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CONSUMER PRODUCT SAFETY COMMISSION

[CPSC Docket No. CPSC–2013–0010]

16 CFR Part 1500

Hazardous Substances and Articles; Administration and Enforcement Regulations: Final Rule; Revisions to Supplemental Definition of ''Strong Sensitizer''

AGENCY: Consumer Product Safety Commission.

ACTION: Final rule.

SUMMARY: The U.S. Consumer Product Safety Commission (CPSC or Commission) amends it regulations to revise the supplemental definition of ''strong sensitizer'' under the Federal Hazardous Substances Act (FHSA). The revised definition of ''strong sensitizer'' eliminates redundancy, removes certain subjective factors, incorporates new and anticipated technology, places the criteria for classification of strong sensitizers in the order of importance, defines criteria for ''severity of reaction,'' and provides for the use of a weight-of-evidence approach to determine whether a substance is a strong sensitizer.

DATES: The rule will become effective on March 17, 2014.

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SUPPLEMENTARY INFORMATION:

A. Background

The FHSA, 15 U.S.C. 1261–1278, requires appropriate cautionary labeling on certain hazardous household products to alert consumers to the potential hazards that a product may present. Among the hazards addressed by the FHSA are products containing substances that are toxic, corrosive, an irritant, flammable or combustible, generate pressure through decomposition, heat or other means, or are strong sensitizers.

Included within the FHSA's definition of ''hazardous substance'' is ''any substance or mixture of substances'' that ''is a strong sensitizer,'' 15 U.S.C. 1261(f)1(iv). Section 2(k) of the FHSA, 15 U.S.C. 1261(k), defines ''strong sensitizer'' as a substance which will cause on normal living tissue through an allergic or photodynamic process a hypersensitivity which becomes evident on reapplication of the same substance and which is designated as such by the Commission. Before designating any substance a strong sensitizer, the Commission, upon consideration of the frequency of occurrence and severity of the reaction, shall find that the substance has a significant potential for causing hypersensitivity.

On August 12, 1961, the U.S. Food and Drug Administration (FDA) (which at that time administered the FHSA), issued regulations under the FHSA that supplemented the statutory definition of ''strong sensitizer'' by explaining that a '' 'strong allergic sensitizer' is a substance that produces an allergenic sensitization in a substantial number of persons that come into contact with it'' and specifying that ''[a]n allergic sensitization develops by means of an 'antibody mechanism' in contradistinction to a primary irritant reaction which does not arise because of the participation of an 'antibody mechanism.' '' 26 FR 7333, 7334. The regulation (the 1961 supplemental definition) listed five substances that the FDA had determined met the statutory definition for ''strong sensitizer'': (1) Paraphenylenediamine and products containing it; (2) powdered orris root and products containing it; (3) epoxy resins systems containing in any concentration ethylenediamine, diethylenetriamine, and diglycidyl ethers of molecular weight less than 200; (4) formaldehyde and products containing 1 percent or more of formaldehyde; and (5) oil of bergamot and products containing 2 percent or more of oil of bergamot. *Id.* at 7335. Neither the FDA nor the CPSC has added any strong sensitizers to this list in the 1961 supplemental definition.

In 1973, Congress transferred the responsibility for the administration of the FHSA to the Commission. On May 30, 1984, the Commission revoked the 1961supplemental definition because the 1961 supplemental definition did not account for more recent scientific theories and was narrower than the statutory definition. 49 FR 22464.

On August 14, 1986, the Commission issued a rule supplementing the statutory definition of ''strong sensitizer'' (1986 supplemental definition). 51 FR 29094. The 1986 supplemental definition clarified how the statutory definition should be interpreted and explained the factors the Commission would consider in determining whether a substance is a strong sensitizer. The 1986 supplemental definition stated that an ''allergic'' response is one that is directed by the immune system, such that a sensitization reaction could not be caused by an irritant or other nonallergenic qualities of the substance. The 1986 supplemental definition also clarified that active sensitizers—substances that produce a sensitivity reaction solely as the result of a person's first exposure to the substance as opposed to a reaction after reapplication of the same substance—are included in the class of substances that can be determined to be strong sensitizers. The 1986 supplemental definition did not address strong sensitizers that cause hypersensitivity by a photodynamic process, principally because Commission staff was unaware of any household product subject to the FHSA that would cause significant exposure of consumers to a photodynamic chemical.

