



UNITED STATES  
CONSUMER PRODUCT SAFETY COMMISSION  
BETHESDA, MD 20814

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approved and signed.

**BALLOT VOTE SHEET**

**DATE:** November 8, 2012

**TO:** The Commission  
Todd A. Stevenson, Secretary

**THROUGH:** Mary T. Boyle, Acting General Counsel  
Kenneth R. Hinson, Executive Director

**FROM:** Patricia M. Pollitzer, Assistant General Counsel  
Andrew J. Kameros, Attorney, OGC

**SUBJECT:** Final Rule: PPPA Rule Requiring Child-Resistant Packaging for Imidazolines

Ballot Vote Due: November 15, 2012

Staff prepared a briefing package recommending that the Commission issue the attached draft final rule pursuant to the Poison Prevention Packaging Act of 1970 (PPPA). The rule would require child-resistant (CR) packaging for any over-the-counter drug product containing the equivalent of 0.08 milligrams or more of an imidazoline (tetrahydrozoline, naphazoline, oxymetazoline, and xylometazoline) in a single package. Imidazolines are a family of drugs that are vasoconstrictors indicated for nasal congestion and/or ophthalmic irritation. Imidazolines can cause serious adverse reactions, such as central nervous system (CNS) depression, decreased heart rate, and depressed ventilation in children who accidentally ingest them.

Please indicate your vote on the following options:

I. Approve publication of the attached document in the *Federal Register*, as drafted.

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(Signature)

\_\_\_\_\_  
(Date)

II. Approve publication of the attached document in the *Federal Register*, with changes. (Please specify.)

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(Signature)

\_\_\_\_\_  
(Date)

III. Do not approve publication of the attached document in the *Federal Register*.

\_\_\_\_\_  
(Signature)

\_\_\_\_\_  
(Date)

IV. Take other action. (Please specify.)

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(Signature)

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(Date)

Attachment: Draft *Federal Register* Notice of Final Rule: Products Containing Imidazolines Equivalent to 0.08 Milligrams or More

Billing Code 6355-01-P

CONSUMER PRODUCT SAFETY COMMISSION

16 CFR Part 1700

CPSC Docket No. CPSC-2012-0005

**Final Rule: Requirements for Child-Resistant Packaging: Products Containing Imidazolines Equivalent to 0.08 Milligrams or More**

**AGENCY:** Consumer Product Safety Commission

**ACTION:** Final Rule.

**SUMMARY:** The Consumer Product Safety Commission (CPSC, Commission, or we) is issuing a rule to require child-resistant (CR) packaging for any over-the-counter or prescription product containing the equivalent of 0.08 milligrams or more of an imidazoline, a class of drugs that includes tetrahydrozoline, naphazoline, oxymetazoline, and xylometazoline, in a single package. Imidazolines are a family of drugs that are vasoconstrictors indicated for nasal congestion and/or ophthalmic irritation. Products containing imidazolines can cause serious adverse reactions, such as central nervous system (CNS) depression, decreased heart rate, and depressed ventilation in children who accidentally ingest them. Based on the scientific data, the Commission has determined that availability of 0.08 milligrams or more of an imidazoline in a single package, by reason of its packaging, is such that special packaging is required to protect children under 5 years old from serious personal injury or illness due to handling or ingesting such a substance. The Commission takes this action under the Poison Prevention Packaging Act of 1970 (PPPA).<sup>1</sup>

**DATES:** This rule is effective [INSERT DATE 1 YEAR AFTER PUBLICATION IN THE FEDERAL REGISTER]. This rule applies to products packaged on or after that date.

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<sup>1</sup> The Commission voted \_\_\_ to publish this notice in the **Federal Register**.

**FOR FURTHER INFORMATION CONTACT:** Carol Afflerbach, Compliance Officer, Office of Compliance and Field Operations, Consumer Product Safety Commission, 4330 East West Highway, Bethesda, MD 20814; telephone (301) 504-7529; cafflerbach@cpsc.gov.

**SUPPLEMENTARY INFORMATION:**

**I. Background**

*A. Relevant Statutory and Regulatory Provisions*

The Poison Prevention Packaging Act of 1970 (PPPA), 15 U.S.C. 1471-1476, authorizes the Commission to establish standards for the “special packaging” of any household substance if: (1) the degree or nature of the hazard to children in the availability of such substance, by reason of its packaging, is such that special packaging is required to protect children from serious personal injury or serious illness resulting from handling, using, or ingesting such substance, and (2) the special packaging is technically feasible, practicable, and appropriate for such substance.

Special packaging, also referred to as “child-resistant (CR) packaging,” is: (1) designed or constructed to be significantly difficult for children under 5 years of age to open or obtain a toxic or harmful amount of the substance contained therein within a reasonable time, and (2) not difficult for “normal adults” to use properly. 15 U.S.C. 1471(4). Household substances for which the Commission may require CR packaging include (among other categories) foods, drugs, or cosmetics, as these terms are defined in the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321). 15 U.S.C. 1471(2)(B). The Commission has issued performance requirements for special packaging. 16 CFR §§ 1700.15, 1700.20.

Section 4(a) of the PPPA, 15 U.S.C. 1473(a), allows the manufacturer or packer to package a nonprescription product subject to special packaging standards in one size of non-CR packaging, only if the manufacturer (or packer) also supplies the substance in CR packages of a

popular size, and the non-CR packages bear conspicuous labeling stating: “This package for households without young children.” 15 U.S.C. 1473(a), 16 CFR § 1700.5.

To protect children younger than 5 years old from serious personal injury following ingestion, the rule requires CR packaging for any over-the-counter (OTC) or prescription product containing the equivalent of 0.08 milligrams or more of an imidazoline (including tetrahydrozoline, naphazoline, oxymetazoline, or xylometazoline) in a single package.

*B. Imidazolines*

Imidazolines are a family of drugs that are used as decongestants in eye drops and nasal products. Imidazolines are used as topical decongestants because they produce vasoconstriction when administered to the eye or nasal mucosa. In the eye, the imidazolines relieve redness due to minor eye irritations by causing vasoconstriction of the blood vessels on the surface of the eye and eyelid (Facts and Comparisons, Ophthalmic Decongestants, Pharmacology, 2011). The onset of vasoconstriction after topical application is within minutes. As nasal decongestants, imidazolines temporarily relieve nasal congestion or stuffy nose due to the common cold, hay fever, or other upper respiratory allergies (Facts and Comparisons, Nasal Decongestants, Pharmacology 2011). The imidazolines cause vasoconstriction in mucous membranes, which decreases blood flow and leads to shrinking of swollen nasal mucosa and increased drainage of the sinuses.

Topical and nasal administration of imidazolines results in little absorption into the general circulation. Orally ingested imidazolines, however, are absorbed into the general circulation leading to systemic effects. Even though death from ingesting imidazolines is rare, ingestion can result in severe life-threatening consequences, such as central nervous system (CNS) depression and cardiovascular effects. Specific symptoms of CNS depression upon ingestion of imidazolines range from drowsiness to coma, with a concurrent depression of the

respiratory system. Other reported CNS side effects include: headache, lightheadedness, dizziness, tremor, insomnia, nervousness, restlessness, giddiness, psychological disturbances, prolonged psychosis, and weakness. Imidazolines have led to CNS depression and insomnia in different children. Prominent cardiovascular effects in response to overdose include low blood pressure and slowed heart rate. The medical literature and evidence from collected samples demonstrate that despite the danger of ingesting imidazolines, imidazoline-containing products are not manufactured in CR packaging.

Eye drops containing imidazolines are widely available at drug, grocery, and mass market retailers. Imidazoline eye drops generally come in small squeeze bottles. The most common size is the 1/2-ounce (15 milliliters) bottle, and the second most common size appears to be a 1-ounce bottle (30 milliliters). One-quarter ounce (8 milliliters) bottles are also available.

Nasal sprays containing imidazolines are widely available at drug, grocery, and mass market retailers. Some packages are used by rapidly squeezing the bottle to spray the product into a nostril. Other packages have a pump mechanism that activates the spray. As with eye drops, 1/2-ounce containers are the most common container size, and 1-ounce bottles are the second most common size.

We are aware of approximately 45 manufacturers who sell topical decongestant products under about 64 different labels. Because some manufacturers produce both nasal and ophthalmic products, the number of manufacturers within the market for topical decongestants is not the sum of the manufacturers of ophthalmic products, plus the manufacturers of nasal products.

We estimate that approximately 45 million units of ophthalmic decongestants containing imidazolines are sold annually, with estimated annual sales receipts of approximately \$180

million. We estimate that approximately 39 million units of nasal products containing imidazolines are sold annually, generating annual sales receipts of approximately \$233 million.

Commission staff examined 12 packages—10 eye drops, 1 nasal spray, and 1 nasal drops—of over-the-counter products that contain imidazolines. The 10 eye drop samples were packaged in squeeze-to-dispense plastic dropper bottles. The nasal spray was packaged in a plastic bottle with an attached metered pump sprayer, and the nasal drop was packaged in a squeeze-to-dispense plastic dropper bottle. All of the eye drop product bottles were finished with continuous threads, and the bottle openings were fitted with plastic dropper plugs. The nasal spray bottle was finished with continuous threads onto which a metered pump dispenser was attached. The pump mechanism was not child resistant. The nasal drops were packaged in a squeeze-dropper bottle, finished with continuous threads, and the bottle opening was fitted with a dropper plug. None of the samples of eye drops, nasal spray, or nasal drops was packaged using special packaging.

*C. The Proposed Rule*

On January 25, 2012, the Commission issued a notice of proposed rulemaking (NPR) that proposed requiring CR packaging for imidazoline preparations containing 0.08 milligrams or more of imidazolines in a single package. 77 FR 3646.

The Commission received five comments in response to the proposed rule. Two comments address the amount of time necessary to develop, test, and produce CR packaging for imidazolines, and they request additional time beyond the 1-year effective date proposed in the NPR. Two comments pertain to imidazoline nasal and ophthalmic packaging, and one comment concerns the derivation of the proposed regulation level of 0.08 milligrams or more of imidazolines in a single package. We respond to each of these comments below.

Effective Date

*Comment:* Two commenters indicate that the proposed effective date of 1 year is too short. One commenter concludes: “it is not feasible for manufacturers to comply with the proposed one (1) year effective date” and opines that 2 years would be required at a minimum. Regarding nasal products, the commenter contends that this amount of time is required because it will probably be necessary to replace the commonly used single-piece cap with two-component CR protection caps. The commenter also notes that most ophthalmic finishes<sup>2</sup> are 13mm–15mm; that there are no CR closures available smaller than 18mm; and therefore, new CR packages will also be required for ophthalmic products. The commenter provides a timeline identifying the various steps of the CR packaging development, testing, and approval process, and the time range for the expected completion of each stage. The commenter requests that the Commission consider a 1-year stay of enforcement in addition to the 1-year effective date recommended in the NPR to allow manufacturers 2 years after publication of the rule to comply. This commenter also states that additional time beyond the one year effective date and one year stay of enforcement may be required by some manufacturers, especially if the products in question are subject to U.S. Food and Drug Administration (FDA) requirements for new drug applications (NDAs) or abbreviated new drug applications (ANDAs). This additional approval process, the commenter reports, could require an additional 6 to 12 months. This commenter also requests that manufacturers be granted extended stays of enforcement on a case-by-case basis, if required.

A second commenter states that it manufactures sterile eye drops that require “specialized aseptic processing,” notes that the process for developing CR packages suitable for sterile

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<sup>2</sup> The word “finish,” in this sense, refers to the protruding threads on the bottle’s opening, which hold the cap or closure. A container and its corresponding closure must have matching finishes.



ophthalmic products is complex and “based upon historical experience with the regulated design and qualification activities required for aseptically filled sterile products,” and requests that the effective date of the rule be extended to 24 months.

*Response:* We agree with the first commenter’s analysis of the steps necessary to comply with a CR packaging requirement and the time frames associated with each step. We also agree with the second commenter’s statement that producing sterile products will take 24 months, such that a conditional 12-month stay of enforcement is warranted. We address our assessment of the anticipated duration of each step in the process of developing, testing, and producing CR packaging, and we highlight each step identified in the commenter’s submission. The first commenter states that *design development* will take 2 to 4 months, and we believe that this range is typical for modern computer-assisted design processes. We note that there are several nonpatented designs, and one patented design for CR packaging for imidazoline products that, if purchased or licensed by a manufacturer, could reduce the duration of the design development stage to 1 month or less. The commenter states that *prototype tooling* will take from 4 to 6 months, and we have been advised by independent sources that mold tool production typically takes 4 to 5 months, with an additional month for production testing to ensure that the mold tool can be used at the intended production rate. The commenter estimates that *CR protocol testing* will take approximately 3 months, and we have been advised by CR protocol test providers that such testing for child-resistant and senior-friendly packaging typically takes 2 to 4 months, depending on the complexity of the CR system. The commenter states that *industrial scale-up for packaging and validation* will take from 7 to 11 months because of the possibility that existing filling and capping equipment will need to be replaced, or at least significantly modified, depending on the design of the CR closure. Independent sources have advised us that this work

should take less than 6 months if a similar sterile process is already in place and between 6 and 12 months if new equipment must be installed. According to the commenter, *adoption and validation of the new filling line* will take between 3 and 6 months, which is the time range provided by manufacturers of similar products in connection with previous regulatory activity. The commenter states that *stability testing* will take between 3 and 12 months, a timeframe that is consistent with FDA Stability Test Guidelines of 1 year for regular stability testing and 6 months for accelerated stability testing, which is intended to increase the rate at which the degradation reactions take place. The commenter states that the *FDA review process* for an NDA or an ANDA can take from 6 months to a year. The FDA advises that 10 months is the median review time for NDAs, while the ANDA review process typically does not take as long; however, permission must be obtained before filing an ANDA, which can take up to 6 months alone.

Based on the foregoing review and analysis of the steps necessary to develop, test, and produce CR packaging for products that contain imidazolines, as well as the time frames for each of those steps, the Commission agrees that more than 1 year may well be necessary. Thus, the Commission will grant a conditional 1-year stay of enforcement to provide additional time to produce CR packaging for these products. This issue is discussed further in Section VI of the preamble.

#### Packaging Issues

*Comment* — One commenter notes that the NPR failed to consider one type of nasal spray package. The package in question “is a glass bottle which houses the imidazoline drug product, with a crimped seal holding the pump in place and with [a] detachable nozzle.” The metered pump is housed in a metal case, the rim of which is crimped to the glass bottle. A plastic nozzle

is placed over the pump, and the overcap is attached to the nozzle. Consumers access the product by squeezing the package between the thumb and first two fingers, causing an aerosolized form of the product to be released from the nozzle's tip.

The commenter believes that this package is inherently child resistant because it is a unit-dose package. The commenter requests that CPSC staff provide clarification "as to what could constitute a pass or failure of such a package."

*Response:* We disagree with the commenter's fundamental premise that unit-dose packages are inherently child resistant. In fact, we believe that unit-dose packages are not inherently CR. It is likely that a child can easily access the contents because neither the pumping action, nor the overcap or nozzle attachments are CR, and it is reasonably foreseeable that a child could access more than the regulated quantity of the contents. Either the pump action or the overcap must be child resistant.

*Comment* – One commenter asks: "for nasal sprays that contain Imidazoline equivalent to 0.08 milligrams or more, is Child-Resistant packaging required for crimp-on pumps?" The commenter acknowledges that continuous thread (CT) closures and squeezable packages permit a child to have access to the entire contents, but states that metered-dose pumps crimped onto a rigid bottle would permit a child access to "only one dose at a time." In addition, the commenter states: "it is not likely to be ingested due to its aerosol form."

*Response* – As stated in the response to the previous comment, unit-dose packaging is not inherently CR. Child-resistant packaging is required for the pump action and/or the overcap. We also disagree that an aerosolized form of the product would not be ingested by a child.

Regulated Level of Imidazoline

*Comment*— One commenter asks whether the lowest observed adverse effect level (LOAEL) (*i.e.*, 0.75 mg) should first be normalized to mg/kg and then extrapolated to a 25-pound child before applying a tenfold safety factor, resulting in a no observable adverse effect level (NOAEL) of 0.18 mg.

*Response* - The proposed regulated level (0.08 mg imidazoline) was based upon an actual imidazoline case with a safety factor applied to the dose ingested. Notably, ingestions expressed as normalized doses show that adverse effects occurred at levels within about the same range of imidazoline (0.1–0.3 mg/kg). Moreover, another case in the medical literature documents an adolescent who developed persistent cardiovascular and neurological effects after ingestion of approximately 0.07 to 0.1 mg/kg of tetrahydrozoline, which is also consistent with the proposed imidazoline level *e.g.*, 0.07 mg/kg (lower end of range) x 11.4 kg child = ~ 0.8 mg ÷ 10 fold-safety factor = 0.08 mg.

**II. Toxicity of Imidazolines**

The Commission’s Directorate for Health Sciences reviewed the toxicity of imidazolines. Imidazolines are used as topical decongestants because they produce vasoconstriction when administered to the eye or nasal mucosa. In the eye, the imidazolines relieve redness due to minor eye irritations by causing vasoconstriction of the blood vessels on the surface of the eye and eyelid (Facts and Comparisons, Ophthalmic Decongestants, Pharmacology, 2011). The onset of vasoconstriction after topical application is within minutes. As nasal decongestants, imidazolines temporarily relieve nasal congestion or stuffy nose due to the common cold, hay fever, or other upper respiratory allergies (Facts and Comparisons, Nasal Decongestants, Pharmacology 2011). The imidazolines cause vasoconstriction in mucous membranes, which

decreases blood flow and leads to shrinking of swollen nasal mucosa and increased drainage of the sinuses.

The therapeutically effective dose of imidazolines occurs within a narrow dose range, with toxic effects occurring at doses close to, or at, therapeutic levels. CNS depression (ranging from drowsiness to deep sedation) may occur after recommended doses in infants. Overdoses (doses not specified) of these medications have caused initial spikes of high blood pressure, leading to slowed heart rate, drowsiness, and rebound low blood pressure in adults. A shock-like syndrome with abnormally low blood pressure and slowed heart rate may also occur. Warnings on tetrahydrozoline- and naphazoline-containing OTC drugs state that their use may cause CNS depression, leading to coma in pediatric patients. Xylometazoline and oxymetazoline symptoms of overdose include: extreme tiredness, sweating, dizziness, a slowed heartbeat, and coma.

When the drug is absorbed, it can act systemically within the body. Topical administration of imidazolines to the eye produces local effects to the blood vessels of the eye, but little is absorbed into the general circulation. (For purposes of this document, we interpret “absorption” as the passage of a drug from its site of administration into the blood plasma.)

