron Preparations | Children's Vitamins and Liquids | Prenatal Vitamins and Supplements | Unspecified |
|-------------------|-----------------------|---------------------------------|-----------------------------------|-------------|
| 1998-2003 Average | 946                   | 451                             | 46                                | 450         |
| 2003              | 1,009                 | 523                             | 76                                | 410         |
| 2002              | 877                   | 414                             | 6                                 | 456         |
| 2001              | 715                   | 264                             | 62                                | 390         |
| 2000              | 1,263                 | 497                             | 118                               | 648         |
| 1999              | 1,106                 | 620                             | 11                                | 476         |
| 1998              | 704                   | 387                             | 0                                 | 318         |
| 1994-1997 Average | 2,565                 | 1,008                           | 251                               | 1,384       |
| 1997              | 2,105                 | 658                             | 76                                | 1,370       |
| 1996              | 2,488                 | 1,184                           | 93                                | 1,330       |
| 1995              | 2,541                 | 1,258                           | 317                               | 1,114       |
| 1994              | 3,127                 | 933                             | 519                               | 1,720       |

Source: Children and Poisoning (CAP). Estimates for 1994-1996 weights adjusted for the change in NEISS sample frame. Categories for types of iron preparations in 1994-1996 as a result may not add to totals.

All types of iron preparations showed decreases in the 1998-2003 period as compared with 1994-1997. The largest decrease was found in the unspecified category which decreased by about 67%. It is impossible to determine from the data how many of these unspecified emergency department treated injuries were for prenatals, children's vitamins or liquids.

**TAB C**



UNITED STATES  
CONSUMER PRODUCT SAFETY COMMISSION  
WASHINGTON, DC 20207

## Memorandum

Date: **AUG 31 2004**

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

THROUGH: Lori Saltzman, M.S., Director, Division of Health Sciences *W*

FROM : Suzanne Barone, Ph.D., Project Manager for Poison Prevention Directorate for Health Sciences *SB*

SUBJECT : International Standards for Non-reclosable Packaging

The purpose of this memorandum is to provide information on international child-resistance standards for non-reclosable packaging such as unit dose blister packaging.

### BACKGROUND

The U.S. Consumer Product Safety Commission (CPSC) was petitioned by the Healthcare Compliance Packaging Council (HCPC) to amend the definition of test failure for unit packaging in the regulations of the Poison Prevention Packaging Act (PPPA) to eliminate toxicity of the packaged product as a determinate. Thus, a test failure would become, "any child who opens or gains access to more than 8 individual units during the full 10 minutes of testing" regardless of the toxicity of the packaged product. One of the HCPC's arguments for making this change is to harmonize U.S. standards with those used by other nations.<sup>1</sup>

This memorandum describes the child-resistant packaging standards for non-reclosable packaging in the United States, Canada, United Kingdom, Germany, and Europe. All of the methods test packages with children aged 42 to 51 months. The language of the test method and the number of children tested are different for some of the tests. However, this memorandum will be limited to a discussion of the definition of test failure for non-reclosable packaging in the child test protocols because this is the focus of the petition. A discussion of the timing of the adoption of the various standards is also presented.

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<sup>1</sup> Petition PP 03-1 from Peter Mayberry, Executive Director of HCPC to Todd Stevenson, March 17, 2003.

## UNITED STATES

The United States adopted child-resistance requirements for packaging in the early 1970s when the PPPA was enacted. The purpose of the PPPA is to protect children from serious injury or serious illness resulting from handling, using, or ingesting hazardous household substances including drugs and cosmetics by requiring special packaging. Special packaging is defined in the PPPA 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 packaged substance within a reasonable time and not difficult for normal adults to use properly. However, special packaging is not packaging which all children under five years of age cannot open or obtain a toxic or harmful amount within a reasonable time (15 U.S.C. 1471(4)).

The Food and Drug Administration (FDA) administered the PPPA in the early 1970s. Since the PPPA prohibits prescribing specific packaging designs, product content, or packaging quantity (15 U.S.C. 1472(d)), human performance test protocols for child-resistance and adult-use-effectiveness were developed and put into place in 1971. The test protocols were derived from data generated in pilot studies conducted by a Joint Industry-FDA Committee on Safety Closures convened in 1966 and chaired by Dr. Edward Press, a prominent pediatrician. The protocols applied to all package types including bottle/closure and blister packaging that contained a substance regulated under the PPPA.

The original 1971 protocol for child-resistance included testing 200 children aged 42 to 51 months in pairs. The children were given 5 minutes to open a package. If they were not successful, they were given a single visual demonstration. If they did not use their teeth during the first 5 minutes, they were told that they could use their teeth if they wanted. The test then continued for an additional 5 minutes (36 FR 22151).

A test failure was defined as any child who opened a package or gained access to the contents. A test failure for unit packaging was a child who opened or gained access to the number of units which constitute the amount that may produce serious personal injury or illness, or a child who opened or gained access to more than 5 units, whichever number was lower during the full 10 minutes of testing. The determination of the amount of substance that may produce serious personal injury or serious illness was to be based on a 25-pound child.

The cutoff level of 5 units was established to provide the packaging industry with parameters within which to develop unit packaging. In 1973, the level was increased to 8 units because the FDA determined that access to 5 units was restrictive and tended to limit the development of unit packaging (38 FR 1510). In finalizing the more than 8 restriction, the FDA stated that the increase from 5 to 8 would not compromise safety or reduce the child protection quality of special packaging because the number of units constituting the amount that could produce serious personal injury or serious illness

would still govern in establishing the test failure when such number is 8 or less (38 FR 12738).

The child test is conducted in the same fashion today with minor modifications. In 1995, the CPSC streamlined the child test to allow testing of sequential groups of 50 children instead of 200. At that time, the statement, "the number of units that a child opens or gains access to is interpreted as the individual units from which the product has been or can be removed in whole or in part," was added to clarify access to unit packaging.

The packaging standards apply to all packaging types that contain substances regulated under the PPPA (16 CFR § 1700.14). These include drugs, cosmetics, and household chemical products.

## **CANADA**

The Canadian Standards Association (CSA) is an independent not-for-profit membership association involved with the development of voluntary standards. The CSA has individual standards for reclosable (Z76.1-99) and non-reclosable child-resistant packages (Z76.2-00). The non-reclosable packaging standard was published in March 2000 and will be up for review in 2005.

CSA Z76.2-00 describes adult and child test protocols, reports, and recordkeeping that are specific to non-reclosable packaging. The test instructions are similar to those found in the PPPA with language specific for testing unit packaging. The test failure in Z76.2-00 is the same as the PPPA definition of a package failure for unit packaging. "A test failure shall consist of any child's opening or gaining access to more than 8 individual units, or the number of individual units that constitutes the amount that may produce serious personal injury or serious illness, whichever is lower during the full 10 minutes of testing."<sup>2</sup>

CSA Z76.2-00 does not apply to any specific products. To date, the Canadian government (Health Canada) regulations do not reference CSA Z76.2-00.

## **UNITED KINGDOM**

The British Standards Institution (BSI) is an independent national standards body of the United Kingdom that is responsible for facilitating, drafting, publishing and marketing British standards and other guidelines. BSI serves as the United Kingdom's member of the European Committee for Standardization (CEN).