In 2005, recognizing that the science on sensitization had changed since promulgation of the 1986 supplemental definition, the CPSC convened a panel of scientific experts from academia, industry, and the federal government to examine the available scientific and medical information concerning sensitizers, and if appropriate, propose revisions to the supplemental definition of ''strong sensitizer.'' Based on the panel's input, CPSC staff developed a draft technical report on proposed revisions to the supplemental definition. In 2007, the draft technical report underwent federal agency and external scientific peer review. In 2008,

CPSC staff revised the draft technical report based on the input received from federal agency and external scientific peer reviewers. Subsequently, CPSC staff drafted a revision of the ''strong sensitizer'' supplemental definition, based on the peer reviewed technical report.

The Commission approved publication of a notice of proposed rulemaking (NPR) to revise the supplemental definition of ''strong sensitizer'' (proposed definition or proposed rule). 78 FR 15660 (March 12, 2013). The proposed definition of ''strong sensitizer'' eliminates redundancy, removes certain subjective factors, incorporates new and anticipated technology, ranks the criteria for classification of strong sensitizers in the order of importance, defines criteria for ''severity of reaction,'' and provides for the use of a weight-of-evidence approach to determine whether a substance is a strong sensitizer.

In addition, the Commission approved publication of a notice of availability for a document prepared by CPSC staff titled, ''Strong Sensitizer Guidance.'' 78 FR 15710 (March 12, 2013). This guidance document was intended to clarify each component of the revised ''strong sensitizer'' definition and assist manufacturers in understanding how CPSC staff would assess whether a substance or product containing that substance should be considered a strong sensitizer and how the Commission would make such a determination.

B. Response to Comments on the Proposed Rule

We received five comments on the NPR. The following individuals or entities submitted comments: a consulting toxicologist; the International Fragrance Association of North America; the People for the Ethical Treatment of Animals (PETA); the International Science Consortium and the Physicians Committee for Responsible Medicine; the American Chemistry Council; and the Diisocyanates Panel of the American Chemistry Council.

Several commenters expressed general support for the proposed rule and made statements supporting specific aspects of the rule. For example, several commenters supported deleting the reference to sensitizers that occasionally induce an allergic response on first exposure so that substances that merely cause irritation upon initial exposure will not be considered strong sensitizers. Similarly, a commenter agreed with the proposal's emphasis that sensitization is an immunologically mediated, multi-stage process that occurs over a period of time. Several commenters raised issues that resulted in minor organizational and terminology changes to the proposed rule. All of the comments can be viewed at: *www.regulations.gov*, by searching under the docket number of the rulemaking, CPSC–2013–0010. Following is a summary of, and responses to, the comments.

Harmonization with International Criteria

Comment: Two commenters recommended that the CPSC take action to align the agency's chemical classification regulations and practices with internationally harmonized criteria, encouraging the Commission to implement the Globally Harmonized System of Classification and Labeling of Chemicals (GHS). One of the commenters argued that harmonization of chemical classification and labeling will promote regulatory efficiency and facilitate trade without lowering the level of health and environmental protection afforded by current U.S. laws and regulations. One of the commenters recommended that the Commission use the GHS cut-off value criteria for determining whether a substance is a sensitizer, unless there has been sensitization testing on the substance or product containing the substance.

Response: The GHS is a system for standardizing and harmonizing the classification and labeling of chemicals, but the GHS is not a regulation or a standard. The intent of the GHS is to provide an internationally comprehensible system for communicating chemical hazards to all sectors (*e.g.,* consumers, workers, emergency responders, and the public) along the entire life cycle of the chemical. The GHS establishes agreed-upon hazard classification and communication criteria with explanatory information on how to apply the system. Implementation of the GHS by the Commission would be broad-reaching, with potential impact beyond the FHSA, possibly involving the revision of existing CPSC statutes and regulations. The request that the Commission implement the GHS, therefore, goes well beyond the limited scope of this rulemaking proceeding.

Description of Strong Sensitizer Determination Process

Comment: Two commenters requested a description of the administrative process that would be used to make a determination that a substance or product containing a substance is a strong sensitizer so that stakeholders will be aware of opportunities for participation in the process.