Nasal administration of imidazolines causes an intense degree of vasoconstriction, and therefore, negligible absorption of the drug into the general circulation (POISINDEX,<sup>®</sup> 2011). However, with oral ingestion, imidazolines are absorbed into the general circulation, leading to systemic effects. These drugs are absorbed quickly, and symptoms can occur in as little as 1 hour, peaking at 8 hours, and resolving after 12–36 hours. Even though the symptoms resolve in a relatively short amount of time, ingestion of imidazolines can result in severe life-threatening consequences, including decreased breathing, decreased heart rate, and loss of consciousness, which require hospitalization to ensure recovery.

FDA regulations pertaining to “Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use,” at 21 CFR § 341.80(c)(2)(iv), require the product label for products containing naphazoline hydrochloride at a concentration of 0.05 percent to state: “Do not use this product in children under 12 years of age because it may cause sedation if swallowed.” Specific symptoms of CNS depression upon ingestion of imidazolines range from drowsiness to coma, with a concurrent depression of the respiratory system. Other observed CNS side effects include: headache, lightheadedness, dizziness, tremor, insomnia, nervousness, restlessness, giddiness, psychological disturbances, prolonged psychosis, and weakness. Imidazolines have led to CNS depression and insomnia in different individuals. The insomnia, seen in a few cases, may be an unpredictable, idiosyncratic reaction (*i.e.*, a drug effect that occurs in a small number of people due to age, genetics, or disease state). Prominent cardiovascular effects in response to overdose include rebound low blood pressure and slowed heart rate.

No specific treatment for imidazoline overexposure exists. Naloxone (an opioid blocker) has been used without consistent success. Gastric lavage is not recommended more than 1 hour after ingestion because the imidazolines are absorbed quickly after ingestion, leading to CNS depression and a greater risk of aspiration into the lungs. Activated charcoal may be used up to 1 hour after ingestion; but again, due to the CNS depression, there is a greater risk of aspiration into the lungs. Therefore, treatment of the clinical effects from imidazolines is supportive, based on symptoms. For example, mechanical respiration would be administered to those with severe respiratory depression.

### III. Ingestion and Injury Data

As discussed more extensively in the NPR, staff reviewed several sources for information on adverse health effects from ingestion of imidazolines. These sources are the National Electronic Injury Surveillance System (NEISS), and the FDA's Adverse Event Reporting System (AERS).

The CPSC's Directorate for Health Sciences maintains the Children and Poisoning (CAP) system, a subset of NEISS records containing additional information obtained through NEISS involving children under 5 years old. NEISS is a statistically valid injury surveillance and follow-back database that the Commission maintains of consumer product-related injuries occurring in the United States. Injury data are gathered from the emergency departments (ED) of approximately 100 hospitals selected as a probability sample of all 5,000+ U.S. hospitals with emergency departments. The system's foundation rests on emergency department surveillance data, but the system also has the flexibility to gather additional data at either the surveillance or the investigation level. Surveillance data enable the Commission to make timely national estimates of the number of injuries associated with (but not necessarily caused by) specific consumer products. This data also provides evidence of the need for further study of particular products. Subsequent follow-back studies yield important clues to the cause and likely prevention of injuries and deaths. For additional information on NEISS, see the CPSC's website at: <http://www.cpsc.gov/cpsc/pub/pubs/3002.html>.

CAP includes data on each pediatric poisoning, chemical burn, or ingestion case reported from a NEISS hospital, as well as data on some ingestions that could lead to poisoning. We searched the CAP database for incidents between January 1997 and December 2011, involving

household products that typically contain imidazolines. During that time, there were an estimated 6,650 emergency room-treated injuries associated with household products containing imidazolines involving children under 5 years old. Table 1 below shows the injury estimates for each of the product groups involved in these incidents. Four-fifths of the estimated injuries (82 percent) involved eye drops.

**Table 1: Estimated Imidazoline Product-Related Injuries to Children Under 5 Years Old, 1997–2011, by Product Group**

<b>Product</b>	<b>Estimated Injuries</b>	<b>Coefficient of Variation</b>	<b>Sample Size</b>	<b>95% Confidence Interval</b>
Eye drops	5,437	0.18	161	3,564–7,309
Nose Sprays <sup>3</sup>	1,213	0.29	37	534–1891
<b>Total</b>	<b>6,650</b>	<b>0.16</b>	<b>198</b>	<b>4,550–8,749</b>

Source: U.S. Consumer Product Safety Commission National Electronic Injury Surveillance System and Children and Poisoning System, 2011.

As set forth in tabular form in the NPR, In-Depth Investigations (IDIs) were assigned in connection with certain NEISS-reported imidazoline ingestion incidents. A selection of these IDIs reveals various scenarios in which children between the ages of 13 months and 4 years gained access to imidazoline products including young children who removed caps from eye drop bottles left within their reach; obtained an eye drop bottle from an older sibling; used a chair to access an eye drop bottle in a medicine cabinet; and took a bottle of eye drops out of his mother’s purse. See NPR, Table 2, section III.A (77 FR 3649), for a summary of IDIs of selected incidents.

The AERS is a database of voluntary reports from health care professionals and consumers, along with mandatory reports from manufacturers. AERS is maintained by the FDA and contains reports of adverse events and medication errors for all FDA-approved drugs and therapeutic biologic products. We asked the FDA for all AERS reports mentioning the

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<sup>3</sup> The estimate for this category is highly variable due to small sample size and high coefficient of variation. These numbers should be interpreted with caution.



imidazolines tetrahydrozoline, oxymetazoline, xylometazoline, or naphazoline. FDA provided 1,041 reports for 772 distinct cases for us to review involving both children and adults occurring between October 1968 and August 2010. We checked for cases related to imidazolines, excluded the cases with concomitant drugs, and determined that 67 cases (with 115 total reports) were in scope for consideration in this rulemaking.

Reports through the AERS system show a wide variety of adverse events associated with the use of imidazolines across all ages. The top three system/organ classes with reported adverse events were psychiatric disorders (52 reports); nervous system disorders (47 reports); and respiratory, thoracic, and mediastinal disorders (38 reports). Sixty-two out of 67 in-scope cases (93 percent) reported an adverse event in one of the top three system/organ classes. (Reports can include more than one adverse event, so individual reports may be recorded in more than one system/organ class.) Our review of these cases is contained in the January 11, 2012, Staff Briefing Package: <http://www.cpsc.gov/LIBRARY/FOIA/FOIA12/brief/imidazolines.pdf>.

The volumes of imidazoline ingestions in children (under the age of 5) that were reported from two sources, the FDA's AERS database (MedWatch reports) and the medical literature, ranged from several drops to a high of 30 mL (2 tablespoons). The volume ingested was unknown in several imidazoline cases. As set forth in Table 3 in the NPR, very serious adverse effects occurred in response to small oral doses of imidazolines. For example, a 2-year-old child who ingested between 1 and 1.5 mg of tetrahydrozoline, experienced decreased blood pressure and respiration, and he was placed on mechanical respiration in the pediatric intensive care unit for 18 hours. Also, a 16-month-old child who ingested between 1.25 and 2.5 mg of tetrahydrozoline experienced decreased heart rate, depressed respiration, and was admitted to the hospital overnight.

**DRAFT 11/13/12**

In MedWatch reports of adverse events occurring in response to ingestion of imidazolines, 43 cases occurred in children under 5 years old. Tetrahydrozoline ingestions constituted the majority of the cases (88 percent). There were no reported deaths related to imidazoline ingestion. *See:*

<http://www.cpsc.gov/LIBRARY/FOIA/FOIA12/brief/imidazolines.pdf>: January 11, 2012, Staff Briefing Package, for a complete list of cases.

The most recent imidazoline ingestion case cites the lowest dose of ingestion of which we are aware that caused severe adverse symptoms in a child. The case involved a 25-day-old infant who suffered apnea after being treated with tetrahydrozoline nasal drops (0.05 percent). The mother inadvertently administered the nasal drops by the oral route three times per day with 0.5 ml/day (0.25 mg). The immature kidney and liver function of the newborn caused the drugs to clear the newborn's system more slowly than in an adult. CPSC staff reviewing this case report considered the three doses of nasal drops to be additive and calculated the total dose for this case to be 0.75 mg. After the second dose, the child was not feeding well and had low muscle tone. Two hours after the second dose, he developed apnea. After the third dose was administered, the child was brought to the hospital and admitted with a respiratory rate of four breaths per minute and a slowed heart rate. The infant was treated with naloxone, resolving the apnea and bradycardia. After 2 days, the child was in good condition and was discharged. After follow-up 10 days later, the child was in normal condition (Katar et.al. 2010).

Our review of the ingestion data is contained in:

<http://www.cpsc.gov/LIBRARY/FOIA/FOIA12/brief/imidazolines.pdf>: January 11, 2012, Staff Briefing Package.

**IV. Level for Regulation**

The Commission is issuing a rule requiring special packaging for any over-the-counter or prescription product containing the equivalent of 0.08 milligrams or more of an imidazoline in a single package. The absorption of imidazolines after oral ingestion can lead to unpredictable and profound CNS depression, including depressed respiration and cardiovascular events. Data indicate that children under 5 years old are accidentally ingesting imidazoline-containing products. Even though death from imidazoline exposure is rare, many of these events result in serious life-threatening consequences requiring hospitalization and intensive care monitoring for recovery. *See* NPR, Section Table 3, section III.C (77 FR 3650), for a summary of relevant cases of imidazoline ingestion.

Mindlin (1966) reported a case in which a 1-year-old girl ingested ½ to 1 teaspoon (2.5–5 mL) of tetrahydrozoline eye drops and suffered CNS depression with slowed respiration and decreased heart rate. Based on this ingestion, recent publications define 2.5 mL tetrahydrozoline (0.05 percent, 1.25 mg) as the dose at which serious toxicity from imidazoline exposure can occur after ingestion (Holmes and Berman, 1999; Eddy and Howell 2000). The preamble to the proposed FDA rule for OTC nasal decongestants reported that the minimum oral dose of oxymetazoline in an adult causing measurable cardiovascular effects (on blood pressure and heart rate) was 1.8 mg of oxymetazoline (41 FR 38312, 38398 (September 9, 1976)). This minimum dose may be lower for children because they appear to be more sensitive to imidazoline effects than adults (Brainerd and Olmstead, 1956). Cases indicate that ingestion of as little as 0.75 mg of imidazolines can result in serious illness in children, requiring supportive therapy (Katar et al., 2010; Summary see Table 3). The most recent case of imidazoline ingestion is reviewed in section III of this preamble. It involved a 25-day-old infant who

suffered apnea after being treated with tetrahydrozoline nasal drops (0.05 percent). CPSC staff reviewing this case report calculated the total dose for this case to be 0.75 mg, which is the lowest dose the ingestion of which we are aware, caused severe adverse symptoms in a child.

Because serious effects on the heart and breathing rates occur with the ingestion of as little as 0.75 mg of tetrahydrozoline, we consider this the lowest observed adverse effect level (LOAEL). All of the imidazolines cause potent central and peripheral sympathetic effects, but tetrahydrozoline has the highest potency for CNS sedative/depressive effects and the lowest potency for cardiac effects. Oxymetazoline and naphazoline are the most potent imidazolines for peripheral cardiac effects and have an 8–10 times lower maximum daily dose than tetrahydrozoline (0.4 mg, 0.3 mg and 3.2 mg, respectively). Xylometazoline and oxymetazoline have a longer duration of action than tetrahydrozoline (12 hrs., 10 hrs., and 4–6 hrs., respectively).

Applying a safety factor of 10 to the LOAEL to derive a recommended regulated level of 0.08 mg for all imidazolines is appropriate in order to protect children from serious health effects following ingestion of this family of drugs. The level of 0.08 mg would require all known imidazolines currently on the market to be placed in CR packaging. The assumptions underlying the use of safety factors are that by using these factors, both the public health and sensitive populations are protected. Further assumptions hold that humans are somewhere between 10 and 1,000 times more sensitive to some toxic agents than animals, and adults are less sensitive than children. Hence, a safety assessment can be conducted using the proper toxicological evaluation with different populations to establish the NOAEL (no observable adverse effect level) or its equivalent. We used a tenfold safety factor to divide the LOAEL to reach a NOAEL level.

The regulated dose level is expected reasonably to protect children under 5 years of age from serious personal injury or illness. The Commission proposed this level and received one comment on it, which we addressed in Section I of the preamble.

**V. Statutory Considerations**

*A. Hazard to Children*

As noted above, the toxicity data concerning children's oral ingestion of imidazolines demonstrate that they can cause serious illness and injury to children. Moreover, imidazolines are available to children in common household products, such as eye drops and nasal sprays. Products containing imidazolines currently do not use CR packaging. The Commission concludes that a regulation is needed to ensure that products subject to the regulation will be placed in CR packaging by any current, as well as new manufacturers.

Pursuant to Section 3(a) of the PPPA, 15 U.S.C. 1472(a), the Commission finds that the degree and nature of the hazard to children from handling, using, or ingesting imidazolines is such that special packaging is required to protect children from serious illness. The Commission bases this finding on the toxic nature of imidazolines and the accessibility of products containing imidazolines in the home.

*B. Technically Feasibility, Practicability, and Appropriateness*

In issuing a standard for special packaging under the PPPA, the Commission also is required to find the special packaging is "technically feasible, practicable and appropriate." 15 U.S.C. 1472 (a)(2). For special packaging to be technically feasible, the technology must be available, or can be readily developed and implemented 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. 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. All three of these conditions must be met before we can require special packaging for a product.

The definition of “packaging” 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.” The PPPA defines “special packaging” as packaging that is designed or constructed to be significantly difficult for children under 5 years of age to open or obtain a toxic or harmful amount of substance within a reasonable time and not difficult for normal adults to use properly. 15 U.S.C. 1471(4). The child-resistance and adult-use-effectiveness of special packaging are measured by performance, testing packaging with children and senior adults, respectively.

We evaluated packaging representative of OTC products that contain imidazolines. The specimens represent products from all four imidazoline families: naphazoline hydrochloride (HCL), oxymetazoline HCL, tetrahydrozoline HCL, xylometazoline, and a naphazoline HCL combination product. None of the samples used special packaging. The eye drops were packaged in squeeze-to-dispense plastic dropper bottles. The nasal spray was packaged in a plastic bottle with an attached metered-pump sprayer, and the nasal drops were packaged in a squeeze-to-dispense plastic dropper bottle. *See* January 11, 2012, Staff Briefing Package, for a more detailed discussion of the products:

<http://www.epsc.gov/library/foia/foia12/brief/imidazolines.pdf>.

With changes to package size and/or type, certain types of packaging, such as ASTM Type IA, ASTM Type ID, and a CR metered-pump sprayer design, are available to the market to replace the non-CR continuously threaded (NCRCT) and the non-CR (NCR) metered-spray pump packages. Product packaging assembly line techniques used for the NCR packages can be

adapted for some of the CR packages already in the marketplace. Other product manufacturers may use packages that could require changes in assembly- and filling-line techniques. New package sizes also may need to be designed. These new packages would require new tools to be produced. It could take up to 2 years from initiating tool design to final production of a new package, depending upon the complexity of the package. The Commission did not receive any comments asserting that CR packaging for products containing imidazolines was not technically feasible, practicable, or appropriate; although two comments addressed the amount of time required to develop, test, and produce CR packaging for products containing imidazolines. As will be discussed in further detail in Section VI, we have determined that a 12-month effective date, with an additional 12-month conditional stay of enforcement will provide sufficient time for manufacturers to produce CR packaging in compliance with this rule.

Based on the foregoing, the Commission concludes that available data support the findings that CR packaging for household products containing imidazolines is technically feasible, practicable, and appropriate.

*C. Other Considerations*

In establishing a special packaging standard under the PPPA, the Commission must consider the following:

1. reasonableness of the standard;
2. available scientific, medical, and engineering data concerning special packaging and childhood accidental ingestions, illness, and injury caused by household substances;
3. manufacturing practices of industries affected by the PPPA; and
4. nature and use of the household substance.

15 U.S.C. 1472(b). The Commission has considered these factors with respect to the various determinations made in this notice, and finds that the rule is reasonable and otherwise appropriate.

**VI. Effective Date**

The PPPA provides that no regulation shall take effect sooner than 180 days or later than 1 year from the date such final regulation is issued, except that, for good cause, the Commission may establish an earlier effective date if it determines an earlier date to be in the public interest.

15 U.S.C. 1471n.

The Commission stated in the preamble to the NPR that because it could take up to 1 year to produce a new package for some companies, any final rule would become effective 1 year after publication of the final rule in the Federal Register.

As discussed in section I.C. of this preamble, the Commission received comments indicating that more than 12 months would be necessary to design, develop, test, and manufacture CR packaging for many of the products containing imidazolines currently on the market. Two commenters indicated that a design could be modified, tested, and in commercial use in approximately 24 months. The Commission agrees that this time seems reasonable because companies will need to develop custom packaging, and the FDA must approve the packaging for acceptable sterilization and stability qualities.

Because there are more than 60 products manufactured by approximately 45 companies that will be affected by this rule, and because the vast majority of these companies will likely require more than 1 year to comply with this rule, the Commission has determined to grant a 12-month conditional stay of enforcement of the rule for products containing the equivalent of 0.08 milligrams of imidazolines in one package, rather than require each manufacturer to request a



stay of enforcement for each affected product. The Commission believes that it is important to establish accountability in meeting the CR requirements for products containing imidazolines within 24 months of the publication of this rule.

Therefore, the Commission sets the following conditions for the 1-year stay of enforcement. First, the manufacturer of an imidazoline product containing the equivalent of 0.08 milligrams of imidazolines or more must notify the Commission prior to the effective date of the final rule of its intent to avail itself of the stay, which notice shall include a detailed time line setting forth the steps necessary to produce CR packaging for its product(s) and the range of time anticipated for completion of each step. Manufacturers should be aware that submitting the required notice on or near the effective date of the rule may not allow Commission staff sufficient time to review their notice for completeness prior to the effective date of the rule. Second, each manufacturer providing notice of its intent to avail itself of the stay must submit quarterly reports to the Commission for each affected product, beginning on the effective date of the rule, and on or before the first day of each subsequent quarter during the one year stay period. The quarterly report must provide the following information: (a) proposed packaging specifications; (b) estimated initial production date; (c) progress made and/or steps completed during the quarterly reporting period; and (d) reports of any incidents or exposures involving the firm's imidazoline-containing products that are subject to the rule. If a manufacturer fails to provide the above-referenced notice in a timely fashion or timely submit any quarterly report, its imidazoline-containing products will be subject to enforcement of the CR packaging requirement set forth in this rule as of the effective date of the rule.

The rule would add a new paragraph 33 to 16 CFR § 1700.14(a), which contains a list of substances requiring special packaging. Pursuant to § 1700.14(a), all substances listed in §

1700.14 must meet the requirements for special packaging contained in § 1700.20(a) (on testing procedures for special packaging). Section 1700.14(a)(33) provides that any over-the-counter or prescription product containing the equivalent of 0.08 milligrams or more of an imidazoline (tetrahydrozoline, naphazoline, oxymetazoline, or xylometazoline) in a single package, must be packaged in accordance with the provisions of § 1700.15(a), (b), and (c). Section 1700.15(a) contains general requirements for special packaging, such as the special packaging must continue to function with the effectiveness specifications set forth in § 1700.15(b). Section 1700.15(b), pertaining to effectiveness specifications, provides criteria that special packaging tested pursuant to § 1700.20 must meet. Finally, § 1700.15(c) provides that special packaging subject to this paragraph (c) may not be reused.