There are two British human performance standards related to child-resistance of non-reclosable packages, BS EN 862:2001 (for non-pharmaceutical products) and BS 8404:2001 (for pharmaceutical products).

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<sup>2</sup> CSA Z76.2-00 Clause 8.2.2(k) under Child-resistant effectiveness testing – test procedures.

## BS EN 862

BS EN 862 was originally adopted in 1997, revised in 2001, and is intended to apply only to non-reclosable packages for non-pharmaceutical products. This British Standard is the official English language version of the European standard EN 862:2001 discussed below in the Europe section.

## BS 8404:2001

For many years the United Kingdom considered a unit dose package for pharmaceutical products to be "safe" if the unit dose package was opaque or dark tinted. The BSI published BS 7236:1989, "Code of Practice for Non-reclosable Packaging for Solid Dose Units of Medicinal Products." The intent of this code of practice was to, "give recommendations for properties of materials used for strip and blister packaging and guidance about design features which are thought important for child resistance." This is not a human performance standard.

In December 2001, the BSI published a human performance test standard for pharmaceutical non-reclosable packaging. The standard BS 8404:2001 is entitled, "Packaging – Child-resistant packaging – Requirements and Testing Procedures for Non-reclosable Packages for Pharmaceutical Products."

The BS 8404 test is conducted with two five-minute test periods. The test uses the following failure criterion (Section 5.4.1.1):

- The test shall be considered a failure in relation to unit, strip or blister packages if within 10 minutes the child removes more than 8 units from the packaging provided.

The failure criterion does not take into account the toxicity of the product being packaged. The standard does not name individual substances that must use the packaging standard.

## GERMANY

The German child-resistant standards were developed by the Deutsches Institut für Normung (DIN), the German Institute for Standardization. The DIN is an association that has been recognized by the German government as the national standards body.

The standard for child-resistance, DIN 55559 has been in existence since the late 1970s.<sup>3</sup> It was modified in 1998 to narrow the coverage to cover non-reclosable child-resistant packaging for medicinal products. This was done following the adoption

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<sup>3</sup> Editions of DIN 55559 in 1978-11 and 1980-10.

of EN 862 and EN 28317 which cover non-reclosable packaging for non-pharmaceuticals and reclosable child-resistant packaging respectively. In DIN 55559 a package failure is a child who opens more than eight units.<sup>4</sup>

## EUROPE

The European Committee for Standardization (CEN) was founded in 1961 by the national standards bodies in Europe. CEN develops voluntary technical standards which promote free trade, the safety of workers and consumers, and environmental protection.

The CEN has two standards related to non-reclosable packaging, EN 862 (non-pharmaceutical products) and EN 14375 (pharmaceutical products).

### EN 862

The acceptance criteria for the child test in EN 862:2001 (section 5.3) are:

- at least 85 percent of 200 children tested shall be unable to open the package within 3 minutes without a demonstration
- at least 80 percent of 200 children test shall be unable to open the package within 6 minutes (3 minutes without a demonstration and 3 minutes after a demonstration)

While the percentages of children who do not open the packages are the same as the PPPA, the test period of a total of 6 minutes is shorter than the 10 minutes prescribed by the PPPA. The rationale for this is explained in Note 3 of EN 862 which states, "A fundamental change to the test period philosophy is applied because; 1) there is a significant difference in the performance required from a non-reclosable packaging and; 2) there is the difficulty in keeping the children motivated during a test period of 5 minutes."

An alternative sequential method that uses a grid scheme to determine the number of children to be tested can be used instead of 200 children. The German, UK, Canadian, and European standards allow the use of this sampling to minimize the number of children tested. The grid requires testing a specified minimum number of children then adding pairs until the standard is met.

The failure criteria in EN 862 is opening the package or gaining access to the contents. Any access is considered a failure.

This standard is currently undergoing revision. The new draft increases the time of the testing periods to 10 minutes total (two 5-minute time periods). The failure

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<sup>4</sup>Comment CP-03-1-15 and Personal communication with Colin Scaife, May 5, 2004.

criterion would remain access to one or more units. The sequential grid would replace the standard for 200 children to minimize the number of children tested.

The European Commission (EC) has a directive related to the classification, packaging and labeling of dangerous substances (67/548/EEC). This directive specifies that products classified as dangerous (i.e. toxic, corrosive, aspiration hazard) must be packaged in child-resistant packaging that meets EN 862 if non-reclosable packaging is used. All EU member states must use these standards.

## EN 14375

EN 14375 is entitled "child-resistant non-reclosable packaging for pharmaceutical products – requirements and testing." This standard was approved in September 2003 by a narrow margin and published in November 2003.

EN 14375 is very similar to BS 8404:2001. The definition of failure is "in relation to unit, strip, or blister packages if within 10 minutes the child accesses more than 8 unit doses from the packaging provided" (4.2.1).

EN 14375 failure criterion does not address toxicity. However, a NOTE under 4.2.1 states, "The figure of eight units is based on existing national standards published by certain CEN members and does not address the issue of toxicity. Some pharmaceutical products on the market can cause harm to children by the ingestion of fewer than eight units. However, reliable data on child toxicity exists for few pharmaceutical products. A harmful dose can be established for some existing pharmaceutical products and a maximum safe dose can be established for all pharmaceutical products by one means or another. Such information is not currently available for all products and there is no central register where this information could be held. In the absence of European legislation on this topic the drafters of this European Standard acknowledge these concerns and believe that research and collection of data should continue with a view to considering the substitution of a toxicity based pass/fail criterion for the child panel test in a later revision."

As the note above indicates, there is no European Communities' (EC) directive that requires child-resistant packaging for pharmaceutical products. However, EN 14375 must be adopted by countries that have their own requirements such as UK and Germany by May 2004.<sup>5</sup> Therefore, EN 14375 will replace BS 8404 and DIN 55559.

## DISCUSSION

The United States has been the leader in the area of child-resistant packaging for over 30 years. The PPPA contains requirements for both child-resistant packaging and the products that require it. The definition of failure for unit packaging takes into account

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<sup>5</sup> EN 14375 states, "this European standard shall be given the status of a national standard, either by publication of an identical text or by endorsement, at the latest by May 2004, and conflicting national standards shall be withdrawn at the latest by May 2004."

the toxicity of products packaged in it. This is important since the intent of the PPPA is to protect children from serious injury or illness from handling, using or ingesting hazardous household products including drugs. There is no distinction in the PPPA test methods between pharmaceuticals and non-pharmaceuticals as is the case for non-reclosable packaging in Europe.

The situation in the United States is different from other countries such as Canada where there are voluntary packaging standards developed specifically for non-reclosable packaging. These voluntary packaging standards do not name substances that are required to be in child-resistant packaging. While Europe has requirements for non-pharmaceuticals that are defined as toxic or corrosive, there are no requirements for child-resistant packaging of pharmaceuticals. Until such time as an EC directive is adopted, each European country has discretion to determine which pharmaceutical products should require child-resistant packaging.