Response: Under the FHSA, the Commission must first designate a substance a ''strong sensitizer'' for the substance to be considered a ''strong sensitizer.'' (15 U.S.C 1261(k)). Such a designation would occur in a separate proceeding that is outside the scope of this action. The current action relates only to the regulatory definition of a ''strong sensitizer,'' not to the designation of a particular substance as a strong sensitizer.

Labeling Requirement for Strong Sensitizers

Comment: One commenter requested that the Commission set forth the circumstances under which a substance or product containing a substance that has been designated a strong sensitizer would not require labeling under Section 2(p) of the FHSA (15 U.S.C. 1261(p).

Response: A substance that is a strong sensitizer or a product containing a strong sensitizer would not require labeling, unless the substance met the FHSA definition of ''hazardous substance.'' A ''hazardous substance'' is one that is a strong sensitizer (or has another of the specified ''hazardous substance'' characteristics) and ''may cause substantial personal injury or substantial illness during or as a proximate result of any customary or reasonably foreseeable handling or use, including reasonably foreseeable ingestion by children.'' 15 U.S.C. 1261(f). Thus, manufacturers of products containing a strong sensitizer would have to determine whether the concentrations and availability of the substance in their products could cause substantial injury or illness as a result of reasonably foreseeable handling or use. Labeling under section 2(p) of the FHSA would only be required if the product containing a strong sensitizer would cause substantial injury or illness as a result of reasonably foreseeable handling or use.

The Commission would also have the option of issuing a rule under Section 3(a) of the FHSA to designate a strong sensitizer as a hazardous substance to reduce uncertainty about which products would be considered a hazardous substance. *Id.* 15 U.S.C. 1262(a)(1). A hazardous substance that is not labeled properly with appropriate cautionary statements in accordance with section 2(p) of the FHSA is considered a ''misbranded hazardous substance.'' *Id.* 15 U.S.C. 1261(p). Introducing, delivering for introduction, or receiving in interstate commerce a

misbranded hazardous substance is a prohibited act. *Id.* 15 U.S.C. 1263(a) and (c).

Effect of Rule on Regulation of Products and Risk Management Actions

Comment: One commenter asserted that replacing the 1986 supplemental definition with the proposed definition could have far-reaching effects on the regulation of products at a broader level and stated that classifying substances as strong sensitizers may prompt risk management actions by the CPSC or other regulatory bodies. The commenter encouraged the CPSC to see that classification determinations fully reflect a science- and risk-based approach that considers the degree of hazard and extent of exposure potential.

Response: The Commission does not believe that replacing the 1986 supplemental definition with the final rule definition will have ''far-reaching effects.'' The rule does not designate any particular substance as a strong sensitizer, but the rule revises the regulatory definition of ''strong sensitizer.'' A separate proceeding involving a specific substance would be required before the agency could declare a substance to be a strong sensitizer. This rule simply provides guidance about the information and data that CPSC would consider and the relative importance of the information in making a strong sensitizer determination.

Moreover, the determination that a substance is a strong sensitizer does not, by itself, require any action by a manufacturer. Under the FHSA, labeling or other regulatory action implicating risk management factors is required only when a substance meets the definition of ''hazardous substance.'' (15 U.S.C. 1261(f)). A substance that the Commission designates as a strong sensitizer could be a ''hazardous substance'' under the FHSA, ''if such substance or mixture of substances may cause substantial personal injury or substantial illness during or as a proximate result of any customary or reasonably foreseeable handling or use, including reasonably foreseeable ingestion by children.'' Therefore, by definition, the FHSA considers exposure and requires a case-by-case hazard assessment. The final rule definition reflects both a science- and risk-based approach so that the decision for classification is not based solely on a product's ingredients.

Separate Treatment of Type I and Type IV Allergies in Sensitizer Definition

Comment: One commenter recommended that Type I and Type IV allergies be addressed separately in the final rule definition because these types of allergies have different potential for causing illness, discomfort, and chronic morbidity; and consideration of different types of data would be necessary to evaluate the potential of substances that trigger these two different types of reactions to cause substantial illness.