#### **VII. Environmental Impact**

Generally, our regulations are considered to have little or no potential for affecting the human environment, and environmental assessments and impact statements are not usually required. *See* 16 CFR 1021.5(a). More specifically, requiring CR packaging for certain imidazoline-containing products is not expected to have an adverse impact on the environment. Accordingly, the rule falls within the categorical exclusion in 16 CFR 1021.5(b)(2) for product certification rules and an environmental assessment or environmental impact statement is not required.

#### **VIII. Executive Order 12988 (Preemption)**

According to Executive Order 12988 (February 5, 1996), agencies must state in clear language the preemptive effect, if any, of new regulations. Section 7 of the PPPA provides that, generally, when a special packaging standard issued under the PPPA is in effect, “no State or political subdivision thereof shall have any authority either to establish or continue in effect, with

respect to such household substance, any standard for special packaging (and any exemption therefrom and requirement related thereto) which is not identical to the [PPPA] standard.” 15 U.S.C. 1476(a). A state or local standard may be excepted from this preemptive effect if: (1) the state or local standard provides a higher degree of protection from the risk of injury or illness than the PPPA standard; and (2) the state or political subdivision applies to the Commission for an exemption from the PPPA’s preemption clause and the Commission grants the exemption through a process specified at 16 CFR part 1061. 15 U.S.C. 1476(c)(1). In addition, the federal government, or a state or local government, may establish and continue in effect a nonidentical special packaging requirement that provides a higher degree of protection than the PPPA requirement for a household substance for the federal, state, or local government’s own use. 15 U.S.C. 1476(b).

Thus, with the exceptions noted above, the rule regarding CR packaging for household products containing an imidazoline above the regulated level would preempt nonidentical state or local special packaging standards for such imidazoline-containing products.

#### **IX. Regulatory Flexibility Act (Economic Analysis)**

When an agency undertakes a rulemaking proceeding, the Regulatory Flexibility Act (RFA) generally requires that agencies review proposed rules for their potential economic impact on small entities, including small businesses. Section 603 of the RFA calls for agencies to prepare, and make available for public comment, an initial regulatory flexibility analysis describing the impact of the proposed rule on small entities and identifying impact-reducing alternatives. 5 U.S.C. 603. Section 605(b) of the RFA, however, states that this requirement does not apply if the head of the agency certifies that the rule, if promulgated, will not have a

significant economic impact on a substantial number of small entities and the agency provides an explanation for that conclusion.

Nasal and ophthalmic products are classified within the NAICS 325412 *Pharmaceutical Preparation Manufacturing* industry. According to the U.S. Small Business Administration's Office of Advocacy, a firm classified within NAICS 325412 is considered a small business if the firm has fewer than 750 employees. Based on such classification, out of the approximately 45 firms that manufacture imidazoline-based eye drops and nasal sprays, approximately 20 firms are defined as "small businesses." There may be more manufacturers, in particular, firms that manufacture under generic labels, which were not identified but that may be small businesses.

As noted in the NPR, the Commission's Directorate of Economic Analysis prepared a preliminary assessment of the impact of a rule to require special packaging for products containing imidazolines equivalent to 0.08 milligrams or more in a single package. Based on this assessment, the Commission concluded that the proposed requirement for products containing imidazolines, if finalized, would not have a significant impact on a substantial number of small businesses. The Commission requested additional information on the possible impact on small businesses, but we received no such comments. Moreover, the preliminary analysis demonstrated that the incremental costs of CR packaging for manufacturers are low, estimated at no more than a few cents per unit for imidazoline products, some of which costs manufacturers are likely to be able to pass on to consumers. The Commission concludes that the rule regarding CR packaging for certain imidazoline products would not have a significant economic impact on a substantial number of small entities.

**X. References**

Please see all citing references in staff’s briefing package for the proposed rule, available at: <http://www.cpsc.gov/library/foia/foia12/brief/imidazolines.pdf> and for the final rule, available at [FILL IN LINK].

**List of Subjects in 16 CFR Part 1700**

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

For the reasons given above, the Commission amends 16 CFR part 1700 to read as follows:

**PART 1700--[AMENDED]**

1. The authority citation for part 1700 continues to read as follows:

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

2. Section 1700.14 is amended by adding new paragraph (a)(33) to read as follows:

**§ 1700.14 Substances requiring special packaging.**

(a) \* \* \* \* \*

(33) *Imidazolines*. Any over-the-counter or prescription product containing the equivalent of 0.08 milligrams or more of an imidazoline (tetrahydrozoline, naphazoline, oxymetazoline, or xylometazoline) in a single package, must be packaged in accordance with the provisions of § 1700.15(a), (b), and (c).

Dated: \_\_\_\_\_

\_\_\_\_\_  
Todd A. Stevenson,  
Secretary, Consumer Product Safety Commission



## **Staff Briefing Package**

Poison Prevention Packaging Act: Imidazoline Products  
Containing 0.08 mg or More per Package  
November 7, 2012

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## Executive Summary

The Poison Prevention Packaging Act (PPPA) was established to protect children from serious personal injury or illness resulting from handling, using, or ingesting hazardous household substances by requiring child-resistant (CR) packaging of these substances. Imidazolines are a class of drugs used as decongestants in nasal and eye products. Topical and nasal administration of imidazolines results in little absorption into the general circulation system of the human body. However, if they are ingested orally, imidazolines are absorbed into the general circulation system, leading to systemic effects. Even though death from ingesting imidazolines is rare, ingestion can result in severe life-threatening consequences, such as central nervous system (CNS) depression and adverse cardiovascular effects. CNS depression symptoms following ingestion of imidazolines range in severity from drowsiness to coma, with a concurrent depression of the respiratory system. Prominent cardiovascular effects in response to an overdose of imidazolines include low blood pressure and slowed heart rate. The medical literature and evidence from collected samples demonstrate that despite the danger of children ingesting imidazolines, these products are not manufactured in CR packaging.

On January 25, 2012, the U.S. Consumer Product Safety Commission (CPSC, the Commission) published a notice of proposed rulemaking (NPR) to require CR packaging, for any over-the-counter (OTC) or prescription drug product containing the equivalent of 0.08 milligrams or more of an imidazoline (such as tetrahydrozoline, naphazoline, oxymetazoline, or xylometazoline) in a single package. A copy of the NPR is online at: <http://www.cpsc.gov/businfo/frnotices/fr12/imidazolines.pdf>.

The Commission received five comments with none opposing the proposed rule. Several commenters requested more time to package their products in CR packaging. Two comments requested a stay of enforcement 12 months beyond the proposed 1-year effective date of a final rule. Another commenter requested that a metered nasal spray with a crimped-on cap be exempted from PPPA child testing because the commenter believes it is inherently child resistant. Staff addresses these and other comments in the briefing package.

Staff previously provided in the NPR (link provided above), evidence that imidazoline products cause serious personal injury or illness to children younger than 5 years old, due to the serious effects on the heart and breathing rates occurring with the ingestion of very small amounts of this class of drugs. Imidazoline products currently are not in CR packaging. However, the data support the conclusion that a special packaging standard for imidazoline prescription and OTC products is technically feasible (producible), practicable (adaptable to mass production techniques), and appropriate (compatible with the substances in the package). Staff analysis indicates that the rule will not have a significant economic effect on a substantial number of small businesses and will not have a significant impact on the environment.

Staff recommends that the Commission issue a final rule requiring CR packaging for OTC and prescription products that contain the equivalent of 0.08 milligrams or more of an imidazoline in a single package. Staff recommends an effective date of 1 year after the issuance of a final rule, with the opportunity for manufacturers to qualify for a 1-year conditional stay of enforcement due to the current lack of appropriate CR packages on the market and the need for manufacturers to design and develop new CR packages.

# Briefing Memo

This document has been electronically  
approved and signed.

Date: November 7, 2012

TO : The Commission  
Todd A. Stevenson, Secretary

THROUGH: Mary T. Boyle, Acting General Counsel  
Kenneth R. Hinson, Executive Director

FROM : DeWane Ray, Assistant Executive Director, Office of Hazard  
Identification and Reduction  
Cheryl Osterhout, Ph.D., Pharmacologist, Directorate for Health  
Sciences

SUBJECT : Child-Resistant Packaging of Products that Contain Imidazolines

## I. INTRODUCTION

Imidazolines (such as tetrahydrozoline, naphazoline, oxymetazoline, and xylometazoline) comprise a class of drugs that are used as decongestants in eye and nasal products. Imidazolines are effective as decongestants because they produce vasoconstriction when applied topically to the small blood vessels in the eye and the nasal mucosa. When applied to the eye or the nose, only a small amount of the drug is absorbed into the body's general circulation system due to the intense vasoconstriction at the area of application. However, if orally ingested, imidazolines are absorbed into the general circulation system and lead to systemic effects.

The therapeutically effective dose of imidazoline occurs within a narrow range, with toxic effects occurring at doses close to, or at, therapeutic levels. For infants, central nervous system (CNS) depression (ranging from drowsiness to deep sedation) may occur after receiving recommended doses. Upon ingestion of imidazolines, in general, CNS depression symptoms, with a concurrent depression of the respiratory system, can occur within minutes. Prominent cardiovascular effects in response to an overdose of imidazolines include rebound low blood pressure<sup>1</sup> and slowed heart rate. Other systemic effects in response to imidazoline overdoses include blanching (temporary whitening of the skin), sweating, nausea, gastric irritation, weakness, and high blood sugar (POISINDEX 2012<sup>®</sup>).

On January 25, 2012, the U.S. Consumer Product Safety Commission (CPSC, Commission) issued a notice of proposed rulemaking (NPR) to require child-resistant (CR) packaging for prescription and over-the-counter (OTC) products containing the equivalent of 0.08 milligrams (mg) or more of an imidazoline (77 FR 3646, <http://www.cpsc.gov/businfo/frnotices/fr12/imidazolines.pdf>). The comment period ended on April 9, 2012.

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<sup>1</sup> Rebound low blood pressure is a blood pressure decrease in response to an initial increase in blood pressure.

This briefing package includes: (1) CPSC staff's responses to comments on the NPR; (2) updates to the toxicology, economic, and epidemiology imidazoline staff memoranda that were provided in staff's NPR briefing package; and (3) Office of Compliance and Field Operations staff's memo comparing several options to address comments regarding the necessity of additional time to develop CR packaging.

## II. DISCUSSION

### A. Staff's Response To Comments

As noted above, the Commission published an NPR on January 25, 2012, proposing to require CR packaging for OTC and prescription products that contain 0.08 mg or more imidazolines per package (77 FR 3646). The Commission received five comments. A summary of those comments and the staff's responses is provided below.

#### *Lowest Adverse Event Level*

Comment: One commenter asks for clarification regarding the use of the term lowest adverse event level (LOAEL) in the text found on page 3651 of Section IV Level for Regulation of the proposed rule (77 FR 3646). The NPR states: "We used a tenfold safety factor to divide the LOEL to reach a NOEL level."

Response: This was a typographical error and "LOAEL" should have been used in this sentence.

#### *The Proposed Regulated Level*

Comment: The same commenter asks about the derivation of the proposed regulated level (0.08 mg or more) of imidazoline that staff calculated (from the same section referred to above). The commenter asks whether the LOAEL (*i.e.*, 0.75 mg) should first be normalized into mg/kg,<sup>2</sup> and then extrapolated to a 25-pound (11.4 kg) child before applying a tenfold safety factor. Using the commenter's approach, and assuming a body weight of 4.8 kg, the calculated no observed adverse effect level (NOAEL) for imidazolines would be 0.18 mg.

Response: The proposed regulated level (0.08 mg or more of imidazoline) was based on an actual imidazoline ingestion case with a safety factor applied to the dose ingested. Notably, ingestions expressed, as normalized doses in the staff briefing package show that adverse effects occurred at levels within about the same range of imidazoline (0.1–0.3 mg/kg).<sup>3</sup> Moreover, another case in the medical literature

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<sup>2</sup> Milligram per kilogram.

<sup>3</sup> See Table 3 (pg 7) and Table 5 (pp 34-35) in:  
<http://www.cpsc.gov/LIBRARY/FOIA/FOIA12/brief/imidazolines.pdf>.

documents an adolescent who developed persistent cardiovascular and neurological effects after an estimated ingestion of approximately 0.07 to 0.1 mg/kg of tetrahydrozoline, which is also consistent with the proposed imidazoline level e.g., 0.07 mg/kg (lower end of range) x 11.4 kg child = ~ 0.8 mg ÷ 10 fold-safety factor = 0.08 mg.<sup>4</sup>

### *The Effective Date and Sufficient Time for Implementation of the Rule*

Two commenters raised concerns about the proposed 1-year effective date and noted that additional time would be necessary to comply with a CR packaging rule.

Comment: One commenter who manufactures sterile eye drops that require “specialized aseptic processing,” including sterile packaging processes states: that (1) “controls to ensure product sterility, safety and efficacy must be qualified and implemented with any significant primary package change” before full-scale implementation is possible; and (2) “proven” CR packages—those with the necessary form factor and closure finish—are not “a standard technology available at this time” within the ophthalmic packaging industry. The commenter requests a 24-month implementation period, “given the additional requirements associated with package formats for sterile products.”

Response: In order to assess whether additional time is indeed needed for implementation, CPSC staff needs a timeline for the development of the CR packages. This commenter did not provide such a timeline. However, the next commenter did submit a timeline, and we address the issue more fully in response to that comment.

In regard to the specialized aseptic processes for sterile packages, sources contacted by CPSC staff indicate that this work should take less than 6 months, if a similar sterile process is already in place. If new equipment must be installed to implement the controls to ensure product sterility, this time increases to as much as 6 to 12 months. Therefore, CPSC staff agrees that additional time is needed to set up a *new* sterile process. However, if a sterile process is already in place (for example with the non-CR package) the changeover to a new package should not require as much time.

Comment: A national trade association representing leading manufacturers of OTC medicines requests that: (1) the Commission consider a 1-year stay of enforcement in addition to the 1-year effective date proposed in the NPR to allow manufacturers to comply starting 2 years after publication of the rule; and (2) manufacturers be granted extended stays of enforcement on a case-by-case basis, if necessary. Regarding nasal

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<sup>4</sup> Spiller, H. and Griffith, J. Prolonged Cardiovascular Effects after Unintentional Ingestion of Tetrahydrozoline. Clin. Toxicol. 46(2):171–2.

products, the commenter argues that additional time is required because it will probably be necessary to replace the commonly used single-piece cap with two-component CR protection caps. The commenter also notes that most ophthalmic finishes<sup>5</sup> are 13mm–15mm, and there are no CR closures available smaller than 18mm; therefore, new CR packages also will be required for ophthalmic products. The commenter further states that additional time (6–12 months) beyond the 2 years may be required by some manufacturers, especially if the products in question are subject to U.S. Food and Drug Administration (FDA) requirements for new drug applications (NDAs) or abbreviated new drug applications (ANDAs) (step #7 in Fig. 1, below). To support its request, the commenter provides the following timeline summarizing the steps required to develop and implement CR packaging for imidazoline-containing products:

1. Design development – 2 to 4 months
2. Prototype tooling – 4 to 6 months
3. CR protocol testing – approximately 3 months (depending on CR testing facility capacity)
  - o If CR protocol fails, return to step 1
4. Industrial scale up for packaging and validation – 7 to 11 months
5. Adoption filling line and validation – 3 to 6 months (depending on complexity)
6. Stability testing – 3 to 12 months (if necessary)
7. Regulatory filings – 6 to 12 months (if necessary)

Figure 1: Proposed rule compliance timeline included with comment.

Response: As discussed in the Laboratory Sciences (LS) memorandum (Appendix D), staff agrees that nasal products' caps and the nozzle attachment to the container must be CR, and new CR packaging will be required to maintain 13mm–15mm closures on ophthalmic packages, if manufacturers choose not to use existing designs. Staff reviewed each step of the commenter's timeline (Fig. 1) to assess its validity. Although there are some steps that can be performed concurrently, the commenter estimates the time to develop, manufacture, test, pass FDA regulations, and implement production of their products in CR packaging to be between 28 and 54 months. The staff discusses the steps of the commenter's timeline below.

**1. Design Development and 2. Prototype Tooling.** CPSC staff believes the design and prototype tool fabrication timing given in Figure 1 are typical for modern computer-assisted design processes. Staff is aware of new, purportedly CR designs developed since the NPR was published that could be used for imidazoline packages. There is a patented design that requires the consumer to line up the arrows on the cap and then squeeze the arrows and pull the cap off to open. There

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<sup>5</sup> The word "finish," in this sense, refers to the protruding threads on the bottle's opening, which holds the cap or closure. A container and its corresponding closure must have matching finishes.

are also several similar non-patented designs that can be adapted to produce different size packages for eye and nasal drops that have not been CR tested yet. If these designs were bought or licensed by manufacturers, the timing for the design-development stage could be reduced to 1 month or less. However, longer times could be required if the engineering and tooling firms are busy, and therefore, are not 100 percent dedicated to a given project. The package sterilization process (discussed in the previous comment) is distinct from the mold tooling fabrication process. Industry sources contacted by CPSC staff estimate 4 to 5 months typically for mold tool production, plus an additional month for qualification (production tests to ensure that the tool can be used at the intended production rate). This corroborates the 4 to 6 months reported by the commenter.

3. **CR protocol testing** of both children and seniors requires a minimum of 6 weeks, although 2–4 months is a typical timeframe and depends on the complexity of the CR system, according to third party CR protocol test providers. If the package fails CR protocol tests, the next design and prototype tooling iteration will take considerably less time than the original, typically about 1 month per additional iteration. The CR protocol testing may take longer than the 2–3 months the commenter estimates.
4. **Industrial scale-up for packaging and validation.** Existing filling and capping equipment on a sterile production line probably would not have to be replaced. This assumes manufacturers will produce similar size and shape products to capitalize on existing brand recognition. However, the capping equipment could require significant modifications, depending on the design of the CR closure. Sources contacted by CPSC staff indicate that this work should take less than 6 months if a similar sterile process is already in place. If new equipment must be installed, this time increases to 6 to 12 months.
5. **Adoption of new filling line and validation of the line** can take 3–6 months, according to manufacturers who made previous stay of enforcement requests for similar reasons. Therefore, staff agrees with the estimate of 3–6 months to adopt a new filling line.
6. **Stability Testing.** The FDA Stability Test Guidelines refer to two timeframes for stability testing: the first is a regular timeframe of 1 year, and the second is an accelerated test method performed over 6 months. The accelerated test method is also referred to as “stress testing.” The accelerated testing conditions are at least 15 °C higher than the long-term study conditions and are intended to increase the rate at which degradation reactions take place, thus revealing quality changes at an early stage. Staff agrees with the estimate of 3–12 months for stability testing.