EN 14375, the European voluntary standard for non-reclosable packaging for pharmaceuticals was recently put into place. The approval of EN 14375 was not unanimous. The standard met considerable resistance. The European Association for the Co-ordination of Consumer Representation in Standardisation (ANEC) commissioned a study to identify toxic medications and to develop a methodology for determining toxicity.<sup>6</sup> ANEC was not successful in defeating the standard which attained a 72 percent approval (minimum requirement for adoption is 71 percent). However, countries, including Austria, Iceland, Netherlands, Norway, and Spain rejected the EN 14375 standard due to the lack of consideration of the toxicity of the packaged products. Germany abstained from voting and stated that they would apply for an immediate revision in order to make the failure criterion for the standard more stringent. The need for future revisions of the standard is also voiced in the note (4.2.1) in the standard itself.

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<sup>6</sup> ANEC submitted their study to CPSC as a comment on the HCPC petition (PP03-1-1).

**TAB D**



UNITED STATES  
CONSUMER PRODUCT SAFETY COMMISSION  
WASHINGTON, DC 20207

Memorandum

Date: SEP 2 2004

To : Suzanne Barone, Ph.D. Project Manager, PPPA

Through : Mary Ann Danello, Ph.D., Associate Executive Director for Health Sciences *mad*

: Lori E. Saltzman, M.S., Director, Division of Health Sciences ✓

From : John W. Boja, Ph.D., Pharmacologist, Division of Health Sciences *JWB*

Subject : Technical feasibility, practicability, and appropriateness assessment of currently available child-resistant and senior-friendly (special) unit packaging

## I. INTRODUCTION

Under the Poison Prevention Packaging Act (PPPA) of 1970 the U.S. Consumer Product Safety Commission (CPSC) may require special packaging that is both child-resistant and senior-friendly for certain substances stored and used in the household. In addition to finding that special packaging is necessary to protect children from serious personal injury or serious illness, the Commission must also find that special packaging is technically feasible, practicable, and appropriate for these products (15 U.S.C. 1472 (a)(2)). For special packaging to be technically feasible, the technology must be available to produce packaging that conforms to established standards. A package is practicable if the special packaging is adaptable to modern mass production and assembly line techniques. And finally packaging is appropriate if the packaging will adequately protect the integrity of the substance and will not interfere with its intended storage or use.

The definition of package is "the immediate package or wrapping in which any household substance is contained for consumption, use or storage by individuals in or about the household". This means that the container that holds the product must be special packaging. Special packaging is defined by the PPPA as packaging that is designed or constructed to be difficult for children under 5 years of age to open or obtain a toxic or harmful amount of the substance within a reasonable time, and not difficult for normal adults to use properly (16 CFR §1700.1(4)). Child-resistance and adult-use-effectiveness of packaging are measured by performance testing packaging with children and senior adults, respectively.

When testing the child-resistance effectiveness of unit packaging, a test failure is defined in 16 CFR 1700.20(a)(2)(B)(ii) as any child who opens or gains access to the

number of units which constitute the amount that may produce serious personal injury or serious illness, or 8 individual units, whichever number is lower. Staff refers to the number of units accessed that would produce serious personal injury or serious illness as the failure level or "F value". The F value varies according to the substance contained within the unit packaging, with the most toxic substances requiring packaging with an

F level equal to 1. Under the current regulations, substances that are less toxic than this could use this packaging or packaging with a lesser degree of child-resistance, i.e. F=2 – 8.

The criteria used to determine if a package meets the definition of special packaging involve human performance testing. The PPPA regulations at 16 CFR § 1700.20 describe protocols that test children to determine child-resistance and senior adults to determine adult-use-effectiveness<sup>1</sup>. The sequential protocol testing criteria for children are presented below in Table 1. For example, if 50 children were tested using an F=1 package, then no more than 5 children could open or gain access to the contents of the package, as shown in Table 1. The testing protocol for this type of unit packaging is somewhat different from other packaging types such as cap and vial packages. In unit dose testing, once a child opens an individual blister, the test does not stop as it would with a cap and vial test. Instead, the child is allowed to open the maximum number of units (blisters) that he or she is able to open during the entire 10 minute testing session. However, the number of units that were accessed by the 5 children who constituted test failures is not taken into account for determination of a test failure. For example, if all 5 children accessed 6 – 10 units, and no other children in the test accessed any units, this package would still be considered F=1 since no more than 5 out of 50 children accessed 1 or more units. For an F=2 package no more than 80% of the children can access 2 or more units (40 children, assuming a full 200 children were tested), etc. The criteria for senior adult-use effectiveness for unit packaging are also similar to that used for other types of packaging. In the case of unit packaging the adult need only open one unit, and in most cases, the package cannot be reclosed, except for reclosable unit packages (ASTM Type XIII).

Table 1. Pass, Continue Testing and Fail Criteria for the first 5 minutes and the full 10 minutes of Child-Resistance Protocol Test

| Test Panel | Cumulative # of children | Number of children successful in package openings |          |      |                 |          |      |
|------------|--------------------------|---|----------|------|-----------------|----------|------|
|            |                          | First 5 minutes                                   |          |      | 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+  |

<sup>1</sup> See sequential pass-fail Table 1 in 16 CFR 1700.15.

This memo will discuss the types of unit packaging currently available which have been classified by the ASTM<sup>2</sup> into three standard types. There are two types of non-reclosable packaging, a pouch (much like the condiment pouches found in fast-food restaurants) and blisters. There is a third type of unit packaging that is called reclosable blister packaging by the ASTM. In this packaging, the blisters that contain the product are an integral part of the total package (immediate package) and must be permanently attached to the entire package. While the blisters themselves are not reclosable, the integral housing for the blisters is reclosable. If the blisters were separate from the remainder of the package configuration, the reclosable remainder of the package configuration would be considered an overpackage and would not fit the ASTM definition of reclosable blister packaging, nor would it fit the definition of special packaging under the PPPA. The three packaging types designated by the ASTM are (1) ASTM Type IV Non-reclosable packaging – flexible (strip/pouch), (2) ASTM Type VIII Non-reclosable packaging – semi-rigid (blister), and (3) ASTM Type XIII Reclosable packaging – semi-rigid (blister).

## II. UNIT PACKAGING TYPES

### A. Type IV Non-reclosable packaging – flexible (strip/pouch)

The simplest type of unit packaging is ASTM Type IV Non-reclosable packaging. This packaging is made using two sheets of a material that have been sealed together along the edges to form a pouch. There are three main types of pouches: pillow, three-sided, or four-sided pouches<sup>3</sup>. A pillow pouch is formed with a back seam, a top seam, and a bottom seam. A common example of a pillow pouch is a potato chip bag. A three-sided pouch has 2 side seams and a top seam, the bottom is formed by folding the material horizontally. A four-sided pouch has seams on the 2 sides of the pouch, a top seam and a bottom seam. The seams of these pouches are generally formed using heat sealing, however adhesives have also been used. The sheets of material forming the pouch usually consist of a plastic, metalized plastic, or metallic foil. However, each of these materials alone may have certain limitations that decrease their usefulness as a packaging material. By using a multimaterial laminate, the structural properties and characteristics of each individual material can be combined. Laminates made from combinations of plastic, metalized plastic, metallic foil, and/or paper are commonly used. Desirable properties of laminates include: high physical strength, puncture resistance, abrasion resistance, tear resistance, an effective barrier resistance to the environment (air and moisture) and low cost.