Response: A Type I allergy or immediate hypersensitivity is an allergic reaction provoked by reexposure to a specific type of allergen due to the production of specific antibodies. A Type IV allergy or delayed hypersensitivity is an allergic reaction that typically arises 1 to 3 days after exposure to an allergen and is not an antibody-mediated response. We agree that evaluating whether a substance is a strong sensitizer will depend on the substance and the allergic response the substance induces. However, we believe that the final rule definition would be significantly and unnecessarily more complex if these two types of allergies were separated into different categories.

The criteria contained in the supplemental definition allow for flexibility in assessing all types of allergic reactions to sensitizers. In addition, the final rule definition includes the various potential routes of exposure for sensitizers, as well as anatomic sites of an allergic response. The outcome of exposure, whether a dermal or respiratory response, likely will require the analysis of different data for evaluation. Evaluating whether a substance is a strong sensitizer requires a case-by-case inquiry, based on high-quality relevant data. The Strong Sensitizer Guidance document explains the approach CPSC staff would take in evaluating the potential causal link between exposure to strong sensitizers and these two types of hypersensitivity. We believe that the final rule definition provides the flexibility for assessing these two types of allergic reactions to sensitizers without the need for specifically differentiating them.

Acceptance of Data From Certain QSAR Models

Comment: One commenter requested that the Commission revise the proposed definition to provide for the acceptance of data from Quantitative Structure-Activity Relationship (QSAR) models (mathematical models that relate a quantitative measure of chemical structure to biological activity) that the Organisation for Economic Co-operation and Development (OECD) has evaluated and approved for specific applicability domains.

Response: The final rule definition specifically states that in determining whether a substance has a significant potential for causing hypersensitivity, chemical or functional properties of the substance of interest, in addition to QSAR data, can be considered. The panel of experts and external peer reviewers determined that QSAR data are not sufficient as stand-alone analyses for determining potency of a sensitizer but that QSAR analysis could be used in a weight-of-evidence approach.

The OECD Council Act relating to the Mutual Acceptance of Data (MAD), which was agreed to by all OECD member countries, established that safety data developed in one member country will be accepted for use by the relevant registration authorities in assessing the chemical or product in another OECD country (*i.e.,* the data do not have to be generated a second time for the purposes of safety assessment), under the assurance that the data were developed in compliance with the Principles of Good Laboratory Practice. Therefore, if a manufacturer submitted QSAR data to the Commission when the Commission was determining whether a substance is a strong sensitizer, the Commission would take the QSAR data into consideration. However, this QSAR data would not take precedence over high-quality human and animal data. The Commission believes that modifying the proposed definition in response to this comment is not warranted.

Ordering of Factors To Be Considered in Determining Whether a Substance Is a Strong Sensitizer

Comment: One commenter suggested revising the order of the factors that would be taken into consideration to determine whether a substance is a ''strong'' sensitizer and including a reference in that paragraph to unranked data that appears elsewhere in the proposed definition. The commenter requests: (1) Shifting the order of factors as they appear in the paragraph listing the factors to be considered in determining whether a sensitizer is ''strong''—for example moving ''well-conducted animal studies'' to the end of the list; (2) moving two of the unranked factors listed in the proposed supplemental definition (quantitative structure-activity relationship information and bioavailability data) into the list of ranked factors as the third and fourth priority position; and (3) separating existing versus new *in vitro* and *in vivo* studies into different factor categories.

Response: CPSC based the order of ranked data criteria in the proposed definition on extensive input from the international panel of scientific experts from academia, industry, and the federal government. We concurred with the panelists' suggestion to rank and list the qualifying factors in order of importance in the final rule definition, instead of ''any or all,'' which is how the factors appear in the 1986 supplemental definition.

The Commission believes that the ranked list of criteria for determining whether a substance or product containing a substance is a ''strong'' sensitizer should remain as stated in the proposed definition but that the reference to unranked factors, such as quantitative structure-activity relationship information, *in silico* data and bioavailability data, should be moved to the end of the list of ranked factors so that the order is more logical. The list of criteria reflects Commission policy that human data take precedence over animal data and takes into consideration the value and relevance that the particular data would provide in making a determination of sensitizing strength, and therefore, the potential to cause hypersensitivity. The criteria list is consistent with the CPSC Animal Testing Policy, the FHSA Chronic Hazard Guidelines, and Commission policy that strongly encourage the use of scientifically validated alternatives to animal testing and the use of existing information, including expert opinion, prior human experience, and prior animal testing results.