**7. Regulatory filings.** The commenter estimates 6–12 months for the FDA review process of a new drug application (NDA) or an abbreviated new drug application (ANDA). The FDA Center for Drug Evaluation user-fee reports for 2011<sup>6</sup> indicate that 10 months was the median review time for NDAs. To file an ANDA, permission must be obtained first. This requires an ANDA petition process that can take up to 6 months. Once the ruling is received, the ANDA may be filed. In general, ANDAs do not take as long to review in the FDA system as NDAs do. This analysis does not include the time it takes for manufacturers to prepare the submissions. CPSC staff concurs with the estimate of 6–12 months for FDA filings.

In summary, staff agrees that the information provided by the commenter supports the need for a longer timeframe of 2 years (1 year effective date plus a conditional stay of 1 year) to comply with the new regulations.

#### *Particular Types of Packaging*

Comment: One commenter is seeking clarification on the test value threshold for a metered nasal sprayer with a crimped seal and detachable nozzle for a child testing protocol and also proposes a different approach to calculate the test value threshold.

Response: Staff appreciates the commenter’s concern about submitting its nasal sprayer into child testing expeditiously. Staff has recommended proceeding with the 0.08 mg or more imidazoline level, as stated in response a previous comment. If the Commission finalizes the rule, staff encourages the commenter to discuss its other concerns with staff.

Comment: One commenter requests that its metered nasal package be exempt from child testing because it is inherently child resistant due to the crimped metal seal.

Response: As discussed in the LS memorandum (Tab D), staff disagrees with the commenter’s fundamental premise that unit-dose packages are inherently child resistant. A CPSC staff study (Wilbur and Barone, 1998) showed that unit-dose packages are not inherently CR.<sup>7</sup> A child can access the contents because neither the pumping action, nor the overcap or nozzle attachments are CR; therefore, the package is not inherently CR. It is reasonably foreseeable that a child could access more than the regulated quantity of the contents. Staff is aware of two designs of CR metered pumps being developed and patented, however it is not known when they will be available.

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<sup>6</sup> <http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/PDUFA/default.htm>.

<sup>7</sup> Wilbur, C. J., Barone, S., “[Is Unit Dose Packaging Inherently Child-Resistant?](#)” U.S. CPSC, Directorate for Epidemiology and Health Sciences, April 1998.

## B. Updated Data

### 1. Toxicology Literature

The briefing package for the NPR reviewed the toxicity of imidazolines.<sup>8</sup> One additional scientific paper<sup>9</sup>, identified since publication of the NPR, included three case reports of tetrahydrozoline overdose in young children. Some pharmacokinetic data were included in the assessment of these children. The first involved a 2-year-old/13.2 kg child who could not be aroused after his afternoon nap. He presented at the emergency room (ER) with hypothermia, slowed heart rate, and had a Cheyne-Stokes<sup>10</sup> respiratory pattern. A drug screen was positive for tetrahydrozoline, which correlated with an empty bottle found in the home. The second case also involved a 2-year-old child weighing 11.4 kg, who was found chewing on a bottle of 0.05% tetrahydrozoline eye drops. An estimated dose of 0.33 mg/kg was calculated based upon what was missing from the bottle. She became lethargic and bradycardic (slowed heart rate) with gasping respirations 90 minutes after ingestion. Urinalysis was positive for tetrahydrozoline. The third case involved a 20-month-old found with an empty bottle of tetrahydrozoline eye drops (0.05%). The calculated dose ingested was 0.3 mg/kg because the bottle had been half full. Within 15 minutes, the child became tired, and by 1 hour, he could not be aroused. On arrival to the ER, the child had a slowed heart rate, was hypertensive (high blood pressure) with gasping respirations, and had constricted pupils. A urine drug screen was positive for imidazolines. Due to CNS depression, the child was intubated for 24 hours. The pharmacologic half-life or  $t_{1/2}$  (time of drug concentration to decrease by half) of tetrahydrozoline was calculated by the authors to be 4.4 hours with the help of two blood plasma levels measured in case number one.

### 2. NEISS

Since publication of the NPR, the staff completed two In-Depth Investigations (IDIs) in response to incidents received through the National Electronic Injury Surveillance System (NEISS) maintained by the CPSC.

The first incident involved a 23-month-old child who was found playing with a bottle of eye drops she found in her grandmother's handbag. The child opened the container and possibly ingested some, as she was biting at the end of the opening. The child told her mother "it was all gone"; it is not known whether the child ingested any of the eye drops or none at all. She was taken to the emergency room, examined, and released (Case # 100324HEP9017).

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<sup>8</sup> <http://www.cpsc.gov/library/foia/foia12/brief/imidazolines.pdf> (Tab A).

<sup>9</sup> JA Lowry and U Garg. (2011) Serum concentrations in three children with unintentional tetrahydrozoline overdose. *Clinical Toxicology*. 49:434-435.

<sup>10</sup> Deep and rapid breaths followed by shallow slow breaths, or a period of no breathing; often seen at the end of life.

The second incident involved a 2-year-old child who found a bottle of eye drops after bedtime that her sister left on her dresser. The child's father found the 2-year-old with the empty bottle and her nightgown and sheets were wet. She said she drank some of the eye drops. The child was brought to the emergency room where she was examined and released (Case # 100324HEP9001).

### 3. Updated Epidemiology Data

The NPR briefing package presented incident data from the Children and Poisoning (CAP) System (a subset of the National Electronic Injury Surveillance System (NEISS)) for incidents between January 1997 and December 2009, involving household products that typically contain imidazolines<sup>11</sup>. The Directorate for Epidemiology provides a memo that updates injury data related to incidents of imidazoline ingestion by children younger than 5 years old from the CAP system at Tab D of this package. Searches using CAP reveal that young children are being exposed to, and injured by, household products containing imidazolines. The majority of injuries are associated with eye drops. For the 13 years between 1997 and 2011, an estimated 6,650 injuries to children under 5 years old treated in U.S. hospital emergency rooms were associated with these products, based on CAP data.

### 4. Final Regulatory Flexibility Act Analysis

In connection with the NPR, the Directorate for Economic Analysis analyzed the potential impact that a proposed special packaging standard for imidazolines could have on small entities. Based on that analysis, in the NPR the Commission preliminarily concluded that the proposed rule would not have a significant economic impact on a substantial number of small entities. Likewise, Economics staff determines that the final rule will not have a significant impact on a substantial number of small businesses (Tab B).

### 5. Technical Feasibility, Practicability, and Appropriateness

At Tab C, the Directorate for Laboratory Sciences states that data exist to support a Commission finding that special packaging for imidazolines is technically feasible (capable of being produced), practicable (lends itself to mass production techniques), and appropriate (compatible with the substances in the package). Staff is aware of two designs of CR metered pumps being developed for production, as well as new CR designs for ophthalmic and nasal spray packages that are available.

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<sup>11</sup> <http://www.cpsc.gov/library/foia/foia12/brief/imidazolines.pdf> (Tab B)

### III. Effective Date

The PPPA provides that no regulation shall take effect sooner than 180 days or later than 1 year from the date such regulation is issued, unless the Commission determines that an earlier effective date is in the public interest. For imidazolines, staff recommends an effective date of 1 year after the issuance of a final rule, with the opportunity for manufacturers to qualify for a conditional 1 year stay of enforcement due to the current lack of appropriate CR packages on the market and the need for manufacturers to design and develop new CR packages. The conditional stay would allow manufacturers an additional year to comply with the rule. In order to do so, the manufacturer of an imidazoline product must notify the Commission prior to the effective date of the final rule to avail itself of the stay, which notice shall include a detailed time line setting forth the steps necessary to produce CR package for its product(s) and the range of time anticipated for completion of each step. Manufacturers should be aware that submitting the required notice on or near the effective date of the rule may not allow Commission staff sufficient time to review their notice for completeness prior to the effective date of the rule. Manufacturers are then required to follow up with quarterly reports on the progress toward producing special packaging for imidazoline products subject to the rule. Staff recommends this approach because it provides incentive for manufacturers to bring their products into compliance within a reasonable time frame. It also allows for compliance oversight over manufacturers progress, while preserving staff resources that would otherwise be needed to review, evaluate and respond to individual stays of enforcement.

While the companies have known about this potential regulation for some time now, it is not clear how many will need a stay of 1 year after the 1 year effective date. There are about 45 manufacturers producing imidazoline products, as estimated by CPSC Directorate for Economic Analysis staff. Because the commenters have demonstrated a legitimate need for the 1 year stay of enforcement, staff recommends that the CR packaging requirements in the final rule not be enforced for 1 year after the effective date against any manufacturer that submits notice of intent to avail itself of the stay of enforcement and follows up with reports detailing its progress in bringing its products into compliance with the rule. More details on this process are in the Office of Compliance memo at Tab E.

#### 2. Stay of Enforcement

Several approaches exist for crafting a 1 year stay of enforcement.

The Commission could provide a blanket stay of enforcement for 1 year. This would require very little staff time, and few, if any, resources because any manufacturer of imidazoline-containing products subject to the rule would automatically be granted a 1 year stay of enforcement without the need to submit any information or documentation to the Office of Compliance. The downside of this approach is that granting a blanket stay will preclude any compliance oversight of a manufacturers' progress in developing CR packaging for its imidazoline containing products.

Alternatively, the Commission could require that manufacturers who need more time to comply, individually request temporary stays of enforcement, then provide quarterly progress reports on design, development, testing, and production of the required CR packaging. This certainly would require more staff time than a blanket stay. Based on the information available, it is likely that many manufacturers would request a stay of enforcement under this option. Staff would be required to review, analyze, and evaluate thoroughly the submissions from each manufacturer to determine if the stay should be granted. This option requires the greatest compliance oversight. It requires the review and approval of the stay of enforcement requests, as well as the review of the quarterly updates from manufacturers.

The staff recommends, and the draft final rule provides, a one year conditional stay of enforcement that would be granted to any manufacturer of an imidazoline product containing the equivalent of 0.08 milligrams of imidazoline or more who notifies the Commission of its intent to avail itself of the conditional stay prior to the effective date and who meets certain conditions for the stay. The manufacturer shall include with this notice of intent a detailed time line setting forth the steps necessary to produce CR packaging for its product(s) and the range of time anticipated for completion of each step. Manufacturers should be aware that submitting the required notice on or near the effective date of the rule may not allow Commission staff sufficient time to review their notice for completeness prior to the effective date of the rule. The manufacturer shall then provide quarterly reports, updating its progress toward producing special packaging for imidazoline-containing products that are subject to the rule. This option provides an incentive for manufacturers to bring their products into compliance within a reasonable timeframe and ensures, through staff's review, that manufacturers are undertaking the process efficiently and are demonstrating a good faith effort to meet the compliance deadline. It will also provide feedback to staff regarding the commercial availability of the packaging for the products and any problems encountered during the process. Finally, it will preserve the considerable staff resources that would be expended to review, evaluate, and respond to the numerous requests for stays of enforcement, which staff anticipates manufacturers would file.

#### **IV. Options**

Option 1: Issue the Imidazoline FR as drafted with a 1 year effective date and a conditional stay of enforcement for 1 year.

Option 2: The Commission may decline to issue the rule as drafted with the conditional stay.

Option 3: The Commission may handle the stay of enforcement in a different manner than the conditional stay as discussed in section III (2) above.

#### **IV. Recommendation**

Based on available information, staff recommends that the Commission issue a final rule requiring CR packaging for over-the-counter and prescription products containing 0.08 mg or more imidazolines per package, with a 1 year effective date. Staff also recommends that the Commission grant a 1 year conditional stay of enforcement to any firm that provides the Office of Compliance with notice of its intent to avail itself of the 1 year stay, with the requirement that such firms submit quarterly reports providing specified information on the progress being made in the design, development, testing, and production of the required CR packaging.

**TAB A: Public Submissions Products Containing  
Imidazolines Equivalent to 0.08 Milligrams or More. CPSC-  
2012-0005. Comments Due: April 9, 2012**

**T  
A  
B  
A**

# PUBLIC SUBMISSION

As of: April 10, 2012
Received: April 09, 2012
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Posted: April 09, 2012
Category: Manufacturer
Tracking No. 80feb884
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Submission Type: Web

Docket: CPSC-2012-0005  
Products Containing Imidazolines Equivalent to 0.08 Milligrams or More

Comment On: CPSC-2012-0005-0003  
Products Containing Imidazolines Equivalent to 0.08 Milligrams or More

Document: CPSC-2012-0005-0004  
Comment from Dwain Sparks

---

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Organization: Eli Lilly and Company

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## General Comment

Please see attached Word File. Thank you.

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## Attachments

CPSC-2012-0005 Comments.040912



Products Containing Imidazolines Equivalent to 0.08 Milligrams or More  
CPSC Docket No. CPSC-2012-0005

Thank you for the diligence and thoroughness with which CPSC Toxicologists and Pharmacologists have reviewed this data and for the opportunity to provide comments. We would like to ask for two clarifications about terminology and translation of the LOAEL described in this Docket as they apply to the establishment of child resistant packaging for oral prescription drug products.

1. Our first request for clarification concerns text found on page 3651 of Section IV. *Level for Regulation* of the proposed rule. We understand the use of LOAEL and the recommended regulated level of 0.08 mg (which derives from application of a safety factor of 10 to the LOAEL). However, the change to LOEL and use of NOEL in the last sentence of this section is not clear. Do NOEL and LOEL signify an alternate assessment method or should these terms be LOAEL and NOAEL? Is our edited text below consistent with the intent of the CPSC?

Excerpt from Page 3651 with clarification:

"Because serious effects on the heart and breathing rates occur with the ingestion of as little as 0.75 mg of tetrahydrozoline, we consider this the lowest observed adverse effect level ("LOAEL"). All of the imidazolines cause potent central and peripheral sympathetic effects, but tetrahydrozoline has the highest potency for CNS sedative/depressive effects and the lowest potency for cardiac effects. Oxymetazoline and naphazoline are the most potent imidazolines for peripheral cardiac effects and have an 8-10 times lower maximum daily dose than tetrahydrozoline (0.4 mg, 0.3 mg and 3.2 mg, respectively). Xylometazoline and oxymetazoline have a longer duration of action than tetrahydrozoline (12 hrs, 10 hrs, and 4-6 hrs, respectively).

"Applying a safety factor of 10 to the LOAEL to derive a recommended regulated level of 0.08 mg for all imidazolines is appropriate in order to protect children from serious health effects following ingestion of this family of drugs. The level of 0.08 mg would require all known imidazolines (see Tables 1 and 2) currently on the market to be placed in CR packaging. (The assumptions underlying the use of safety factors are that by using these factors, both the public health and sensitive populations are protected. Further assumptions hold that humans are somewhere between 10 and 1,000 times more sensitive to some toxic agents than animals, and adults are less sensitive than children. Hence, a safety assessment can be conducted using the proper toxicological evaluation with different populations to establish the NOAEL (no observable adverse effect level) or its equivalent. In the present case of tetrahydrozoline, we used a tenfold safety factor to divide the LOAEL (0.75 mg) in children to reach a NOAEL level of 0.08 mg.)"

2. Our second request for clarification involves the determination of the amount of a substance that may produce serious personal injury or serious illness as described in 16 CFR 1700. That is, a point of departure for derivation of the NOAEL appears to be the total dose administered to an accidentally exposed newborn (i.e., the LOAEL from a case study). Please clarify whether the total dose should first be normalized for an infant's body weight and then extrapolated for a 25-pound (11.4-kg) child (16 CFR 1700.20). For example, the EPA Child-Specific Exposure Factors Handbook (2009) indicates that an infant 0- to <1-month old weighs 4.8 kg. Therefore, normalizing the reported exposure for the infant's body weight would mean a LOAEL of 0.16, mg/kg (i.e., 0.75 mg/4.8 kg). Applying a ten-fold safety factor to the LOAEL would then result in a NOAEL of 0.18 mg for an 11.4-kg child."

To contact us about these points, please call Dwain L Sparks (317-276-5597), Lorrene Buckley, PhD (317-277-7324), or Courtney Callis (317-277-5067). We appreciate your time reviewing and responding to our comments.

Sincerely,

Dwain L Sparks  
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Eli Lilly and Company  
dlsparks@lilly.com  
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# PUBLIC SUBMISSION

<b>As of:</b> April 10, 2012
<b>Received:</b> April 09, 2012
<b>Status:</b> Posted
<b>Posted:</b> April 09, 2012
<b>Category:</b> Trade Association
<b>Tracking No.</b> 80feb890
<b>Comments Due:</b> April 09, 2012
<b>Submission Type:</b> Web

**Docket:** CPSC-2012-0005

Products Containing Imidazolines Equivalent to 0.08 Milligrams or More

**Comment On:** CPSC-2012-0005-0003

Products Containing Imidazolines Equivalent to 0.08 Milligrams or More

**Document:** CPSC-2012-0005-0005

Comment from Alison Manhoff

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## Submitter Information

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**Organization:** Consumer Healthcare Products Association

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## General Comment

Please see attached comments from the Consumer Healthcare Products Association

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## Attachments

CHPA CPSC Final Imidazoline Comments 4.9.12



*founded 1881*

April 9, 2012

Office of the Secretary  
Consumer Product Safety Commission  
4330 East West Highway, Room 802  
Bethesda, MD 20814

**Submitted electronically via [www.regulations.gov](http://www.regulations.gov)**

Re: Docket No. CPSC-2012-0005: *Products Containing Imidazolines Equivalent to 0.08 Milligrams or More*

Dear Mr. Stevenson:

The Consumer Healthcare Products Association ("CHPA") appreciates the opportunity to provide comments on the Consumer Product Safety Commission's ("CPSC" or "Commission") proposed rule, "Products Containing Imidazolines Equivalent to 0.08 Milligrams or More," published in the Federal Register on January 25, 2012. The proposed rule will require child-resistant ("CR") packaging for over-the-counter and prescription products containing the equivalent of 0.08 milligrams or more of an imidazoline (includes tetrahydrozoline, naphazoline, oxymetazoline, and xylometazoline drug classes). The CPSC, consistent with statutory requirements of the Poison Prevention Packaging Act ("PPPA"), has proposed that such a rule become effective one (1) year after the publication of a final rule.

Founded in 1881, CHPA is a national trade association representing leading manufacturers of over-the-counter ("OTC"), non-prescription medicines and dietary supplements. A number of CHPA member companies manufacture nasal congestion and/or ophthalmic products that would be affected by this proposed rule. Together, CHPA members manufacture more than forty (40) affected products. These OTC medicines provide consumers with important relief from symptoms such as nasal congestion and itchy and red eyes due to allergies or other irritants. Consumers rely on these medicines and depend on the ability to purchase them OTC.