ASTM Type IV Non-reclosable packaging (pouches) has been sub-classified into three types, Type IV(A) which has an internal (hidden) tear notch, Type IV(B) which has an oriented tear, and Type IV(C) which requires a tool (scissor or knife) to open.

<sup>2</sup> Standard Classification of Child-Resistant Packages, Designation: D 3475-03a, ASTM International, 100 Barr Harbor Drive, PO Box C700, West Conshohocken, Pennsylvania, USA 19428-2959

<sup>3</sup> *Understanding Plastics Packaging Technology*. Susan E.M. Selke, 1997, Hanser/Gardner Publications, Cincinnati OH

## Protocol Test Results for ASTM Type IV Packages

CPSC's Health Science's staff has child-resistance effectiveness (CRE) and senior adult-use effectiveness (SAUE) protocol testing data on two ASTM Type IV(A) packages; a plastic/foil/plastic laminate used to make a 3" by 3" pouch<sup>4</sup> and a 2<sup>3</sup>/<sub>4</sub>" x 2<sup>3</sup>/<sub>4</sub>" polyester/foil laminate pouch<sup>5</sup>.

ASTM Type IV(C) packaging requires the use of a tool such as scissors to open. CPSC's Health Science staff has protocol testing data on two ASTM Type IV(C) packages; a 92 mm (approximately 3<sup>5</sup>/<sub>8</sub>" square pouch made of a plastic/foil/plastic laminate<sup>6</sup> and an ASTM Type IV(C) pouch (3<sup>1</sup>/<sub>4</sub> square) made from valeron plastic and metalized film<sup>7</sup>.

The results of the protocol tests for ASTM Type IV packages are summarized in Table 2; details of the testing results can be found in the Appendix. In this table the F value for the package is given. This is the maximal F value for a product that is suitable for use with this packaging. For example if the F value is equal to 1, then products that require F=1 packaging could use that package. If however the F value given in the table was equal to 2, then products that require F=1 packaging could not use that packaging.

Table 2 Protocol Testing Results for ASTM Type IV Packages

| ASTM Type | Reference | CRE Results | SAUE Results | F Value |
|-----------|-----------|-------------|--------------|---------|
| IV(A)     | 4         | 90%         | 99%          | F=1     |
| IV(A)     | 5         | 90%         | 94%          | F=1     |
| IV(C)     | 6         | 88%*        | 100%         | F=1     |
| IV(C)     | 7         | 98%         | 100%         | F=1     |

\* Additional testing will be required to confirm these results, see Table 1.

Both of the ASTM Type IV(A) packages were of similar design, size, and were constructed using similar materials, as a result they both had similar protocol test results. Both of the ASTM Type IV(C) packages were also of similar design and size, the only difference between the 2 packages was the materials used and perhaps the heat sealing process (temperature, adhesive or both). The observed difference in the CR results of the above examples illustrates the importance of the materials used to create a pouch. In summary, differences in the laminates, machinability of the materials, the sealability of the package, the tear properties of the materials, bonding methods used to assemble the package, the format of the blister card, as well as

<sup>4</sup> Laboratory Report #3758, Tewabe Asebe, September 2, 1999

<sup>5</sup> Laboratory Report #3249, Tewabe Asebe, June 11, 1998

<sup>6</sup> Laboratory Report #3761, Tewabe Asebe, September 9, 1999

<sup>7</sup> Laboratory Report #3843, Tewabe Asebe, November 11, 2000

differences in the physical properties of the tablet within the blister all have an effect on the barrier properties of a package<sup>8</sup>.

### **B. Type VIII Non-reclosable packaging – semi-rigid (blister)**

A second type of unit packaging is a cavity or blister that is formed in a sheet of polymer plastic. In this type of packaging the product is placed within the cavity, then the cavity is closed by heat sealing a backing of an aluminum foil to the polymer plastic sheet. While this may seem like a simple package consisting of only two elements, in reality a number of factors contribute to the degree of child-resistance for this type of unit packaging. Some of these factors include the size and shape of the blister, the total number of blisters within the package, the thickness of the polymer material used to form the blister, the thickness of the backing, the adhesive used to adhere the backing to the blister, the position of the cavity on the card, the total surface area of the polymer film fo, adhesion to the foil backing, and even the size and shape of the material within the blister itself. A number of these factors are interrelated. For example, as the number of blisters increases or the size of the blister cavity increases, there may be a reduction in the surface area available for adhesion of the polymer film to the backing. In addition, each foil has unique heat seal lacquer requirements and each PVC-film has unique properties. This means that the degree of adhesion for a foil from one manufacturer may not be the same as that for a similar foil from a different manufacturer.

### **Protocol Test Results for ASTM Type VIII Packages**

Just as ASTM Type IV non-reclosable packaging has been sub-classified into different types, ASTM Type VIII non-reclosable packaging – semi-rigid (blister), has various sub-types based on how the backing and the tablets are removed. CPSC's Health Science's staff has examples and child-resistance effectiveness (CRE) and senior adult-use effectiveness (SAUE) protocol testing data on an ASTM Type VIII(B) [remove portion (tab), peel back, and push out] in a 2 x 5 tablet pattern with perforation separating each tablet. This packaging is constructed using a paper backing over a foil heat sealed to PVC plastic<sup>9</sup>. Staff also has protocol data on an ASTM VIII(C) design (peel back the backing) using a paper/foil/plastic construction with blisters in a 3 x 4 pattern with an 8 mm unsealed area at the corners<sup>10</sup>, and a package of similar construction but in a 2 x 3 pattern<sup>11</sup>. ASTM Type VIII(D) designs require the user to peel back the backing and push out the product. Health Science's staff has data on this type of packaging in three different blister patterns or formats: a prototype of paper/foil/plastic construction with a 5 x 4 tablet pattern<sup>12</sup>; an ASTM Type VIII(D) package constructed with paper/foil/plastic, but with a 3 x 4 design produced<sup>13</sup>; and an

<sup>8</sup> Fundamentals of Packaging Technology, 2nd Edition, Walter Soroka, 1999, Institute of Packaging Professionals, Herndon, VA

<sup>9</sup> Laboratory Report #3739, Tewabe Asebe, October 10, 1999

<sup>10</sup> Laboratory Report #3757, Tewabe Asebe, September 2, 1999

<sup>11</sup> Laboratory Report #3963, John Boja, May 9, 2002

<sup>12</sup> Laboratory Report #3780, Tewabe Asebe, February 24, 2000

<sup>13</sup> Laboratory Report #3965, John Boja, May 23, 2002

ASTM Type VIII(D) package constructed with paper/foil/plastic in a 2 x 2 tablet design<sup>14</sup>. Packages with an ASTM Type VIII(K) design have a visible internal tear notch; Health Science's staff has data on an ASTM Type VIII(K) package in a 2 x 4 tablet pattern blister<sup>15</sup>. Health Science staff is aware of one package of ASTM Type VIII(M) packaging that is designated as bend, peel back and push out<sup>16</sup>. Table 3 presents a summary of the protocol testing results for the ASTM Type VIII unit packages. The CRE values presented are those for the F value given in the last column.