Consistency of Order of Factors Listed Throughout the Rule

Comment: One commenter pointed out that the factors to be considered in determining whether a substance has a ''significant potential for causing hypersensitivity'' were not listed in the same order when listed as factors to be considered in determining whether a substance is a ''strong'' sensitizer. The commenter requested that the Commission be consistent when listing the types of data in these two paragraphs.

Response: We agree that the order of factors should be consistent in these paragraphs. Therefore, we have modified the proposed definition by: (1) moving ''chemical or functional properties of the substance'' to the end of the last sentence in the first paragraph of section (ii); and (2) in the same sentence reversing the positions of *in vitro* and *in vivo.*

Use of Existing Animal Testing Data

Comment: One commenter recommended that we specify that existing animal testing data be submitted to the CPSC for consideration in making a strong sensitizer determination before additional animal testing data is generated.

Response: As stated in the CPSC Animal Testing Policy, codified at 16 CFR 1500.232, neither the FHSA, nor the regulations issued under the FHSA, require animal testing to determine whether a hazard exists. The Commission's regulations under the FHSA concerning toxicity and irritancy allow the use of animal tests to determine the presence of the hazard when human data or existing animal data are not available. However, the Commission's policy encourages manufacturers subject to the FHSA to use existing alternatives to animal testing wherever possible; supports limiting animal testing to a minimum number of animals; and advocates measures that eliminate or reduce the pain or discomfort to animals that can be associated with such tests. The Commission's animal testing policy encourages manufacturers of products subject to the FHSA to use existing alternatives to animal testing, whenever possible, such as: prior human experience (*e.g.,* published case studies); *in vitro* or *in silico* test methods that have been approved by the Commission; literature resources containing the results of prior animal testing or limited human tests; and expert opinion. We believe that the animal testing policy codified at 16 CFR 1500.232, sufficiently communicates the preference for alternatives to animal testing, whenever possible, including the submission of relevant existing data resulting from prior animal testing.

Consideration of in Vitro Studies in Making Strong Sensitizer Determinations

Comment: One commenter asked why *in vitro* studies were added to the list of factors to consider in determining whether a substance is a strong sensitizer when such studies are not validated to determine potency. Another commenter requested that data from well-conducted *in vitro* assays be considered by the Commission in making this determination.

Response: The 1986 supplemental definition and the final rule definition both list *in vitro* data as a factor to be considered in determining whether a substance is a strong sensitizer. We agree that currently, there are no validated *in vitro* assays for sensitizer potency determination. However, a large number of *in vitro* assays are in development, undergoing validation, or have completed validation for the determination of sensitization. The European Union Reference Laboratory for Alternatives to Animal Testing (EURL–ECVAM) completed validation of an *in vitro* assay and an *in chemico* assay this year. EURL–ECVAM recommended that neither assay could be used as a stand-alone test; although EURL–ECVAM determined that the assays could be included in a weight-of-evidence approach or integrated testing strategy. Although the assays have some limitations, EURL–ECVAM concluded that with further work, these assays might be able to contribute to the assessment of sensitizer potency. As stated in the strong sensitizer guidance document, the CPSC would follow a weight-of-evidence approach, using all available validated tools (including both positive and negative data), in determining whether a substance is a strong sensitizer.

Consideration of Reports of Consumer Incidents

Comment: One commenter recommended including in the list of factors to be considered in determining whether a substance is a strong sensitizer, the CPSC's and manufacturers' records of incidents of consumer hypersensitivity to a substance or product containing a substance.

Response: We agree that incident reports are an important consideration in determining a substance's ability to cause hypersensitivity. The final rule definition lists ''case histories'' as information that the Commission may consider in determining whether a substance has a significant potential for causing hypersensitivity. The term ''case histories'' includes reports of incidents of consumer hypersensitivity to a substance or product containing the substance that are received by manufacturers or the CPSC. Commission staff will consider revising the Strong Sensitizer Guidance document to provide additional clarification regarding the types and sources of incident reports that CPSC should consider when determining whether a substance is a strong sensitizer.