As described in more detail below, based on discussions with member company experts and a global supplier of packaging for these types of medicines, CHPA has concluded it is not feasible for manufacturers to comply with the proposed one (1) year effective date. At a minimum, manufacturers will require approximately two (2) years to implement

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the packaging changes. Accordingly, in order to ensure continued consumer access to these important medicines, we respectfully request the Commission issue a one (1) year stay of enforcement after the effective date of the final rule (therefore providing at least two (2) years after the publication of the final rule for manufacturers to comply). In addition, we ask the Commission to grant extended stays of enforcement for manufacturers with special circumstances requiring additional time. CPSC has a history of recognizing that unique circumstances may require additional time as the Commission explicitly noted that companies could request a stay of enforcement in the preamble to the final rule on minoxidil CR packaging. *See* 62 Fed. Reg. 63602, at 63606-7 (Nov. 16, 1998).

### **One (1) Year is Not Sufficient Time to Design, Develop, Test, and Manufacture New CR Packaging for Applicable Products**

The statutory requirement for new CR packaging rules to be effective within one (1) year after publication of a final rule does not allow manufacturers sufficient time to design, develop, test, and manufacture new product packaging for the affected products. Due to the unique qualities of the imidazoline-containing nasal and ophthalmic OTC medicines and their packaging, manufacturers will require additional time to implement CR packaging.

There are no "off-the-shelf" or "stock" CR packaging solutions currently available and therefore significant package development work and associated stability and manufacturing qualifications are needed. While CR screw closure technologies are available, given the range of bottle designs and thread sizes associated with nasal and ophthalmic products, custom solutions will need to be developed. For example, with nasal products, existing packaging involves one-piece protection caps whereas a CR feature would most likely require at least two different components (and potentially introduce a new material). As another example, for ophthalmic products, CR bands are not currently available in sizes less than 18mm and most ophthalmic bottle neck finishes are 13-15mm and will require smaller bands. Such adaptations may adversely impact the CR and senior-friendly features of the packaging so additional testing and/or design development will likely be required.

Further, the Food and Drug Administration ("FDA"), which regulates the drug products impacted by the proposed rule, classifies nasal sprays and ophthalmic products as having a "high degree of concern associated with the route of administration" and a "high likelihood of packaging component-dosage form interaction."<sup>1</sup> Consequently, any proposed changes to the container-closure system may require specific considerations and significant qualification activities to ensure that the packaging remains "suitable" from the perspectives of protection (e.g., light, solvent loss, microbial ingress), compatibility (e.g., sterilization process, absorption,

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<sup>1</sup>FDA Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics (May 1999), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070551.pdf>.

stability), and safety (e.g., USP biological reactivity, extractables/leachables). Specifically, sterilization techniques, required for ophthalmic products, can affect the integrity of packaging components. Multiple iterations of testing are typically required to determine package functionality and acceptability following the sterilization process, extending the development timeline.

### **CPSC Should Issue a One (1) Year Stay of Enforcement After the Effective Date of the Final Rule**

As noted above, based on discussions with member company experts and packaging industry authorities, we have concluded manufacturers will require a minimum of approximately two (2) years to implement the packaging changes for the relevant products. Accordingly, CHPA requests CPSC issue a blanket one (1) year stay of enforcement therefore providing at least two (2) years after the publication of the final rule for manufacturers to comply with the requirement.

Recognizing that timelines will vary based on individual product requirements, the following is a high-level summary of the anticipated steps involved in implementation of CR packaging for these nasal and ophthalmic product classes:

- 
1. Design development – 2 to 4 months
  2. Prototype tooling – 4 to 6 months
  3. CR protocol testing – approximately 3 months (depending on CR testing facility capacity)
    - o If CR protocol fails, return to step 1
  4. Industrial scale up for packaging and validation – 7 to 11 months
  5. Adoption filling line and validation – 3 to 6 months (depending on complexity)
  6. Stability testing – 3 to 12 months (if necessary)
  7. Regulatory filings – 6 to 12 months (if necessary)

While this high-level timeline incorporates some steps that may be able to be performed in parallel, based on the above outline, CHPA anticipates manufacturers will require at least 19-24 months to implement the new packaging. There are a number of variables involved in the process and some manufacturers will require additional time to select suppliers, repeat CR testing with final production samples, and modify distribution packaging. In addition, an unsuccessful design that does not pass CR testing on its initial attempt will require time for modification and re-testing. It is not possible to define the upper limit of the timeline but due to the number of variables involved in the process and diversity of the medicines implicated, it is reasonable to expect that the process may take even longer than two (2) years in a number of cases.

### **Manufacturers Should be Granted Extended Stays of Enforcement as Special Circumstances Require**

Depending on the specific product, packaging development activities could range from design modifications and/or adaptations of existing CR technologies, to full-scale changes to the packaging design and materials of construction. Based on the complex nature of the affected products and sensitivity to packaging-related changes, the number of products and package sizes involved, and the extent of the packaging development, qualification, and regulatory activities, some CHPA members estimate that introduction of CR packaging for all of the impacted products will take more than two (2) years. For this reason, CPSC should expressly permit manufacturers to petition for longer stays of enforcement as needed and grant such stays until such time as it is determined that an enforcement stay is no longer appropriate. As noted above, CPSC has a history of recognizing unique circumstances that require additional time as this is the approach the Commission took with regard to implementation of the final rule for minoxidil CR finger sprayer packaging (62 Fed. Reg. at 63606-7). In the minoxidil situation, the Commission explicitly noted that development of the applicable CR packaging may take 27-36 months.

As an example of a potential scenario where additional time may be required for medicines containing imidazolines, some of the products affected by the proposed rule are subject to new drug applications ("NDAs") or abbreviated new drug applications ("ANDAs"). In these instances, even after the CR packaging development and associated qualification work are completed, preparation, submission and approval by FDA may also be required prior to implementation. This process can take an additional 6-12 months. In addition, many of these products, as well as some non-NDA/ANDA products, may require stability testing. While stability testing may be able to occur in parallel with other steps, it can take 3-12 months and add time to the already lengthy process. Further, as noted above, ophthalmics and other products that are sold as sterile may also require more development time as the sterilization process can have an adverse effect on the packaging componentry (and possibly CR functionality) and potentially compromise the integrity and quality of the affected drug product(s). Due to the additional assessments required in the situations described above, products subject to NDAs or ANDAs, products requiring stability data, and products sold as sterile, represent examples of special circumstances warranting consideration for extended implementation times. Specifically, many of the ophthalmic products affected by the proposed rule will fall into one or more of these categories requiring additional time.

Additionally, it is important to recognize that many companies have multiple products and packaging sizes that are affected and it may not be possible to develop, qualify, and implement CR packaging concurrently for all of the medicines-a staggered approach will be needed. The quantity of products may also adversely impact product capabilities since final qualifications and validations will need to take place on the actual production line.

As described above, there are a number of factors that may prohibit a manufacturer from being able to implement new CR packaging for the affected products within a two (2) year timeframe. In order to ensure consumers have continued access to these important medicines, CPSC should grant additional enforcement stays to manufacturers upon petition as appropriate.

\*\*\*

CHPA thanks the CPSC for the opportunity to provide comments. If the Commission has any questions or if CHPA can be of any assistance, please let me know.

Sincerely,

Alison Manhoff  
Deputy General Counsel  
Consumer Healthcare Products Association

As of: April 10, 2012 Received: April 09, 2012 Status: Posted Posted: April 10, 2012 Category: Manufacturer Tracking No. 80fec3ee Comments Due: April 09, 2012 Submission Type: Web
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# PUBLIC SUBMISSION

Docket: CPSC-2012-0005

Products Containing Imidazolines Equivalent to 0.08 Milligrams or More

Comment On: CPSC-2012-0005-0003

Products Containing Imidazolines Equivalent to 0.08 Milligrams or More

Document: CPSC-2012-0005-0006

Comment from Richard Cooke

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Organization: The Procter & Gamble Company

## General Comment

P&G is seeking clarification from CPSC for a specific package form that was not considered in the briefing documents provided by CPSC in the Docket as background material ("Update of the technical feasibility, practicability, and appropriateness assessment of child-resistant and senior-friendly packages for imidazoline-containing household products," dated January 11, 2012). This package is a glass bottle which houses the imidazoline drug product, with a crimped seal holding the pump in place and with an detachable nozzle (additional details and images are provided in the uploaded attachment to this submission). Drug product can only be dispensed from the bottle when the nozzle is attached over the pump. Actuation requires a degree of dexterity on the part of the user, typically requiring placement of the index and middle fingers on either side of the rim of the actuator nozzle and then placement of the thumb under the base of the bottle. The index and middle fingers are pushed down causing the actuator to be pushed down over the pump of the bottle and product is released.

THIS DOCUMENT HAS NOT BEEN REVIEWED

CLEARED FOR PUBLIC RELEASE

OR ACCEPTED BY THE COMMISSION.

UNDER CPSA 6(b)(1)



Should such a package be placed in a child resistant test protocol , P&G is seeking clarification from CPSC as to what would constitute a failure threshold, based on the number of actuations for a given concentration of imidazoline and specific amount of imidazoline per actuation (calculations are provided in the uploaded attachment to this submission).

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## Attachments

P&G Submission CPSC Imidazolines April9 2012



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April 9, 2012

Office of the Secretary  
Consumer Product Safety Commission  
4330 East West Highway, Room 802  
Bethesda, MD 20814

Submitted electronically via [www.regulations.gov](http://www.regulations.gov)

Re.DocketNo.CPSC-2012-0005

*Products Containing Imidazolines Equivalent to 0.08 Milligrams or More*

Dear Mr. Stevenson,

The Procter & Gamble Company ("P&G") appreciates the opportunity to provide comments on the Consumer Product Safety Commission's ("CPSC" or "Commission") proposed rule, *"Products Containing imidazolines Equivalent to 0.08 Milligrams or More,"* published in the Federal Register on January 25, 2012. The proposed rule will require child-resistant ("CR") packaging for over-the-counter and prescription products containing the equivalent of 0.08 milligrams or more of an imidazoline (includes tetrahydrozoline, naphazoline, oxymetazoline, and xylometazoline drug classes).

P&G notes that in one of the briefing documents provided by CPSC in the Docket as background material (*"Update of the technical feasibility, practicability, and appropriateness assessment of child-resistant and senior-friendly packages for imidazoline-containing household products,"* dated January 11, 2012] several different package forms were considered. One package form that was not considered in this document is provided in Figures 1A and B below. This package is a glass bottle which houses the imidazoline drug product, with a crimped seal holding the pump in place and with an detachable nozzle. Drug product can only be dispensed from the bottle when the nozzle is attached over the pump. Actuation requires a degree of dexterity on the part of the user, typically requiring placement of the index and middle fingers on either side of the rim of the actuator nozzle and then placement of the thumb under the base of the bottle. The index and middle fingers are pushed down causing the actuator to be pushed down over the pump of the bottle and product is released (see Figure 2 below).

**Should such a package be placed in a child resistant test protocol. P&G is seeking clarification from CPSC as to what would constitute a pass or failure of such a package.**

For example, it has been proposed by the CPSC that an amount greater than 0.08 mg should require CR packaging, based on a report of a serious adverse outcome in Katar et al. (2010) and the application of a 10x Safety Factor, then with the following assumptions:

- 
- If the concentration of the active in solution = 0.05 %
  - If each actuation of the metered-dose pump = 50 µl
  - If the amount of the active released per actuation = 25 µg (assuming 100% of the aerosolized active is internalized by the child)
  - If proposed threshold = 0.08 mg = 80 µg
  - Then the number of actuation that is equivalent to 80 µg = 80 µg/25 µg = 3.2 actuations

Therefore the 4th actuation of the metered-dose bottle described above would constitute a failure under this scenario.

Alternatively, by applying the child-resistant testing protocol guidelines as outlined in 16 C.F.R. §1700.20(a)(2)(ii):

- Test failures. *A test failure shall be any child who opens or gains access to the number of individual units which constitute the amount that may produce serious personal injury or serious illness, or a child who opens or gains access to more than 8 individual units, whichever number is lower, during the full 10 minutes of testing.*

Based on the case report of Katar et al (2010) referenced in the advanced notice of proposed rulemaking (77FR p3646), the amount that may produce serious personal injury or serious illness, which according to FDA could result in hospitalization, disability/permanent damage or death, one could follow the precedence of the CPSC and utilize 0.75 mg, the lowest value for adverse events presented in Table 3 of the CPSC document (77FR at p3650). This represents a highly conservative value, noting that 0.75 mg was given to 25 day old neonate, which is both the youngest age reported and well below the 25 pound (11.4 kg) child which is the basis of 16 C.F.R. §1700.20(a)(2)(ii).

Applying an even more conservative approach to the standard outlined in 16 C.F.R. §1700.20(a)(2)(ii), we propose the commission should consider 0.5 mg as the threshold for protection from failure. This value (0.5 mg total dose) represents the second cumulative dose given to 25 day old neonate in the Katar et al. report, the absolute lowest observed adverse effect level (LOAEL) observed in this case report.

If the test failure threshold was acceptably placed at 0.5 mg as we have proposed above,

- The number of actuations that is = 500 µg/25 µg

equivalent to 0.5 mg

= 20 actuations

- (The use of the 0.75 mg value would be 50% larger and would set the test failure threshold at 30 actuations.)

P&G believes the proposed test failure value of 0.5 mg or 0.75 mg does not change the intent of the CPSC proposed rule that would require the child resistant package for the imidazoline class, but helps set a testing value that is consistent with CR testing guidelines.

Figure 1A- metered dose pump spray bottle with crimped pump

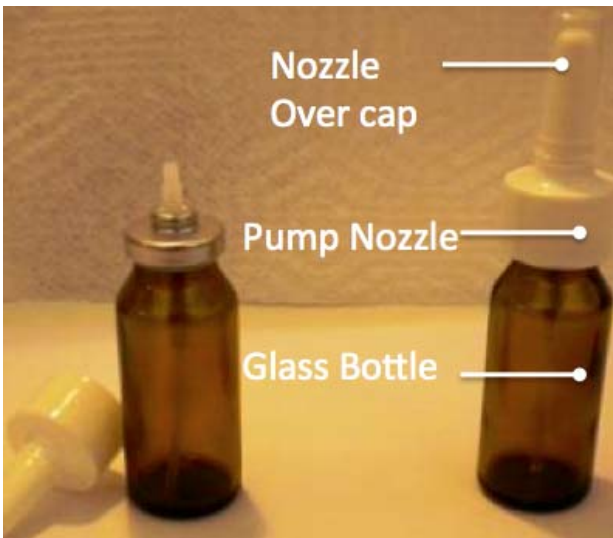


Figure 1B (close-up of crimped on pump)



Figure 2: Image showing placement of fingers and thumb for typical means of actuation



P&G thanks the CPSC for the opportunity to provide comments. If the Commission has any questions, please let me know.

Sincerely,

Richard J. Cooke  
Section Head  
Product Safety & Regulatory Affairs, Personal Health Care  
The Procter & Gamble Company  
Email: cooke.rj@pg.com  
Mobile: (513) 828-1321

# PUBLIC SUBMISSION

**Docket:** [CPSC-2012-0005](#)

Products Containing Imidazolines Equivalent to 0.08 Milligrams or More

**Comment On:** [CPSC-2012-0005-0003](#)

Products Containing Imidazolines Equivalent to 0.08 Milligrams or More

**Document:** [CPSC-2012-0005-0009](#)

Comment from Julie Clifford, PhD

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## Submitter Information

**Name:** Julie Clifford, PhD

**Submitter's Representative:** Julie Clifford, PhD

**Organization:** Alcon Laboratories, Inc.

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## General Comment

See Attached

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## Attachments

Comment from Julie Clifford, PhD



Alcon Laboratories, Inc.  
Novartis Group Companies member  
6201 South Freeway  
Fort Worth, Texas 76134-2099

**Via email**  
**16 April 2012**

Office of the Secretary  
Consumer Product Safety Commission  
Room 802  
4330 East West Highway  
Bethesda, MD 20814

Re: Docket No. CPSC–2012–0005

Dear Sir or Madam:

Alcon, a Novartis company, appreciates the opportunity to provide comments to the Consumer Product Safety Commission's (CPSC) regarding the proposed new rule, "Products Containing Imidazolines Equivalent to 0.08 Milligrams or More".

The Novartis Group of companies provides healthcare solutions that address the evolving needs of patients and societies. Focused solely on healthcare, the Novartis Group has a diversified portfolio of innovative medicines, eye care products, generic pharmaceuticals, consumer health products, preventive vaccines and diagnostic tools. Alcon is the Eye-care Division, and is in a unique position to offer a comment regarding the proposed technical feasibility of child resistant eye drops packaging. This is the initial instance by the CPSC or any other global organization requiring the need for child resistant eye drop packaging. Unlike several of the OTC eye drop and nasal products referenced in the Notice, the affected Alcon eye drop products are sterile and require specialized aseptic processing. The aseptic processes used for the Alcon OTC eye drop products are the same as is used for prescription-only pharmaceutical eye drops, and added controls to ensure product sterility, safety and efficacy must be qualified and implemented with any significant primary package change.

Proven child resistant package formats are not a standard technology available at this time in the ophthalmic packaging industry for sterile products such as those marketed by the Alcon, and additional diligence is required to implement a new sterile primary package technology for use.

Based upon historical experience with the regulated design and qualification activities required for aseptically filled sterile products, Alcon recommends that the implementation target be extended to 24 months for a primary package change of this complexity. The additional time is required to ensure that appropriate child resistant package features can be qualified without negative impact to the package's critical sterility maintenance and moisture barrier attributes over the shelf life of the product.

**Summary**

Alcon requests that this comment be taken into consideration, especially given the additional requirements associated with package formats for sterile products. Your consideration of these responses and comments is appreciated. Please contact me if you have any questions.

Sincerely,

Julie Clifford, PhD  
Director, Packaging  
6201 South Freeway, Fort Worth, TX 76134-2099  
T: (817) 568-6418



# REXAM

CPSC-2012-0005-0007

April 6, 2012

Office of the Secretary  
(CPSC) Room 802  
4330 East West Highway  
Bethesda, MD 20814

Consumer Product Safety Commission

**RE:** CPSC Federal Register Proposed Rule dated January 25, 2012 entitled "Products Containing Imidazolines Equivalent to 0.08 Milligrams or More"  
**Docket No. CPSC-2012-0005**

Dear Sir or Madam:

Rexam Healthcare (Rexam) hereby respectfully submits the attached general question and comments to the aforementioned CPSC Proposed Rule, which was published in the Federal Register on January 25, 2012.

Rexam seeks CPSC's guidance on the attached matter.

We would also like to formally request a meeting with the Agency to further clarify our question and comments, if deemed necessary.

I am the official correspondent for this submission. I may be reached by mail at the below address or via email at [Sandra.Anderson@rexam.com](mailto:Sandra.Anderson@rexam.com) or at any of the numbers provided below.

Thank you for your review of our submission. We appreciate your feedback and assistance.