Table 3 Protocol Testing Results for ASTM Type VIII Packages

| ASTM Type | Reference | CRE Results | SAUE Results | F Value |
|-----------|-----------|-------------|--------------|---------|
| VIII (B)  | 9         | 92%         | 95%          | F=1     |
| VIII (C)  | 10        | 92%         | 95%          | F=8     |
| VIII (C)  | 11        | 83.5%       | N/A          | F=4     |
| VIII (D)  | 12        | 82%         | 90%          | F=1     |
| VIII (D)  | 13        | 87.5%       | 100%         | F=3     |
| VIII (D)  | 14        | 89%         | N/A          | F=2     |
| VIII (K)  | 15        | 90%         | N/A          | F=7     |
| VIII (M)  | 16        | 92%         | 99%          | F=1     |

The ASTM Type VIII(B) package may be suitable for those products that require a F=1 package. Neither of the two ASTM Type VIII(C) packages would be suitable for those products which require F=1, F=2, or F=3 packaging. The three ASTM Type VIII(D) packages demonstrate that variations in the materials used to construct the package and/or the blister pattern used in the package can greatly influence the CRE for packages even within the same ASTM sub-classification. In this ASTM sub-classification the first ASTM VIII(D) package had nine failures when tested with 50 children; this package would require further testing as shown in Table 1. If the package continues to demonstrate a similar degree of child-resistance it may be suitable for use for those products that require F=1 packaging (as stated before F=1 packaging may be suitable with those products requiring packaging of lesser child-resistance, i.e., F=2 – F=8). The second ASTM VIII(D) package may be used for products that require up to F=3 packaging, while the third ASTM VIII(D) package may be suitable for those products requiring packaging up to an F=2 level. These F values assume that any number of variables possibly affecting child-resistance such as the pill size, dimensions of the blister card, format of the blister card, the size of the blister cavity, etc. remain constant.

When the ASTM type VIII(K) package was tested with 50 children, 5 were able to access at least 5 tablets. This unit package type may be suitable for use with those products which require F=7 packaging. Only four children out of 50 were able to access

<sup>14</sup> Laboratory Report #3974, John Boja, July 10, 2002

<sup>15</sup> Laboratory Report #3565, Tewabe Asebe, February 11, 1999

<sup>16</sup> Laboratory Report #3919, John Boja, August 30, 2001

at least 1 tablet during the protocol test of the ASTM type VIII(M) package. This package may be suitable for use with those products requiring F=1 packaging.

### C. Type XIII Reclosable packaging – semi-rigid (blister)

The newest type of special blister packaging to enter the market is the reclosable semi-rigid (blister) packaging. Health Science staff has data on four examples of this type of packaging and other examples of this type of packaging may soon be available. ASTM Type XIII packaging is very flexible in the design pattern that can be used. An example of this type of packaging consists of a standard blister card that is permanently attached to a housing that incorporates some type of mechanism to render it hard for children to open.

#### Protocol Test Results for ASTM Type XIII Packages

ASTM Type XIII(A) packaging requires the user to press in a tab, pull out a sliding blister carrier, and then push out the tablet. Staff has both child-resistant effectiveness (CRE) and adult use effectiveness (SAUE) data on one ASTM Type XIII(A) package<sup>17</sup>. Another type of reclosable blister packaging is the ASTM XIII(B) packaging. This type of packaging requires the user to pull on a trigger ring to release a flap, lift the flap and then lift the lid of the package to reveal the blister card. Tablets may then be pushed out of the card. Staff has data on this type of packaging<sup>18</sup>. ASTM Type XIII(D) packages have the unit blisters in a case. To obtain the tablets, the user must slide the blisters to align with holes in the bottom of the case and then push out the pill. The blisters non-align when released. Health Science staff has data on one ASTM Type XIII(D) product<sup>19</sup>. A fourth type of reclosable unit packaging has just been introduced into the marketplace. The ASTM has just classified this package as ASTM Type XIII(E)<sup>20</sup>. Table 4 presents a summary of the protocol testing results of the ASTM type XIII packages. As in Tables 2 and 3, the CRE values presented are those for the F value given in the last column.

Table 4 Protocol Testing Results for ASTM Type XIII Packages

| ASTM Type | Reference | CRE Results | SAUE Results | F Value |
|-----------|-----------|-------------|--------------|---------|
| XIII(A)   | 17        | 94%         | 99%          | F=1     |
| XIII(B)   | 18        | 98%         | 95%          | F=1     |
| XIII(D)   | 19        | 91%         | N/A          | F=1     |
| XIII(E)   | 20        | 98%         | 96%          | F=1     |

Based on the test results that staff is aware of, all of the above examples appear to be suitable for those products that require F=1 packaging. Just as with other packaging

<sup>17</sup> Laboratory Report #3605, Tewabe Asebe, April 6, 1999

<sup>18</sup> Laboratory Report #4063, John Boja, December 15, 2003

<sup>19</sup> Laboratory Report #3842, Tewabe Asebe, November 7, 2000

<sup>20</sup> Laboratory Report #4064, John Boja, December 15, 2003

types, these packages could also be used with those products that require a lesser degree of child resistance (F=2 through F=8).

### **III. Conclusion**

In order to require special packaging for substances under the PPPA, the Commission must find that special packaging is technically feasible, practicable, and appropriate for these products (15 U.S.C. 1472 (a)(2) Sec.3). In addition to the package type itself (ASTM classification type) a number of factors influence the degree of the effectiveness of unit dose packaging. These factors can include, but are not limited to, the materials used to construct the packaging, the materials used to assemble the packaging, the design of the packaging, and the size, shape and hardness of the material (tablet, pill, etc) contained within the packaging.

Special unit packaging is available in various degrees of child-resistance ranging from F=1 packaging (the most secure) to F=8. The availability of several examples of special unit packaging in the marketplace with an F=1 rating demonstrates that the manufacture and use of F=1 unit packaging is technically feasible. This also demonstrates the practicability and appropriateness of this packaging. Currently there are several examples of F=1 unit packaging in the marketplace that are both child-resistant and senior friendly. Generally, manufacturers could use any of the available F=1 packaging with product requiring lower levels of child-resistance since it would be child-resistant at all F levels. In addition, those manufacturers that do not know or do not wish to determine the appropriate packaging for the toxicity level of their product could use F=1 packaging.

For those manufacturers that know the toxicity of their product, special unit packaging is available over a range of child-resistance requirements other than F=1, (i.e., F=2 to F=8). Special unit packaging with F ratings ranging from 2 to 8 is currently available in the marketplace, thus demonstrating the technical feasibility, practicability and appropriateness of these packaging types.

In summary, special unit dose packaging is available in a number of different types, configurations, and degrees of child-resistance. The examples of the various packaging types with varying degrees of child-resistance presented within this memo are currently available in the marketplace. This demonstrates that the production of special unit packaging in a wide range of F ratings is technically feasible, practicable and appropriate.

## Appendix

### ASTM Type IV Non-reclosable packaging – flexible (strip/pouch)

Laboratory Report #3758 A plastic/foil/plastic laminate 3" by 3" ASTM Type IV(A) design pouch was tested using 100 adults and 50 children. Only 1 adult could not open this package, thus the senior-use effectiveness (SAUE) was determined to be 99%. Five children were able to open this unit package yielding a child-resistance effectiveness (CRE) of 90%.