Sincerely,

Sandra Anderson, M.J., RAC  
Regulatory Compliance Manager  
Rexam Healthcare  
800 Corporate Grove Drive  
Buffalo Grove, IL 60089  
Office: 847-325-3016  
Cell: 224-676-8737  
Fax: 847-325-391

Rexam Healthcare, 800 Corporate Grove Drive, Buffalo Grove, IL  
60089

## Rexam Healthcare General Question/Comments to the Consumer Product Safety Commission (CPSC)

### ***Proposed Rule to Require Child-Resistant (CR) Packaging for any Over-the-Counter or Prescription Products Containing Imidazolines Equivalent to 0.08 Milligrams or More*** **Dated January 25, 2012 (Federal Register Volume 77, Number 16)** **[CPSC Docket No. CPSC-2012-0005]**

Name:	Sandra Anderson, M.J., RAC
Title/Position:	Regulatory Compliance Manager
Company name:	Rexam Healthcare
Phone number	(847) 325-3016
Email address	sandra.anderson@rexam.com

Federal Register Section	Rexam General Question/Comments (Industry Guidance Requested)
<p><b>V. Preliminary Findings Related to Child Resistant Packaging for Imidazolines</b></p>	<div data-bbox="667 948 1033 1438" data-label="Image"> </div> <p>For nasal sprays that contain Imidazoline equivalent to 0.08 milligrams or more, is Child-Resistant packaging required for crimp-on pumps (see attached picture)?</p> <p>In effect, with screw-on pumps nasal sprays and nasal squeezable sprays, children can have access to the full content of the container and drink it in one go. The situation is very different with nasal sprays using crimp-on pumps since they are non-removable. Children would only be able to spray the content and this only one dose at a time, typically between 0.05 and 0.1 ml with each actuation. Such a dose would only represent between 0.5% and 1% of the bottle content and is not likely to be ingested due to its aerosol form.</p>

# **TAB B: Preliminary Economic Analysis: Eye Drops and Nasal Sprays Containing Imidazolines**

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

## Memorandum

Date: May 30, 2012

TO : Cheryl A. Osterhout, Ph.D., Pharmacologist, Directorate for Health Sciences

FROM: Gregory B. Rodgers, Ph.D., Associate Executive Director, Directorate for Economic Analysis  
Deborah V. Aiken, Ph.D., Senior Staff Coordinator, Directorate for Economic Analysis

SUBJECT: Economic Analysis: Eye Drops and Nasal Sprays Containing Imidazoline

This memorandum provides information on the economic effects of requiring child-resistant packaging for imidazoline-containing products under the authority provided by the Poison Prevention Packaging Act (PPPA). It contains:

- 1) a description of the market for imidazolines;
- 2) a description of the societal costs associated with unintentional pediatric exposure to imidazolines;
- 3) data on the cost to industry and consumers of requiring child-resistant (CR) packaging; and
- 4) information concerning small business and environmental considerations.

### I. Market and Exposure Information

#### A. Type of Products

Imidazolines are a group of chemically related products that are vasoconstrictors. When applied topically to the eye, imidazolines constrict the small blood vessels in the eye, which reduces redness due to minor irritants, such as smoke, dust, or chlorine in swimming pools. When applied in the nasal passageway, imidazolines constrict the mucosal blood vessels, which decreases congestion in the nasal tissue. Imidazolines include the following chemicals: tetrahydrozoline, oxymetazoline, xylometazoline, and naphazoline. Imidazoline-based eye drops and nasal sprays are sold over-the-counter (OTC) and by prescription. This analysis is based solely on the OTC market because data on prescription sales are unavailable. The lack of information on the prescription market has little impact on the analysis because the majority of sales are OTC.

## 1. Ophthalmic Products (Eye Drops)

Eye drops containing imidazolines are widely available at drug, grocery, and mass market retailers. Imidazoline eye drops generally come in small squeeze bottles. Based upon observations of shelf space devoted to these products at local retailers, the most common size is the ½-ounce (15 milliliters) bottle. The second most common size appears to be a 1-ounce bottle (30 milliliters). One-quarter ounce (8 milliliters) bottles are also available. Retail prices for the OTC drugs can range from as low as \$3, to more than \$9 per bottle, depending on the size of the bottle, the specific imidazoline used, the brand, and the retailer; however, most prices tend to be clustered toward the lower end of this range.

The number of doses per bottle varies by bottle size and instructions. For example, the label on a ½-ounce bottle of tetrahydrozoline eye drops instructs the consumer to use one to two drops per eye, up to four times a day. It also instructs the user to stop using the product and consult a doctor if the condition persists for more than 72 hours. Provided this bottle is used until exhausted, the ½-ounce bottle contains about 300 drops, or 75 to 150 doses.

## 2. Nasal Sprays

Nasal sprays containing imidazolines are widely available at drug, grocery, and mass market retailers. Some packages are used by rapidly squeezing the bottle to spray the product into a nostril. Other packages have a pump mechanism that activates the spray. As with eye drops, ½-ounce containers are the most common container size, and 1-ounce bottles are the second most common size. Other sizes are available, including 1.25-ounce sizes and 2-ounce sizes. Retail prices for the OTC drugs can range from about \$4 to \$9 a bottle, depending on the size of the bottle, the specific imidazoline used, the brand, and the retailer; however, based on a review of sales data, prices tend to average around \$6 a bottle (Chain Drug Review, 2010a).

The number of doses per bottle varies by bottle size and use instructions. For example, the label on one national brand of nasal spray (oxymetazoline) instructed the user to use 2 or 3 sprays in each nostril every 10 to 12 hours, without exceeding two doses in any 24-hour period. It also warned not to use the product for more than 3 days. A ½-ounce metered pump bottle contains enough product for 150 sprays, or 25 to 38 doses.

### B. Market Information

Imidazoline-based topical decongestants are sold under several brand names and are also available under generic labels. Table 1 (next page) provides industry data, including the number of manufacturers, annual dollar value of retail sales, and unit sales.

Based on an industry review, there are approximately 45 manufacturers that sell topical decongestant products under about 64 different labels (Facts and Comparison, 2007). Because some manufacturers produce both nasal and ophthalmic products, the number of manufacturers within the market for topical decongestants is not the sum of the manufacturers of ophthalmic products plus the manufacturers of nasal products.

For the 52-week period ending November 28, 2010, “Eye/Contact Lens Care Product” sales are estimated at \$1,037.5 million (Chain Drug Review, 2010b). This sales estimate, however, excludes sales at Wal-Mart Stores, Inc., which are estimated to account for between 20 to 30 percent of total sales (Chain Drug Review, 2003). Augmenting annual sales to account for sales at Wal-Mart increases the annual sales estimate to about \$1,383.3 million ( $\$1,037.5 \div 0.75$ ). Because approximately 13 percent of “Eye/Lens Care” product sales are attributed to decongestants (OTC Update, 1997), the dollar value of annual sales for ophthalmic decongestants may be estimated at about \$180 million ( $\$1.383 \text{ billion} \cdot 0.13$ ). Therefore, based on an average price of \$4, annual unit sales are estimated at about 45 million units ( $\$180 \text{ million} \div \$4$ ).<sup>12</sup>

SymphonyIRI Group estimates the dollar value of annual sales for “Nasal Spray/Drops/Inhalers” at \$500.6 million for the 52-week period ending December 27, 2009 (Chain Drug Review, 2010a). This sales estimate, however, excludes sales at Wal-Mart, which are estimated to account for between 20 to 30 percent of total sales (Chain Drug Review, 2003). Augmenting annual sales to account for sales at Wal-Mart increases the sales estimate to about \$667 million. Based on a review of top-selling products, out of all nasal products sold, approximately 35 percent contain imidazoline (Chain Drug Review, 2010a). Therefore, approximately \$233 million ( $\$667 \text{ million} \cdot 0.35$ ) are attributed to the sale of nasal decongestants that contain imidazolines. Assuming an average unit price of \$6, annual unit sales would be about 38.8 million units ( $\$233 \text{ million} \div \$6$ ).

**Table 1: Ophthalmic and Nasal Products Containing Imidazoline**

	<b>Number of Manufacturers</b>	<b>Annual Retail Sales (\$ millions)</b>	<b>Annual Unit Sales (million)</b>
<i>Ophthalmic Products</i>	17	\$180	45.0
<i>Nasal Products</i>	37	\$ 233	38.8
<i>Total</i>		\$ 413	83.8

## II. Societal Cost of Pediatric Exposures to Imidazolines

Exposure to imidazolines may cause serious, potentially life-threatening health effects, including central nervous system depression, respiratory depression, and cardiovascular instability (Osterhout, 2011). Although CPSC staff is not aware of any deaths resulting from accidental pediatric exposures, some patients have required medical treatment in intensive care settings (Osterhout, 2011). In children, these effects have been reported after the child has

<sup>12</sup> As noted above, these figures apply only to products sold OTC, as prescription sales have been excluded due to lack of information.

ingested as little as 1.5 milliliters (three-tenths of a teaspoon) of an imidazoline product (Katar, 2010), or about one-tenth of the contents of the most common size package (15 milliliters or one-half ounce).

This analysis uses CPSC’s Injury Cost Model (ICM) to estimate the societal costs of medically attended injuries associated with imidazolines. The ICM is integrated with the National Electronic Injury Surveillance System (NEISS), a national probability sample of U.S. hospital emergency departments (EDs) that provides estimates of product-related injuries treated in hospital EDs. The ICM estimates the cost of injuries initially treated in EDs. Based on the empirical relationship between the number of medically attended injuries treated in EDs and the number treated in other settings, the ICM also produces estimates of the number and societal costs of medically attended injuries treated outside of EDs, such as at doctors’ offices or clinics. The cost estimates include all costs to society associated with the injuries, including the costs of medical treatment and work loss, as well as the intangible costs of injuries, sometimes referred to as pain and suffering (Miller et al., 2000; Zamula 2007). These cost estimates are based on the injury diagnoses (*e.g.*, poisoning), affected body part(s), age, and gender of the victims.

Table 2 provides *annual* estimates of injuries and the associated societal costs for imidazoline exposures of children younger than age 5 years, based on estimates from the 13-year period from 1997 through 2009. According to NEISS estimates, there were an estimated 5,675 emergency department-treated imidazoline ingestions involving children younger than age 5 years, from 1997 through 2009; about 80 percent involved eye drops, and about 20 percent involved nasal sprays (O’Brien, 2011). As shown in Table 2, NEISS estimates from this 13-year period suggest an estimated annual average of about 351 injuries involving eye drops (with 325 treated and released and 26 admitted to the hospital) and an estimated annual average of about 85 injuries involving nasal sprays (with 78 treated and released and 7 admitted to the hospital). Additionally, based on estimates from the ICM, there were another 496 eye drop and 119 nasal spray incidents medically treated annually outside of hospital EDs.

**Table 2: Estimated Average Annual Medically-Attended Injuries and Societal Costs of Imidazoline Exposures to Children under Age Five, 1997 to 2009**

		Eye drops		Nasal Sprays	
		Number	Societal Cost	Number	Societal Cost
			(millions)		(millions)
1	Treated and Released from Hospital Emergency Department (NEISS)	325	\$ 5.5	78	\$ 1.3
2	Admitted to Hospital Through the Emergency Department(NEISS)	26	\$ 1.9	7	\$ 0.5
3	Medically Treated Outside of Hospital Emergency Department (ICM)	496	\$ 5.9	119	\$ 1.5
4	Total Medically Attended Injuries	848	\$ 13.3	204	\$ 3.3

Note: The average annual estimates presented in this table are based on NEISS and ICM estimates from the 1997 to 2009 time period. Sums may not add to totals due to rounding.

In total, there were an estimated 848 eye drop and 204 nasal spray injuries that were medically treated annually during the 1997–2009 time period. These incidents resulted in annual societal costs of about \$16.6 million, including \$13.3 million for eye drops and \$3.3 million for nasal sprays. Medical costs and work losses accounted for about 23 percent of these injury cost estimates; the intangible costs of injury associated with pain and suffering accounted for about 77 percent of the injury costs (Miller et al., 2000). On a per-unit basis, the societal cost of eye drop injuries was about 29.6 cents per container ( $\$13.3 \text{ million} \div 45.0 \text{ million}$ ), and the societal cost of nasal spray injuries was about 8.5 cents per container ( $\$3.3 \text{ million} \div 38.8 \text{ million}$ ).

### **III. Effectiveness of Child-Resistant Packaging**

The purpose of child-resistant (CR) packaging is to prevent children from opening packages and ingesting toxic products. CR packaging is expected to reduce pediatric ingestions of imidazoline eye drops and nasal sprays, but it will not prevent all of them: some children younger than age 5 years are able to open CR packages<sup>13</sup>; some consumers may not properly close CR packaging after use (Jacobson et al, 1989); and the PPPA allows manufacturers to supply some products covered by CR packaging requirements in non-CR packages (provided that the noncomplying package is offered only in one size, and complying packages are also supplied in popular sizes).

Studies evaluating the effectiveness of CR packaging in preventing child poisonings suggest that CR packaging may reduce poisoning incidents by about 40 percent (Walton, 1982; Rodgers, 1996, 2002). Assuming CR packaging reduces imidazoline poisonings by 40 percent, CR packaging would prevent an estimated 421 medically attended injuries annually (including an estimated 339 eye drop and 82 nasal spray injuries) and reduce the societal costs associated with the incidents by an estimated \$5.3 million ( $\$13.3 \text{ million} \cdot 0.4$ ) for nasal spray and \$1.3 million ( $\$3.3 \text{ million} \cdot 0.4$ ) for eye drops. On a per-product basis, the expected reduction in societal costs is about 11.8 cents per container for eye drops ( $\$5.3 \text{ million} \div 45.0 \text{ million}$ ) and 3.4 cents per container for nasal sprays ( $\$1.3 \text{ million} \div 38.8 \text{ million}$ ).

### **IV. Cost of CR Packaging**

The costs of CR packaging may be separated into two categories: the additional cost to manufacture the products with CR closures and the additional time and effort needed by consumers to use the packaging.

#### **A. Manufacturing Costs**

The manufacturing cost includes the cost of designing the CR closures (including any changes required to the package), making the molds and other equipment required for

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<sup>13</sup> To be considered CR, a package needs to prevent 80 percent of the children from opening it during the qualifying tests.



manufacturing the closures, any additional material costs, the cost of redesigning the production lines to accommodate the redesigned packages, and the cost of any additional time or steps required in the manufacturing process. Some of these costs can exceed several hundred thousand dollars, but when spread over millions of units, the costs may be low on a per-unit basis. Based on cost data that CPSC staff has collected over the years, the manufacturing costs typically range from about 0.5 cents to 4.6 cents per unit (Franklin, 2006). The incremental costs for any particular closure will depend on factors such as the specific changes required in the packaging and production volume. For example, if an existing CR closure can be easily adapted to the product, the costs would probably be low. However, if a manufacturer must make more extensive changes to its package to accommodate a CR closure, and if the production volume for the product is low, the incremental costs for that manufacturer could be higher.

## **B. Consumer Costs**

The primary cost of CR packaging for consumers is the added time and increased difficulty associated with the use of CR closures, as compared to conventional closures. This added time and difficulty will likely vary among consumers and packages. For example, elderly or arthritic consumers may have greater difficulty opening CR packaging than younger and healthier consumers. Additionally, some types of CR closures may be easier to use than others. The time and possible difficulty associated with CR packaging is explicitly recognized in the PPPA, which allows consumers to request pharmacists to provide their prescription drugs in non-CR packaging. Additionally, in order to accommodate consumers who may have difficulty opening CR packaging, manufacturers are also allowed to supply regulated products in one size package that is not CR, provided that the size offered is not the most popular size.

While data on the additional time required for opening and resealing CR packaging is limited, the additional time would apply each time the package is used.<sup>14</sup> The number of times a nasal spray or eye drop product is used can vary, depending upon the size of the bottle and consumer usage patterns. As noted previously, ½-ounce bottles represent the most common sizes for eye drops and nasal sprays. A ½-ounce bottle of eye drops contains about 300 drops, which is enough for 75 to 150 doses, at one to two drops per eye. A ½-ounce bottle of nasal spray contains about 150 sprays, which is enough for 25 to 38 doses, at 2 to 3 sprays per nostril.

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<sup>14</sup> Among other studies, a February 2004 article in ASTM Standardization news reported that older adults, ages 60 to 75 years, who were tested across a variety of CR packaging types, took an average of about 11.7 seconds to open a CR package on the first exposure. A CPSC staff pilot study (O'Brien 2007, Osterhout 2008) found that the difference between the mean time to use a CR package and the mean time to use a non-CR package was small, but statistically significant. The pilot study (which was based on a sample of non-elderly CPSC employees) estimated that the extra time required by subjects to open and close a continuous thread, non-CR closure, versus a comparable push-and-turn CR closure, was 0.59 seconds (95 percent confidence interval, 0.27 to 0.90 seconds). Additionally, studies by Keram and Williams (1988) and Kou (2006) evaluated a number of commonly used CR and non-CR packages with older consumers and found greater mean opening times for the CR packaging.

For purposes of this discussion, we assume that containers of eye drop products are opened and closed an average of 75 times over the product’s life.<sup>15</sup> This estimate is roughly equivalent to assuming that a consumer who purchases a ½-ounce bottle of eye drops uses an average of two drops in each eye, and that a consumer who uses less than two drops per eye or purchases the larger size container “wastes” a substantial portion of the contents (*e.g.*, by losing or disposing of a partially used bottle). Similarly, containers of nasal spray products might be opened and closed an average of about 25 times each. This is roughly equivalent to consumers using an average of three sprays per nostril, and it also assumes that consumers who use fewer sprays or use larger than ½ ounce containers waste a portion of the contents.

Table 3 presents information on the added time and costs that might be associated with the use of CR packaging for eye drops and nasal sprays. Because the added time is not known with certainty, the table provides various alternative estimates, under the assumption that, relative to conventional non-CR packaging, CR packaging adds, on average, anywhere from 0 to 2 seconds per use. For example, if eye drop containers are used 75 times, and the CR packaging adds a second to the opening and closing process, then the added time would be about 75 seconds per package. Similarly, if nasal spray containers are used 25 times, and the CR packaging adds a second, the added time would be about 25 seconds per container.

Table 3 also attempts to monetize the costs associated with the added time. Based on several published studies, Zamula (2011) found that \$12 per hour (in 2008 dollars) may be a reasonable estimate of the value of a consumer’s time when a safety-related change in a product requires additional time to perform a given task. If, for example, the additional time amounts to 1 second per use, and 90 percent of eye drops and nasal spray containers are in CR packaging, the value of the additional time per container would be about 22.5 cents for eye drops [(75 seconds ÷ 3600 seconds per hour) • \$12 per hour • 0.90] and about 7.5 cents for nasal sprays [(25 seconds ÷ 3600 seconds per hour) • \$12 per hour • 0.90]. Of course, if the added time is less than 1 second, or the value of a consumer’s time is less than \$12 per hour, then the CR packaging time costs would be less. Alternatively, if the added time is more than 1 second, or the value of a consumer’s time is more than \$12 per hour, then the CR packaging time costs would be more.