Laboratory Report #3249 A polyester/foil laminate 2¾" by 2¾" ASTM Type IV(A) design pouch was tested using 100 adults and 50 children. Six adults could not open this package (SAUE 94%). Five children were able to open this unit package (CRE) of 90%.

Laboratory Report #3761 A 92 mm (approximately 3½") square pouch made of a plastic/foil/plastic laminate was protocol tested. Six of the 50 children tested were able to open the package (88% CRE). This package would require further testing with another 50 children as specified in Table 1. All of the adults were able to open the package (100% SAUE).

Laboratory Report #3843 A 3¼ square pouch made from valeron plastic and metalized film was tested. Only 2 children out of 100 children were able to open this package (98% CRE). 100% of the adults were able to open this package.

### ASTM Type VIII Non-reclosable packaging – semi-rigid (blister)

Laboratory Report #3739 An ASTM Type VIII(B) (remove portion (tab), peel back, and push out) in a 2 x 5 tablet pattern with perforation separating each tablet constructed using a paper backing over a foil heat sealed to PVC plastic was protocol tested with 50 children. A total of 4 children were able to access 1 tablet (92% CRE). No child was able to access more than 1 tablet. In a separate test of 100 adults, this package was determined to be 95% SAUE.

Laboratory Report #3757 An ASTM Type VIII(C) package of paper/foil/plastic construction with blisters in a 3 x 4 pattern with an 8 mm unsealed area at the corners for easier peeling was tested with 50 children, a total of 28 were able to access at least 1 tablet (44% CRE), 24 accessed at least 2 tablets (52% CRE), 22 accessed at least 3 tablets (56% CRE), 18 accessed at least 4 tablets (64% CRE), 14 accessed at least 5 tablets (72% CRE), 10 accessed at least 6 tablets (80% CRE), 4 accessed at least 8 tablets (92% CRE), and 2 accessed more than 8 tablets (96% CRE). This package was determined to be 95% SAUE when tested with 100 adults.

Laboratory Report #3963 A package constructed of paper/foil/plastic in a 2 x 3 pattern was also tested using 200 children. Of the 200 children tested, 74 were able to open 2 blisters (63% CRE), 45 accessed at least 3 tablets (77.5% CRE), 33 accessed at least 4

tablets (83.5% CRE), 22 accessed at least 5 tablets (89% CRE), and 13 accessed at least 6 tablets (93.5% CRE).

Laboratory Report #3780 A prototype of paper/foil/plastic ASTM Type VIII(D) package in a 5 x 4 tablet pattern was tested with 50 children, 9 children were able to access at least 1 tablet (82% CRE), and 1 of those 9 children accessed 2 tablets, 98% CRE. This package was determined to be 90% SAUE in a test of 100 adults.

Laboratory Report 3965 An ASTM Type VIII(D) package constructed with paper/foil/plastic with a 3 x 4 design when tested in 200 children, a total of 80 were able to access at least 1 tablet (60% CRE), 46 accessed at least 2 tablets (77% CRE), 25 accessed at least 3 tablets (87.5% CRE), 13 accessed at least 4 tablets (93.5% CRE), 9 accessed at least 5 tablets (95.5% CRE), 7 accessed at least 6 tablets (96.5% CRE), 5 accessed at least 7 tablets (97.5% CRE), and at least 4 accessed 8 tablets (98% CRE). This package was determined to be 100% SAUE when tested with 100 adults.

Laboratory Report #3974 Two ASTM Type VIII(D) blister cards in a 2 x 2 tablet design constructed using paper, foil and plastic were packaged together for retail sale. When tested with 100 children (two cards were given to each child) 27 children were able to access at least 1 tablet (73% CRE), 11 accessed at least 2 tablets (89% CRE), 5 accessed at least 3 tablets (95% CRE), 3 accessed at least 4 tablets (97% CRE), 2 accessed at least 5 tablets (98% CRE), and no child accessed at least 6 or more tablets (100% CRE). At this time we do not have senior adult data for this package.

Laboratory Report # 3565 An ASTM Type VIII(K) design with a visible internal tear notch using a 2 x 4 tablet pattern was marketed as a single package that contained three 2 x 4 tablet blister sheets. Protocol testing reflected the actual retail product and each of the 50 children tested were given three blister sheets to open. Twenty six of the 50 children were able to access at least 1 tablet (48% CRE), 23 accessed at least 2 tablets (54% CRE), 20 accessed at least 3 tablets (60% CRE), 19 accessed at least 4 tablets (62% CRE), 5 accessed at least 5 tablets (82% CRE), 8 accessed at least 6 tablets (84% CRE), 5 accessed at least 7 tablets (90% CRE), 4 accessed at least 8 tablets (92% CRE), 2 accessed at least 9 tablets (96% CRE), and 2 accessed 10 - 12 tablets (96% CRE). At this time we do not have senior adult data for this package.

Laboratory Report #3919 An ASTM Type VIII(M) package designated as bend, peel back and push out had 14 tablets arranged in a 2 X 7 pattern. The package was constructed with SBS cardboard and plastic. The package had to be flexed to expose a tear tab. The tab is removed and then the tablet can be pushed through the backing. When this package was tested with 50 children, 4 children were able to access at least 2 tablets (92% CRE), and 3 accessed more than 8 tablets (94% CRE). When tested for SAUE with 100 adults, this package was determined to be 99% SAUE.

### **Type XIII Reclosable packaging – semi-rigid (blister)**

Laboratory Report #3605 This ASTM Type XIII(A) packaging requires the user to press in a tab, then pull out a sliding blister carrier, and then push out the tablet. A permanently attached blister card with a count of 30 tablets (4 X 7 + 2 pattern) was tested using 50 children, while no child accessed 1 or 2 tablets, three children were able to access at least 3 tablets (94% CRE). There were no further tablets accessed with this package. When tested with 100 adults, this package was found to be 99% SAUE.

Laboratory Report #4063 An ASTM Type XIII(B) design of packaging requires the user to pull on a trigger ring to release a flap, the flap is then lifted and the lid of the package can be lifted to reveal the blister card, tablets may then be pushed out of the card. This package was configured as a 14 count blister, when tested with 50 children. However, other blister count cards could be used with this type of packaging. One child was able to access at least 1 tablet, resulting in a 98% CRE. No child accessed more than 1 tablet. This ASTM Type XIII(B) package was determined to be 95% SAUE when tested with 100 adults.

Laboratory Report #3842 ASTM Type XIII(D) packages have the unit blisters in a case. The user must slide the blisters to align with holes in the bottom of the case and then push out the pill. The blisters non-align when released. A 28 tablet blister package in a 4 x 7 pattern was tested using 100 children, 9 children were able to access at least 1 tablet (91% CRE), 3 accessed at least 7 tablets (97% CRE), 2 accessed at least 8 tablets (98% CRE), and 1 accessed more than 8 tablets (99% CRE). At this time we do not have senior adult data for this package.

Laboratory Report #4064 The ASTM has just classified a new package design as ASTM Type XIII(E). This package is constructed of cardboard and when opened reveals a permanently attached unit card constructed of plastic and foil. As with the other reclosable blister packages, the unit dose card can be configured in several ways. This package is opened by pressing a dot on the package, flexing the entire package and lifting up the exposed edge of the front flap. When this package was tested using 50 children, 1 child was able to access 1 tablet (98% CRE). No other children accessed any the tablets. When tested for SAUE, this package was determined to be 96% SAUE.

# **TAB E**



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

MEMORANDUM

DATE: August 28, 2003

TO : HS

Through: Todd A. Stevenson, Secretary, OS

FROM : Martha A. Kosh, OS

SUBJECT: Petition PP 03-1, Petition for Amendment of the  
Child-Resistance Testing Requirements for Unit  
Dose Packaging

ATTACHED ARE COMMENTS ON THE CP 03-1

| <u>COMMENT</u> | <u>DATE</u> | <u>SIGNED BY</u>   | <u>AFFILIATION</u>  |
|----------------|-------------|--|---|
| CP 03-1-1      | 6/24/03     | T. Vandenberghe<br>Program Manager<br>On behalf of<br>ANEC | The European Consumer<br>in Standardisation<br>Av. de Tervueren 36<br>box 4 - B-1040<br>Brussels, Belgium |
| CP 03-1-2      | 7/28/03     | Robert Brooke<br>Vice President                            | Quality Assurance/<br>Quality Control<br>KV Pharmaceutical<br>St. Louis, MO 63043                         |
| CP 03-1-3      | 7/30/03     | Steven Marcus, MD<br>Executive Director                    | New Jersey Information<br>& Education System  |
| CP 03-1-4      | 7/30/03     | Anthony Manoguerra<br>Pharm.D, DABAT,<br>FAACT, Director   | California Poison<br>University of California   |
| CP 03-1-5      | 7/30/03     | Suzanne Doyon, MD<br>Medical Director                      | Maryland Poison Center<br>University of Maryland  |
| CP 03-1-6      | 8/01/03     | James Mowry<br>Director                                    | Indiana Poison Center<br>Indianapolis, Indiana  |
| CP 03-1-7      | 8/01/03     | Marc Wilenzick<br>Senior Corporate<br>Counsel              | Pfizer Inc.<br>235 East 42 <sup>nd</sup> Street<br>New York, NY 10017                                     |

Petition PP 03-1, Petition for Amendment of the Child-Resistance Testing Requirements for Unit Dose Packaging

|            |         |   |   |
|------------|---------|---|---|
| CP 03-1-8  | 8/04/03 | Robert Geller<br>Medical Director &<br>Assoc. Professor<br>Of Pediatrics  | Georgia Poison Center<br>Emory University School<br>of Medicine   |
| CP 03-1-9  | 8/07/03 | Hugh Lockhart<br>Professor &<br>Laura Bix<br>Asst. Professor  | Michigan State Univ.<br>153 Packaging<br>East Lansing, MI 48824   |
| CP 03-1-10 | 7/23/03 | Laurie Smaldone<br>Sr. Vice President<br>Global Regulatory<br>Sciences  | Bristol-Myers Squibb<br>Pharmaceutical Research<br>Institute<br>P.O. Box 4000<br>Princeton, NJ 08543        |
| CP 03-1-11 | 8/07/03 | Douglas Bierer<br>Vice President<br>Regulatory and<br>Scientific Affairs  | Consumer Healthcare<br>Products Association<br>1150 Connecticut Ave, NW<br>Washington, DC 20036             |
| CP 03-1-12 | 8/11/03 | Stu DeJonge   | <a href="mailto:Pakmax@aol.com">Pakmax@aol.com</a>  |
| CP 03-1-13 | 8/11/03 | K. Baszczewski<br>Director of<br>Compliance   | Sharp Corporation<br>147 Clinton Road<br>West Caldwell, NJ 07006  |
| CP 03-1-14 | 8/12/03 | Alexander Perritt<br>CEO<br>Scott Perritt<br>President<br>Richard Ward<br>Vice President<br>Consumer Product<br>Testing | Perritt Laboratories<br>145 South Main St.<br>P.O. Box 147<br>Hightstown, NJ 08520                          |
| CP 03-1-15 |         | Colin Scaife  | CE Packaging Partnership<br>29, Dene Road<br>Cottingham, East<br>Yorkshire HU16-5PD<br>England              |
| CP 03-1-16 |         | Donna Seger<br>President  | American Academy of<br>Clinical Toxicology<br>777 East Park Drive<br>P.O. Box 8820<br>Harrisburg, PA 17105  |
| CP 03-1-17 |         | Robert Geller<br>Medical Director   | Emory University School<br>of Medicine<br>Department of Pediatrics<br>69 Butler St, SE<br>Atlanta, GA 30303 |

Petition PP 03-1, Petition for Amendment of the Child-Resistance  
Testing Requirements for Unit Dose Packaging

|            |   |   |
|------------|---|---|
| CP 03-1-18 | Kenneth Stewart<br>Regulatory Affairs                         | Alcoa<br>2101 Reymet Rd<br>Richmond, VA 23237   |
| CP 03-1-19 | E. Stephen Edwards, MD<br>President                           | American Academy of<br>Pediatrics<br>The Honor Building<br>601 Thirteenth Street, NW<br>Suite 400 North<br>Washington, DC 20005 |
| CP 03-1-20 | Ken Kulig, MD<br>Chairman                                     | Patient Safety Sub-<br>committee, American<br>College of Medical<br>Toxicology  |
| CP 03-1-21 | Darla J. Williamson   | Closure Manufacturers<br>Association  |
| CP 03-1-22 | Ed Hancock<br>President                                       | American Health<br>Packaging<br>2550 John Glenn Ave.<br>Columbus, Ohio 43217  |
| CP 03-1-23 | Al Goldhammer, PhD<br>Associate VP                            | Pharmaceutical Research<br>& Manufacturers of<br>America<br>1100 Fifteenth Street NW<br>Washington, DC 20005                    |
| CP 03-1-24 | Sandra E. Luciano   | Honeywell<br>Specialty Films<br>Healthcare<br>101 Columbia Road<br>Morristown, NJ 07962   |
| CP 03-1-25 | John M. Coster, Ph.D<br>Vice President<br>Policy and Programs | National Association of<br>Chain Drug Stores<br>413 North Lee Street<br>P.O. Box 1417-D49<br>Alexandria, VA 22313               |
| CP 03-1-26 | Mark R. McMahon<br>Chief Operating<br>Officer                 | MeadWestvaco Corporation<br>World Headquarters<br>One High Ridge<br>Stamford, CT 06905  |
| CP 03-1-27 | James J. Jones<br>Director                                    | US Environmental<br>Protection Agency<br>Washington, DC 20460   |
| CP 03-1-28 | Hipolito Paul<br>Corbacho                                     | Corbcohcpc03@aol.com  |

Petition PP 03-1, Petition for Amendment of the Child-Resistance  
Testing Requirements for Unit Dose Packaging

CP 03-1-29

10/27/03

Peter Mayberry  
Exec. Director

Healthcare Compliance  
Packaging Council

**TAB F**



UNITED STATES  
CONSUMER PRODUCT SAFETY COMMISSION  
WASHINGTON, DC 20207

## Memorandum

DATE: September 1, 2004

TO : Suzanne Barone, Ph.D., Project Manager for the HCPC Petition

THROUGH: Mary Ann Danello, Ph.D., Associate Executive Director, Directorate for Health Sciences *mad*

Lori E. Saltzman, M.S., Director, Division of Health Sciences *LS*

FROM : Patricia M. Brundage, Ph.D., Pharmacologist, Division of Health Sciences *PMB*

SUBJECT : Toxicity of Solid-Dose Pharmaceuticals in Children Less Than Five Years of Age

A petition to amend the child-resistant (CR) testing requirements for unit dose-packaging was submitted to the Commission by the Healthcare Compliance Packaging Council (HCPC). The petition requests that the U.S. Consumer Product Safety Commission (CPSC) modify the criteria in the definition of a CR test failure of unit dose packaging in 16 CFR 1700.20 (a)(2)(ii). HCPC recommends the definition of a test failure for unit dose packaging be changed to eliminate all reference to substance toxicity as part of the pass/fail criteria for unit dose packaging. This memo responds to comments received on the petition regarding toxicity and unit dose.