**Table 3: Potential Time Costs of Using CR Packaging, per Container\***

	Eye drops*		Nasal Sprays*	
	Added Time per Container (seconds)	Time Costs‡ (cents)	Added Time per Container (seconds)	Time Costs‡ (cents)
Added Time per Use:				
0 seconds	0.0	0.0 ¢	0.0	0.0 ¢
0.5 seconds	37.5	11.3 ¢	12.5	3.8 ¢

<sup>15</sup> We are implicitly assuming that each container will be used within 1 year, and hence, that all benefits occur within the 1-year timeframe. This assumption would result in a slight overstatement of benefits if the products remained in use for more than 1 year because benefits accruing beyond the first year would need to be discounted.

1.0 seconds	75.0	22.5 ¢	25.0	7.5 ¢
1.5 seconds	112.5	33.8 ¢	37.5	11.3 ¢
2.0 seconds	150.0	45.0 ¢	50.0	15.0 ¢

\*Assumes that a container of eye drops is opened and closed 75 times and that a container of nasal spray is opened and closed 25 times.

‡ Time has been valued at \$12 per hour.

## V. Discussion

The ingestion of imidazoline-containing eye drops and nasal sprays can cause serious health effects in children. While CPSC staff is not aware of any deaths that have resulted from accidental pediatric exposures of imidazoline eye drops and nasal sprays, several hundred children are taken to hospital emergency departments each year because it is suspected that they have ingested imidazoline products. In most cases, the symptoms fully resolve within 36 hours, with no significant lasting effects (Osterhout, 2011).

Using the CPSC’s Injury Cost Model and annual sales estimates, the societal cost of pediatric exposures to imidazoline is about 29.6 cents per container for eye drops and 8.5 cents per container for nasal sprays. Based on studies of the effectiveness of CR packaging at reducing poisonings, CR packaging for imidazoline products may reduce these societal costs by about 11.8 cents per container for eye drops and 3.4 cents per container for nasal sprays. These reduced societal costs represent the expected benefits of a rule requiring the use of CR closures with imidazoline-containing eye drops and nasal sprays.

In comparison to these benefits, the costs of CR packaging include both the added costs associated with manufacturing CR packages and the added time and inconvenience associated with the use of CR packaging. As noted earlier, the added manufacturing costs could range from 0.5 cents to 4.6 cents per container. Additionally, the added time costs, per container, could range from 0 cents, if it were assumed that CR packaging resulted in no added time or inconvenience, to about 45 cents per eye drop container and about 15 cents per nasal spray container, if it were assumed that the use of CR containers added an average of 2 seconds per use.

## VI. Small Business Effects

Nasal and ophthalmic products are classified within the NAICS 325412 *Pharmaceutical Preparation Manufacturing* industry. According to the U.S. Small Business Administration’s Office of Advocacy, a firm classified within NAICS 325412 is considered a small business if the firm has fewer than 750 employees. Based on such classification, out of the approximately 45 firms that manufacture imidazoline-based eye drops and nasal sprays, approximately 20 firms are defined as “small businesses.” There may be more manufacturers, in particular firms that manufacture under generic labels, that were not identified, but that may be small businesses.

There are several reasons to believe that a rule would not have a significant impact on a substantial number of small businesses. First, as noted above, the incremental costs of CR packaging for manufacturers are low, estimated at no more than a few cents per unit. Manufacturers are likely to be able to pass on at least some of these costs to consumers. Second, most manufacturers of over-the-counter drug products have diverse product lines that include other products that would not be covered by this possible regulation. Therefore, the products that would be affected by a proposed regulation may represent a small proportion of any one manufacturer's production. Finally, the requirements would apply only to products packaged after the effective date of the requirements. Therefore, businesses would have time to use up existing inventories of product and packaging.

## **VII. Environmental Impact**

Requirements for CR packaging are not expected to have an adverse impact on the environment. CR packaging has virtually the same impact on the environment as non-CR packaging and is considered to be a "categorical exclusion" for purposes of the National Environmental Policy Act (16 CFR § 1021.5(c) (3)).

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**TAB C: Staff Response to Comments Received Regarding  
Child-Resistant and Senior-Friendly Packages for  
Imidazoline-Containing Household Products.**

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

## Memorandum

Date: August 20, 2012

TO: Cheryl A. Osterhout, PhD., Pharmacologist,  
Division of Health Sciences

THROUGH: Andrew Stadnik, P.E., Associate Executive Director  
Directorate for Laboratory Sciences

James C. Hyatt, P.E., Division Director  
Division of Mechanical Engineering  
Directorate for Laboratory Sciences

FROM: Gregory K. Rea, Mechanical Engineer  
Division of Mechanical Engineering  
Directorate for Laboratory Sciences

SUBJECT: Staff response to comments received regarding child-resistant and senior-friendly packages for imidazoline containing household products.

### I. INTRODUCTION

A notice of proposed rulemaking (NPR), "PPPA Rule Requiring Child-Resistant Packaging for Imidazolines,"<sup>16</sup> was approved by the U.S. Consumer Product Safety Commission (CPSC, the Commission) on January 25, 2012. Staff received five comments to the NPR during the 90-day public comment period, which closed on April 9, 2012. This memorandum contains staff responses to the four packaging-related comments pertaining to imidazoline nasal and ophthalmic products.

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<sup>16</sup> "Notice of Proposed Rulemaking: PPPA Rule Requiring Child-Resistant Packaging for Imidazolines," Jan. 25, 2012. <http://www.cpsc.gov/businfo/fnotices/fr12/imidazolines.pdf>.



The proposed rule that was published in January 2012,<sup>17</sup> would require child-resistant (CR) packaging for any over-the-counter or prescription drug product containing the equivalent of 0.08 milligrams or more of an imidazoline (tetrahydrozoline, naphazoline, oxymetazoline, and xylometazoline) in a single package. Imidazolines are a family of drugs that are vasoconstrictors indicated for nasal congestion and/or ophthalmic irritation. Imidazolines can cause serious adverse reactions, such as central nervous system depression, decreased heart rate, and depressed ventilation in children treated with these drugs or who accidentally ingest them. Data exist to support a Commission finding that special packaging for imidazolines is technically feasible (capable of being produced), practicable (lends itself to mass production techniques), and appropriate (compatible with the substances in the package).<sup>18</sup>

## II. STAFF RESPONSE TO COMMENTS

### A. The Effective Date and Sufficient Time for Implementation of the Rule

Two commenters raised concerns about the proposed 1-year effective date and noted that additional time would be necessary to comply with a CR packaging rule.

Comment: One commenter concludes “it is not feasible for manufacturers to comply with the proposed one (1) year effective date” and that 2 years would be required at a minimum. They support this statement by providing a timeline summarizing the steps required to develop and implement a CR package for imidazoline-containing nasal and ophthalmic products. Regarding nasal products, they argue that this time is required because it will probably be necessary to replace the commonly used single-piece cap with two-component CR protection caps. The commenter also notes that most ophthalmic finishes<sup>19</sup> are 13 mm–15mm, and there are no CR closures available smaller than 18mm; therefore new CR packages will be also required for ophthalmic products. The CHPA also reports in their comment that additional time beyond the 2 years may be required by some manufacturers, especially if the products in question are subject to U.S. Food and Drug Administration (FDA) requirements for new drug applications (NDAs) or abbreviated new drug applications (ANDAs). This additional approval process, they report, could require an additional 6 to 12 months.

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<sup>17</sup> Osterhout, C. A., “Proposed Special Packaging Rule for Imidazolines,” Jan. 11, 2012. <http://www.cpsc.gov/LIBRARY/FOIA/FOIA12/brief/imidazolines.pdf>

<sup>18</sup> Rea, GK, “Update of the technical feasibility, practicability, and appropriateness assessment of child-resistant and senior-friendly packages for imidazoline containing household products,” April, 2011.

<sup>19</sup> The word “finish,” in this sense, refers to the protruding threads on the bottle’s opening that hold the cap or closure. A container and its corresponding closure must have matching finishes.

The commenter requests that the Commission consider a 1-year stay of enforcement in addition to the 1-year effective date proposed in the NPR in order to allow manufacturers 2 years after publication of the rule to comply. They also request that manufacturers be granted extended stays of enforcement on a case-by-case basis, if required.

Response: The commenter's timeline estimates that the time to develop, manufacture, test, pass FDA regulations, and implement production of their products in CR packaging is between 28 and 54 months. Some steps, however, may be performed concurrently, which could decrease the total time required. Staff reviewed each step of the commenter's timeline (Fig. 1) to assess its validity.

1. Design development – 2 to 4 months
2. Prototype tooling – 4 to 6 months
3. CR protocol testing – approximately 3 months (depending on CR testing facility capacity)
  - o If CR protocol fails, return to step 1
4. Industrial scale up for packaging and validation – 7 to 11 months
5. Adoption filling line and validation – 3 to 6 months (depending on complexity)
6. Stability testing – 3 to 12 months (if necessary)
7. Regulatory filings – 6 to 12 months (if necessary)

Figure 1. Commenter's proposed rule compliance timeline included with comment.

1. Design and Prototype Tooling. CPSC staff believes the design and prototype tool fabrication timing given is typical for modern computer-assisted design processes. Staff is aware of new purportedly CR designs developed since the notice of proposed rulemaking was published, which could be used for imidazoline packages. There is a patented design that requires the consumer to line up arrows on the cap and package, then squeeze the arrows to remove the cap. There are also several similar non-patented designs that can be adapted to produce different size eye and nasal drops that have not been CR tested yet. If these designs were bought or licensed by manufacturers, the design-development stage timing could be reduced to 1 month or less. However, longer times could be incurred when the engineering and tooling firms are busy, and therefore, they are not 100 percent dedicated to a given project, the commenter asserts. The package sterilization process is distinct from the mold tooling fabrication process. Sources contacted by CPSC staff estimate 4 to 5 months typically for mold tool production, plus an additional month for qualification (production tests that ensure the mold tool can be used at the intended production rate). This corroborates the 4 to 6 months reported by the commenter.

2. CR protocol testing of both children and seniors requires a minimum of 6 weeks, according to third party CR protocol test providers; although 2–4 months is a typical timeframe; testing depends on the complexity of the CR system. If the package fails CR protocol tests, the next design and prototype tooling iteration will take considerably less time than the original, typically about 1 month per additional iteration. CPSC staff thinks that the CR protocol testing may take longer than the 2–3 months that the commenter estimates.
3. Industrial scale-up for packaging and validation. Existing filling and capping equipment on a sterile production line probably would not have to be replaced. This assumes manufacturers will produce similar size and shape products to capitalize on existing brand recognition. However, the capping equipment could require significant modifications, depending on the design of the CR closure. Sources contacted by CPSC staff indicate that this work should take less than 6 months, if a similar sterile process is already in place. If new equipment must be installed, CPSC staff thinks that this time estimate increases to 6 to 12 months.
4. Adoption of new filling line and validation of the line can take 3–6 months, according to manufacturers with previous stay of enforcement requests for similar reasons. Therefore, staff agrees with the estimate of 3–6 months to adopt a new filling line.
5. Stability Testing. The FDA’s Stability Test Guidelines refer to two timeframes for stability testing: the first is a regular timeframe of 1 year; the second is an accelerated test method performed over 6 months. The accelerated test method is also referred to as “stress testing.” The accelerated testing conditions are at least 15 °C higher than the long-term study conditions and are intended to increase the rate at which degradation reactions take place, thus revealing quality changes at an early stage. Staff agrees with the estimate of 3–12 months for stability testing.
6. Regulatory filings. CHPA requested 6–12 months for the FDA review process of an NDA or an ANDA. The FDA’s Center for Drug Evaluation user fee reports for 2011<sup>20</sup> indicate that 10 months was the median review time for NDAs. To file an ANDA, permission must be obtained first. This requires an ANDA petition process that can take up to 180 days. Once the ruling is received, the ANDA may be filed. In general, an ANDA does not take as long to review in the FDA system as an NDA. This analysis does not include the time it takes for manufacturers to prepare the submissions. CPSC staff concurs with the estimate of 6–12 months for FDA filings.

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<sup>20</sup> <http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/PDUFA/default.htm>

In summary, staff supports the commenter's request for an additional 1-year stay of enforcement, which would allow manufacturers 2 years to comply with the rule after its publication. We agree that nasal products' caps and the nozzle attachment to the container must be CR, and new CR packaging will be required to maintain 13 mm–15 mm closures on ophthalmic packages, if manufacturers choose not to use existing designs. Staff also supports the commenter's request to grant extended stays of enforcement on an individual basis, if circumstances require. We acknowledge that manufacturers may need additional time for "preparation, submission and approval" by the FDA for certain imidazoline-containing products exceeding staff's previous recommended 12-month effective date.

Comment: One commenter manufactures sterile eye drops that require "specialized aseptic processing." To ensure sterility of their products, their packaging processes must also be sterile. They state that this requires, therefore, "controls to ensure product sterility, safety and efficacy [which] must be qualified and implemented with any significant primary package change" before full-scale implementation is possible. The commenter claims that "proven" CR packages—those with the necessary form factor and closure finish—are not "a standard technology available at this time" within the ophthalmic packaging industry. As a result, new packages suitable for sterile ophthalmic products will need to be developed.

The commenter concludes with a request that CPSC staff recommend a 24-month implementation period, "given the additional requirements associated with package formats for sterile products."

Response: This comment, although focused specifically on sterile ophthalmic product packaging, is similar to the first comment above. Staff agrees with the commenter that additional time will likely be required to develop new CR packages, including those used for sterile ophthalmic products containing imidazolines. Sources contacted by staff indicate that this work should take less than 6 months, if a similar sterile process is already in place. If new equipment must be installed to implement the controls to ensure product sterility, this time increases to 6 to 12 months. Therefore, CPSC engineering staff agrees with the additional time to set up a *new* sterile process. However, if a sterile process is in place already (for example with the non-CR package), then the change to a new package should not require as much time.

## **B. Particular Types of Packaging**

Comment: Another commenter notes that in the NPR, the Commission failed to consider one type of nasal spray package. The package in question "is a glass bottle which houses the imidazoline drug product, with a crimped seal holding the pump in place and with [a] detachable nozzle." An example of this type of package is shown in Fig. 2. The metered pump is housed in a metal case, the rim of which is crimped to the glass bottle. A plastic nozzle is placed over the

pump, and the overcap is attached to the nozzle. Consumers access the product by squeezing the package between the thumb and first two fingers (shown in Fig. 3), causing an aerosolized form of the product to be released from the nozzle's tip.

The commenter believes that this package is inherently child resistant because it is a unit-dose package. They requested that CPSC provide clarification "as to what could constitute a pass or failure of such a package." The commenter also proposes the following criteria:

The maximum number of actuations of the metered-dose pump is three, based upon staff's recommended level of imidazoline (0.08 mg or 80 ug) and the assumption that the amount dispensed per actuation is 25 ug.

- 1) A 0.75 mg total dose based upon 16 CFR § 1700.20(a)(2)(ii).
- 2) A 0.50 mg total dose based upon lowest observed adverse effect level (LOAEL).



Figure 2. Glass bottle with a metal-housed, crimped-on, metered-dose pump; detachable nozzle; and overcap (A) assembled and (B) disassembled.



Figure 3. Assembled metered-dose pump package ready for use.

Response: Staff disagrees with the commenter’s fundamental premise that unit-dose packages are inherently child resistant. A CPSC staff study (Wilbur and Barone, 1998) showed that unit-dose packages are not inherently CR.<sup>21</sup> A child can access the contents because neither the pumping action, nor overcap or nozzle attachments are CR; therefore, the package is not inherently CR. It is reasonably foreseeable that a child could access more than the regulated quantity of the contents. If a child can activate the pump once, they could activate it several times. Either the pump action or the overcap must be child resistant. Staff is aware of two designs of CR metered pumps being developed for production.

Comment: A commenter asks: “for nasal sprays that contain Imidazoline equivalent to 0.08 milligrams or more, is Child-Resistant packaging required for crimped on pumps?” See Figure 4 for a picture of the specific package referenced by the commenter. They acknowledge that continuous-thread (CT) closures and squeezable packages permit a child to have access to the entire contents. The commenter states that metered-dose pumps crimped onto a rigid bottle would permit a child access to “only one dose at a time” and that “it is not likely to be ingested due to its aerosol form.”

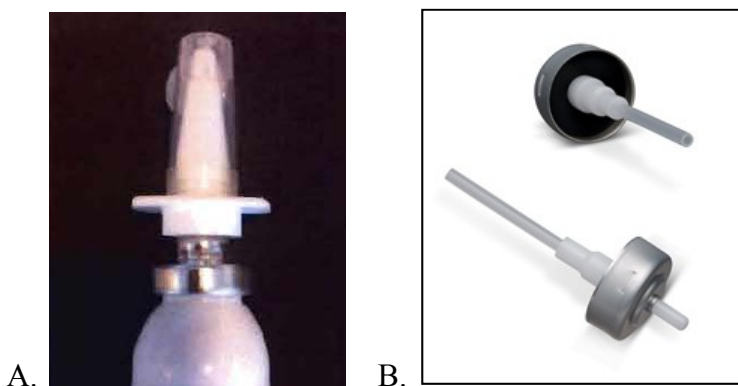


Figure 4. A. Nasal spray package with crimped-on pump (image provided in comment).  
B. Pump before being crimped to bottle.<sup>22</sup>

Response: As stated in staff’s response to the comment immediately preceding this one, unit-dose packaging is not inherently CR. Child-resistant packaging is required for either the pump action or the overcap. If a child activates the pump once, it is reasonably foreseeable that a child would activate the pump many times and deplete the contents. Staff also disagrees that an aerosolized form of the product would not be ingested by a child.

<sup>21</sup> Wilbur, C. J., Barone, S., “[Is Unit- Dose Packaging Inherently Child-Resistant?](#)” U.S. CPSC, Directorate for Epidemiology and Health Sciences, April 1998.

<sup>22</sup> Image obtained from: <http://www.rexamcatalogue.com/healthcare-packaging-and-devices/?SB=2071530> .

Oral exploration is a commonly recognized behavior of children younger than the age of 3 years. Excessive hand-to-mouth behavior, mouthing objects, and tasting or ingesting non-food items are commonplace behaviors. Children are also curious about mechanical devices, such as pump-action mechanisms and what can be done with them. Children in this age group also have a desire to produce effects, such as produce liquid from a squirt bottle, and they imitate adults in a variety of ways. Between the ages of 12 through 18 months, children are increasingly walking and climbing, which allows them more opportunity to explore areas of the home that were once inaccessible to them. Curiosity about the taste and feel of materials in their mouths, such as liquid, combined with curiosity about mechanical devices, the desire to produce effects and imitate adults, as well as their increased mobility and fine motor skills allow them to gain access to products stored in packages. Once they acquire the package, it is reasonably foreseeable that a young child would manipulate it and then explore it orally.<sup>23</sup> With this oral exploration children may be able to access the product from sucking or chewing on the bottle. It does not matter if the effect is a drop or mist, once the package is accessed by the child. Due to the lack of CR overcap or nozzle, it is reasonable foreseeable that a child could access more than the regulated quantity of the contents through activation of the pump or through oral access. If a child can activate the pump once, they could activate it several times. Either the pump action or the overcap must be child resistant. Staff is aware of two designs of CR metered pumps being developed for production.

### **III. SUMMARY OF STAFF RECOMMENDATIONS**

Four packaging-related comments to the imidazoline NPR were received. Two commenters state that there are no CR ophthalmic or nasal packages currently available; therefore, new packages would have to be developed to comply with staff's recommended final rule. Although new CR designs for ophthalmic packages are now available, staff agrees that the normal CR package development time is typically at least 19 to 24 months, and staff also acknowledges that manufacturers need the final rule implementation period extended, as requested by the commenters, by 12 to 24 months. The third and fourth commenters state that nasal spray packages with crimped-on, metered-dose pumps are inherently CR because they are unit-dose packages. Staff disagrees with these commenters. Unit-dose packages are not inherently child resistant. Metered-dose nasal spray packages with crimped-on pumps require CR features to limit child access to the contents. This may be accomplished by either incorporating a pump with CR activation features or a CR overcap.

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<sup>23</sup> This information was obtained from communication with CPSC Engineering Sciences Human Factors staff on October 4, 2012.





**TAB D: Analysis of Data on Pediatric Ingestions and Injuries Involving Household Products Containing Imidazolines**

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

## Memorandum

Date: April 20, 2012

TO : Cheryl A. Osterhout, Ph.D., Pharmacologist  
Directorate for Health Sciences

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

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

SUBJECT : Analysis of Data on Pediatric Ingestions and Injuries Involving Household  
Products Containing Imidazolines

### I. Introduction

This memorandum gives results of an analysis of pediatric ingestions and injuries involving household products containing imidazolines. Data sources include the National Electronic Injury Surveillance System (NEISS), maintained by the U.S. Consumer Product Safety Commission (CPSC); and the Children and Poisoning (CAP) system, maintained by the CPSC's Directorate for Health Sciences. Included in this memorandum are statistics associated with data on children who were treated in hospital emergency rooms from 1997 through 2011 as a result of injuries associated with imidazoline-containing products. This memorandum updates emergency department-treated injury estimates provided in an earlier memorandum dated February 2, 2011.

### II. Background

An imidazoline is a vasoconstrictor indicated for ophthalmic (eye) irritation and nasal congestion. The specific chemicals analyzed in this memo are tetrahydrozoline, naphazoline, oxymetazoline, and xylometazoline. All of these can cause cardiac, central nervous system, and respiratory adverse events when ingested. These events are particularly strong in children (Dunn et. al. 1993). Currently, the Poison Prevention Packaging Act does not require child-resistant (CR) packaging for over-the-counter imidazolines.

### **III. Injury Data**

#### **A. Methodology**

NEISS is a probability sample of 96 U.S. hospitals having 24-hour emergency departments (EDs) and more than six beds. Coders in each hospital code consumer product-related data from the ED record and the data is then transmitted electronically to CPSC. Because NEISS is a probability sample, each case collected represents a number of cases (the case's *weight*) of the total estimate of injuries in the United States. Different hospitals carry different weights, based on stratification by their annual number of emergency department visits (Kessler and Schroeder, 1999).

CPSC's Directorate for Health Sciences maintains the Children and Poisoning (CAP) system, a subset of NEISS records containing additional information obtained through NEISS involving children under 5 years old (Boja, 2001). CAP includes data on each pediatric poisoning, chemical burn, or ingestion case reported from a NEISS hospital, as well as some ingestions that could have lead to poisoning. Staff searched the CAP database for incidents between January 1997 and December 2011 involving household products that typically contain imidazolines.

CPSC Hazard Analysis staff searched CAP for four product codes: NC1000 (decongestants/nose drops), NC1500 (nose sprays), NN2000 (eye drops), and NN2100 (Naphazoline eye drops). These product codes were then grouped into eye drops (NN2000 and NN2100) and nasal sprays (NC1000 and NC1500). The initial search found 1,409 cases. These cases were reviewed by Health Sciences staff for incidents involving imidazolines. A total of 198 relevant cases were identified.

Hazard Analysis staff used SAS<sup>®</sup> version 9 to compute estimates and the associated coefficients of variation for the number of injuries as well as the estimated number of injuries with particular characteristics such as age and gender. A coefficient of variation (C.V.) is the ratio of the standard error of the estimate (*i.e.*, variability) to the estimate itself. This is generally expressed as a percent. A C.V. of 10 percent means the standard error of the estimate equals 0.1 times the estimate. Large C.V.s alert the reader that the estimate has considerable variability. This is often due to a small sample size.<sup>24</sup> Estimates and confidence intervals are not reported unless the number of cases is 20 or more, the estimate is greater than 1,200, and the C.V. is less than 33 percent.

#### **B. Results**

An estimated 6,650 injuries associated with household products containing imidazolines and children under 5 years old were treated in U.S. hospital emergency rooms from 1997 through 2011. Four product codes commonly containing imidazolines were searched. Table 1 (next page)

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<sup>24</sup> For a more detailed discussion of measures of variation associated with NEISS estimates, see Kessler E. and Schroeder T. *The NEISS Sample (Design and Implementation)*. U.S. Consumer Product Safety Commission. October 1999.

shows the estimates for each of the product groups involved in these incidents. Four-fifths of the estimated injuries (82%) involved eye drops.

**Table 1: Estimated Imidazoline Product-Related Injuries to Children Under Five Years Old, 1997–2011, by Product Group.**

<b>Product</b>	<b>Estimated Injuries</b>	<b>Coefficient of Variation</b>	<b>Sample Size</b>	<b>95% Confidence Interval</b>
Eye Drops	5,437	0.18	161	3,564–7,309
Nose Sprays	1,213	0.29	37	534–1,891
<b>Total</b>	<b>6,650</b>	<b>0.16</b>	<b>198</b>	<b>4,550–8,749</b>

Source: U.S. Consumer Product Safety Commission National Electronic Injury Surveillance System and Children and Poisoning System, 2011.

Table 1 presents the coefficients of variation for each estimate in order to illustrate the degree of uncertainty or sampling variation associated with the estimates. Estimates and confidence intervals are not normally reported unless the number of cases is 20 or more, the estimate is greater than 1,200, and the C.V. is less than 33 percent. Given the small sample of imidazoline-related injuries, it is not possible to do a more detailed analysis of the injuries broken down by year, age, or other variables. The estimates for each year or each age fail to meet the above criteria. The vast majority of patients were treated and released.

### **Summary and Conclusion**

Searches using CAP reveal that young children are being exposed to, and injured by, household products containing imidazolines. The majority of injuries are associated with eye drops. For the 15 years between 1997 and 2011, an estimated 6,650 injuries to children under age 5 and treated in U.S. hospital emergency rooms were associated with these products, based on CAP data.

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**TAB E: Temporary Stay of Enforcement for  
Proposed Rule Requiring Special Packaging for  
Products Containing the Equivalent of 0.08 mg of  
an Imidazoline**

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UNITED STATES  
CONSUMER PRODUCT SAFETY COMMISSION  
4330 EAST WEST HIGHWAY  
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## Memorandum

Date: October 2, 2012

TO: Cheryl Osterhout, Ph.D., Pharmacologist, Directorate for Health Sciences

THROUGH: Marc Schoem, Acting Director, Office of Compliance and Field Operations

FROM: Mary Toro, Director, Division of Regulatory Enforcement, Office of Compliance and Field Operations  
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SUBJECT: Temporary Stay of Enforcement for Final Rule Requiring Special Packaging for Products Containing the Equivalent of 0.08 mg of an Imidazoline

This memorandum provides the Office of Compliance and Field Operations (Compliance) recommendations regarding the request for a stay of enforcement from the requirements of a rule issued under the Poison Prevention Packaging Act (PPPA) for products containing the equivalent of 0.08 mg or more of an imidazoline.

The PPPA requires that any regulation establishing a special packaging standard specify the date the standard will take effect, which shall not be sooner than 180 days or later than 1 year from the date the regulation is final. A stay of enforcement is a decision by the U.S. Consumer Product Safety Commission (CPSC or the Commission) to stay or suspend enforcement action against a firm, even if a firm technically violates the regulation to which the stay pertains. While there are many reasons that might prompt firms to request stays of enforcement, the majority of the requests are in response to newly published final rules.

### Background:

Before issuing rules requiring special packaging, the Commission must find that special packaging is technically feasible, practicable, and appropriate. See 15 U.S.C. § 1472(a)(2). Technical feasibility may be found when technology exists or can be readily developed and implemented by the effective date of the rule to produce packaging that conforms to the standards. Practicability means that special packaging complying with the standards can use modern mass production and assembly line techniques. Packaging is appropriate when complying packaging will adequately protect the integrity of the substance and not interfere with its intended storage and use. See S. Rep. No. 91-845, at 10 (1970).

The Commission typically makes the above findings preliminarily based on information supplied by the CPSC Health Sciences and Engineering Sciences staff, and it issues the findings in a notice of proposed rulemaking. If the Commission receives no comments contesting the

technical feasibility, practicability, or appropriateness of special packaging in regard to the substance to which the proposed rule applies, the Commission generally concludes that special packaging is technically feasible, practicable, and appropriate.

Although, as noted above, the effective date for a regulation under the PPPA cannot be longer than 1 year from the date the regulation is final, the Commission has considered staying the enforcement of a final rule under certain circumstances. In some instances, the Commission has issued a “blanket” stay of enforcement from the new rule, based on a determination that it would take longer than 1 year for firms to bring their products into compliance with the new rule. On July 22, 1995, the Commission issued a rule that modified the special packaging test protocol at 16 C.F.R. § 1700.20 to make it more difficult for packages to comply with the special packaging standard. This rule became effective on July 22, 1996. The Commission granted a blanket stay in light of concerns that firms would not be able to bring their products into compliance with the new rule by the effective date of the rule. Therefore, the Commission granted an 18-month blanket stay of enforcement so that firms had until January 21, 1998 to obtain special packaging for products affected by the rule.

On November 16, 1998, the Commission issued a rule to require child-resistant packaging of preparations containing more than 14 mg of minoxidil per package. The Commission stated in the preamble to the final rule that more than 12 months would be necessary to develop a child-resistant finger sprayer. The Commission agreed with the manufacturers that approximately 27 to 36 months would be necessary to bring the finger sprayers and extenders into compliance and that manufacturers requiring additional time could request a stay of enforcement. Although the Commission did not grant a blanket stay of enforcement of this rule, it provided an opportunity for manufacturers to request a stay of enforcement, which it “anticipate[d] granting . . . until such time as it determined that an enforcement stay were no longer appropriate.” The Commission required that companies seeking a stay “provide the Commission with a timeline or schedule that will outline the steps they will take to bring this type of CR packaging to commercial use . . . [and] include an estimated production date and current and proposed packaging specifications.”

On February 1, 2011, the Commission issued a conditional stay of enforcement of the testing and certification requirements for youth all-terrain vehicles because of the scarcity of third party conformity assessment bodies that had the requisite accreditation to test for conformity to the relevant standard. The Commission stated that it would stay enforcement of the testing and certification requirements for firms that submitted: (1) General Certificates of Conformity (GCCs) demonstrating compliance with the mandatory standard, (2) test reports supporting GCCs, if requested, and (3) quarterly reports responding to certain specific questions. A similar conditional stay of enforcement was issued by the Commission on June 30, 2009, regarding lead content limits in certain parts of bicycles, jogger strollers, and bicycle trailers. The stay in that instance was conditioned upon the manufacturers filing a report with the Commission providing certain specific information regarding their covered products and presenting a plan describing how they intended to reduce to permissible levels the lead content in the subject products.



**Issue:**

The Commission published a notice of proposed rulemaking (Federal Register Volume 77, Number 16 (January 25, 2012)) to require special (child-resistant and senior-friendly) packaging for any over-the-counter or prescription products containing the equivalent of 0.08 mg or more of an imidazoline in a single package.

Comments on the NPR from industry indicated that an additional 1 year after the effective date would be needed to develop and market products that comply with the special packaging requirement. The industry requested a 1-year stay of enforcement in addition to the 1-year effective date, arguing that additional time would be needed for compliance of nasal products because the closures currently used would have to be replaced with CR closures and asserting further that there are currently no CR closures available for most ophthalmic products. Industry provided a timeline for bringing these products into compliance. The steps provided in the timeline include time to develop, manufacture, test, and produce the products in the CR packaging. Based on a review and analysis of the information submitted by the commenters, and consultation with outside packaging experts, staff agrees that an additional 12 months beyond the effective date may be needed by certain manufacturers to comply with the regulation.

**Recommendation for Stay of Enforcement:**

There are three possible ways the Commission could provide for a stay of enforcement: (1) provide a blanket stay of enforcement and request no information from individual firms; (2) require each company to apply individually for a stay and submit information justifying its request; or (3) provide for a conditional stay of enforcement that would require manufacturers to notify the Commission of their intent and then provide certain information in quarterly reports. These three approaches, and Compliance's recommendation, are discussed below.

*Blanket Stay of Enforcement*

A blanket stay would require the use of very little staff time and few, if any, resources because any manufacturer of imidazoline-containing products subject to the rule would be granted a 1-year stay of enforcement automatically, without the need to submit any information or documentation to the Office of Compliance. However, the Commission would not have any information about the progress companies are making to come into compliance with the rule.

*Requiring Individual Firms to Request a Stay of Enforcement*

When the Commission requires each company to request a stay of enforcement of a rule requiring special packaging for certain household substances, staff must assess the technical packaging information provided by the firm. This includes details regarding the compatibility of the product with various types of packaging, the commercial availability of suitable packaging, and specific information regarding how the firm must modify its assembly lines to accommodate the change in packaging. Compliance would rely on EXHR staff to determine whether a firm's request for a stay has technical merit. If the staff approves a request for a stay, the firm would be required to file quarterly reports to Compliance, detailing the firm's progress implementing

special packaging for the subject product. Compliance would rely on EXHR staff when assessing these progress reports. Firms often encounter technical difficulties when developing compliant packaging, which delays their schedule and often results in the firm requesting an extension of the stay. Accordingly, EXHR staff must analyze these requests before Compliance staff can respond to the firms.

If the Commission required each firm to request affirmatively a 1-year stay of the enforcement of the final rule, it is likely that the review, evaluation, analysis, and approval or rejection of such requests would involve the expenditure of considerable resources. Upon receipt of a request for a stay of enforcement, staff must assess the technical packaging information provided by the firm. This includes assessing details regarding the compatibility of the product with various types of packaging, the commercial availability of suitable packaging, and specific information regarding how the firm must modify its assembly lines to accommodate the change in packaging. If a stay is granted to a firm, the firm would be required to file quarterly reports with Compliance, detailing the firm's progress implementing special packaging for the subject product during the term of the stay.

A search of the relevant Office of Compliance files revealed that since 1996 at least 64 firms have requested stays of enforcement for more than 301 different products. Only two requests for initial stays were declined. One of these requests was declined because staff determined that the package already complied with the special packaging standards, thereby negating the need for the stay. Firms that have received stays in the past have requested extensions of their initial stays 28 times. Staff has denied these requests six times. Such requests are denied when staff determines that firms have not shown a "good faith" effort to obtain special packaging for their products.

Based on an industry review, CPSC Economics staff estimated that there are about 45 manufacturers producing imidazoline-containing products under about 64 different labels (Facts and Comparison, 2007). Compliance staff estimates 6 hours of staff time is required to review, analyze, and respond to each request for a temporary stay of enforcement and that an additional 6 hours of staff time is required to review each quarterly report received.

Assuming that each of the 45 manufacturers individually requests a stay of enforcement for 1 full year beyond the first year, an estimated 1,350 staff hours could be required to assess and respond to each request and quarterly progress review<sup>25</sup>. This time estimate was calculated using 6 hours for each request for a temporary stay of enforcement; 6 hours per progress review; and 6 hours for each final review. However, more or less time may be required. This estimate assumes the following:

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<sup>25</sup> This estimates 45 X 6 (270) staff hours for initial reviews, 45 X 3 quarterly reviews that take 6 staff hours each (810) and 45 X 6 (270) staff hours for the final review which totals 1350 staff hours.

1. Each manufacturer of imidazoline-containing products will request a stay of enforcement beyond the first year.
2. If granted, each manufacturer will require the entire year to bring its products into compliance.
3. No manufacturers will request a stay of enforcement beyond the additional year

#### *Conditional Stay of Enforcement*

Considering firm and staff resources (discussed below) that would be expended in reviewing, analyzing, evaluating, and deciding potentially numerous requests for stays of enforcement, Compliance recommends that the Commission consider issuing a conditional stay of enforcement to all subject manufacturers who seek to avail themselves of the additional time to develop compliant CR packaging. Compliance recommends that any manufacturer seeking to avail itself of the protections afforded by a conditional stay of enforcement be required to meet the conditions described below.

The notice of intent to receive the benefit of the conditional stay of enforcement must include:

1. A detailed timeline outlining the steps the firm will take to bring its product(s) into compliance with the regulation within 2 years from the date of the issuance of the final rule. Steps should be undertaken concurrently, when possible. The timeline should include an estimated initial production date.
2. A description of each product that is to be covered by the stay.
3. A description and packaging specifications for the proposed packaging, providing sample packaging, if possible.

In addition, Compliance recommends that the firms be required to submit quarterly status reports during the 1-year stay of enforcement period, detailing their progress and including information that may affect the projected compliance date, such as:

1. Any material changes in the milestone dates or timeframes set forth in the above-referenced timeline;
2. Information regarding the status of package development, including steps undertaken, completed, and anticipated that will enable the firm to produce CR packaging by the date the stay of enforcement is expected to be lifted; and
3. Any incidents or exposures involving the firm's imidazoline-containing products subject to the rule.

**Conclusion:**

Compliance recommends that the final rule be published with a 1-year effective date and a 1-year conditional stay of enforcement. Any manufacturer seeking additional time to comply with the rule beyond the effective date would be required to submit a notice of intent to avail itself of the conditional stay of enforcement as determined in the final briefing package and provide quarterly reports updating its progress toward producing special packaging for imidazoline-containing products that are subject to the rule. This option provides incentive for the manufacturers to bring their products into compliance within a reasonable timeframe, and it ensures, through staff's review, that manufacturers are undertaking the process efficiently and are demonstrating a good faith effort to meet the compliance deadline. It will also provide feedback to staff regarding the commercial availability of the packaging for the products and any problems encountered during the process. Finally, it will preserve for other uses, the considerable staff resources that would be necessary to review, evaluate, and respond to the numerous requests for stays of enforcement, which staff anticipates manufacturers would file.