### **Specific pharmaceuticals posing serious poisoning risks for children with the ingestion of fewer than eight units**

In response to the petition by the HCPC to change the pass/fail criteria for unit dose packaging, nine commenters listed numerous pharmaceutical products that would pose serious poisoning risks for children with the ingestion of fewer than eight units. The commenters included poison center directors (CP03-1-3, 4, 5, and 6), a clinical toxicology association (CP03-1-16), a pediatric association (CP03-1-19), a college of medical toxicology (CP03-1-20), a CR packaging testing firm (CP03-1-14), and a package manufacturer (CP03-1-26). A variety of drugs were cited as some of the pharmaceutical products that would be toxic if a child were to consume less than eight units. These include beta-adrenergic antagonists (i.e., timolol, metoprolol, atenolol, propranolol); calcium channel blockers (i.e., nifedipine and verapamil), the sustained release formulation of

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. Two commenters (CP03-1-14 and 26) also voiced concern regarding the potential harm caused by the ingestion of less than eight units of the over-the-counter medications acetaminophen, ibuprofen, diphenhydramine, and loperimide.

The CPSC Health Sciences (HS) staff agree that there are numerous prescribed and over-the-counter drugs that can cause serious, life-threatening toxicity when fewer than eight units are consumed by children under the age of five.

### **Feasibility of determining a toxic dose for children**

In response to the FR notice requesting comments on the HPCP petition, 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.

One commenter, the European Association for the Co-ordination of Consumer Representation in Standardization (ANEC), forwarded to CPSC a commissioned study (May 2002) that included an in-depth toxicity assessment of certain solid-dose medications involved in accidental poisonings of children five years old and younger, and a proposed flow chart for determining a toxic dose for children (i.e., the dose that would require medical intervention) (CP03-1-1). This study was written in response to the draft European standard prEN 14375 to consider packages CR when children could open up to eight units. The ANEC study and its applicability to the petition submitted by HPCP are reviewed below.

The first part of the ANEC study identified and assessed medications that caused severe accidental poisoning in children up to five years of age. Published literature and information from several different databases<sup>1</sup> were examined.

Fourteen drugs<sup>2</sup> were chosen for assessment. These drugs were either associated with at least three accidental ingestions by children under five years of age that resulted in a hospitalization of one or more days (HASS), or were

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<sup>1</sup> Hospital reports of the UK Home Accident Surveillance System (HASS) from 1996-1999, death statistics from England and Wales reported by the Office for National Statistics (ONS) from 1993-1999, records from the National Poisons Information Service (London) (NPIS(L)) from March 1997 through December 2001, and reports of poisoning deaths in the US reported annually by the American Association of Poison Control Centers (AAPCC) from 1983-2000.

<sup>2</sup> Dothiepin, imipramine, carbamazepine, temazepam, hyoscine, atenolol, propranolol, sulphonylurea drugs, methadone, Lomotil, nifedipine, quinine, dapsone, and amoxapine.

identified as the cause of moderate to severe poisoning in NPIS(L) or identified as the cause of death in the ONS or AAPCC data.

Reported deaths of children less than five years old were associated with the ingestion of less than eight units of ten of the drugs (dothiepin, imipramine, carbamazepine, hyoscine, methadone, Lomotil®, nifedipine, quinine, dapson, and amoxapine). One death was caused by propranolol. All fourteen drugs caused moderate to severe toxicity when a child ingested less than eight units. Of the fourteen drugs, only dothiepin is not available in the United States.

The ANEC study reported that financial and time constraints did not permit the determination of the toxicity of other medications believed to be a serious health hazard to children less than five years of age following the ingestion of less than eight dose units. These include tricyclic antidepressants, large doses of opioids, chlormethiazole, chloral hydrate, chlorpromazine (antipsychotic), clozapine (antipsychotic), dextropropoxyphene, codeine, flecainide (antiarrhythmic), clonidine (alpha-adrenergic agonist), verapamil (calcium channel blockers), orphenadrine, risperidone (antipsychotic), thioridazine (antipsychotic), flecainide, theophylline, and chloroquine.

The second part of the ANEC study described a methodology for determining the toxic dose of a drug in children under five for which there is limited or no empirical toxicity information. A guidance document, to be used by an expert panel, was developed in order to determine the dose in children below which no medical intervention is required. This dose is referred to as the No Treatment Dose (NTD), which is multiplied by 7.5 kg (average weight of the age group of six months to five years) to define a safe dose in children under five years of age.

Briefly, the first step is to identify the Maximum Tolerated Dose (MTD), which is the highest dose that a healthy adult or child can take without exhibiting adverse effects. This is established in Phase I clinical trials. If a pediatric MTD is identified, this dose is considered the NTD. If no pediatric MTD is established, an adult MTD is extrapolated to a pediatric MTD by dividing the adult dose by 70 kg (average adult weight). For older drugs without an established MTD, data sources, including poison center data, published literature, and mortality data on pediatric and/or adult ingestions, are evaluated by the panel of experts. In the absence of any case data, data on drugs of the same class that are structurally and pharmacologically similar are examined. As a last resort, the single normal treatment dose (STD), which is the highest single starting dose for any indication, is used as the NTD.

In addition to establishing that severe poisoning and death occur when children five years old or younger ingest less than eight units of high dose medications, the ANEC study provides an approach that can be used by an expert panel for determining the maximum pediatric safe dose. The expert panel would presumably include individuals with experience similar to those who were

involved with the generation of the ANEC study; pharmacists, specialists in poison information, medical toxicology personnel, and scientists.

Although it is only a general guideline, it demonstrates that it may be feasible to develop an approach to determine the toxic dose to children and subsequently, the number of units that are toxic to children. HS staff believe that a standardized methodology or approach for evaluating data to establish a toxic dose in children up to five years of age merits further study, particularly for newer pharmaceutical products for which reliable data from case reports on pediatric toxicity do not exist.

### **Staff Conclusion**

As indicated in the public comments submitted in response to the petition by HCPC, there are numerous prescription and over-the-counter drugs currently available that can cause serious personal injury or illness to children less than five years of age following the ingestion of less than eight dose units. Consequently, eliminating the toxicity based pass/fail criteria would put children at risk for serious injury from these substances. The guidelines developed as part of the ANEC study provide a potential systematic approach for defining a toxic dose of drugs in children which merits future study.