Description of ''Clinically Important Reaction''

Comment: The proposed definition provides that in determining whether a substance is a strong sensitizer, the Commission must consider the severity of the reaction to the substance and only designate substances as strong

sensitizers that cause a ''clinically important reaction.'' The proposed definition includes a list of four potential reactions to strong sensitizer exposure that would be characterized as ''clinically important'' or manifestations of ''substantial illness.'' One of the clinically important reactions listed in the proposed definition is ''substantial physical discomfort or distress.'' One commenter noted that ''discomfort and distress are actually perceptual (mental), although they may be caused by various agents (*e.g.,* physical, chemical agent, biological).'' The commenter suggested replacing the phrase ''substantial physical discomfort and distress'' with the phrase ''physiological stress resulting in discomfort or distress.''

Response: We agree that the phrase ''substantial physical discomfort or distress'' may not be clear, but we believe that ''physiological stress resulting in discomfort or distress,'' as suggested by the commenter, may also be too vague. We have replaced ''substantial physical discomfort or distress'' with ''substantial physiological effects, such as discomfort and distress,'' as a factor to be considered in determining whether a strong sensitizer produces ''substantial illness.'' We believe that this phrase reflects better a scenario such as a systemic allergic contact dermatitis rash.

Meaning of ''Chronic Morbidity''

Comment: One commenter asked whether the reference to ''chronic morbidity'' as a factor in determining whether a strong sensitizer produces ''substantial illness'' was associated with a specific length of time, such as 90 days.

Response: The proposed definition includes a list of four potential reactions to strong sensitizer exposure that would be characterized as ''clinically important'' or manifestations of ''substantial illness.'' One of the clinically important reactions listed in the proposed definition is ''chronic morbidity.'' The Commission does not view the use of the term ''chronic'' as referring to a specific length of time. Under the FHSA Chronic Hazard Guidelines (16 CFR 1500.135), which are broad guidelines containing a number of assumptions, methodologies, and procedures for determining chronic hazard and risk, the Commission does not set a length of time for ''chronic,'' but instead, the Commission leaves the determination open to expert judgment. We have replaced the phrase ''chronic morbidity'' with ''persistent morbidity'' in the final rule definition to clarify that a ''clinically important reaction'' is a substantial illness that occurs over an extended period of time.

Addition of ''Mortality'' to ''Substantial Illness'' Factors

Comment: One commenter suggested that ''mortality'' be added to the list of factors to be considered in determining whether a strong sensitizer produces substantial illness.

Response: Mortality (*i.e.,* death) is not an illness but is a distinct endpoint that in rare cases could result from substantial uncontrolled anaphylaxis. We have revised the definition to include: ''or in rare cases, mortality'' at the end of the section that lists the types of reactions to substances that may be considered ''substantial illness.''

Removal of Oil of Bergamot From List of Strong Sensitizer Substances

Comment: One commenter requested that oil of bergamot (and products containing 2 percent or more of oil of bergamot) be removed from the list of ''strong sensitizer'' substances.

Response: Oil of bergamot is a phototoxin that FDA listed as a ''strong sensitizer'' (the list appears in 16 CFR 1500.13). The current rulemaking proceeding only addresses revisions to the supplemental definition of ''strong sensitizer.'' To make any changes to the existing list of substances currently considered to be strong sensitizers, the Commission would need to conduct a separate proceeding.

C. Revisions to the Strong Sensitizer Supplemental Definition

As discussed in Section B, above, the comments received in response to the NPR generally supported the Commission's replacement of the 1986 supplemental definition of ''strong sensitizer'' with the proposed definition. However, several commenters recommended additional changes that we have determined should be incorporated into the supplemental definition of strong sensitizer. Below, we discuss the differences between the 1986 supplemental definition and the proposed definition, along with the changes we have made to the proposed definition, based on comments and that have been incorporated into the final rule.

1. Definition of ''Sensitizer'' (§ 1500.3(c)(5)(i))

The 1986 supplemental definition specified that a ''sensitizer'' will ''induce an immunologically-mediated (allergic) response, including allergic photosensitivity,'' that will become evident upon reexposure to the same substance, or occasionally, on first exposure, by virtue of active sensitization.

The final rule reflects the traditional definition for ''sensitization''; sensitization is a multi-stage immune-mediated process that occurs over a period of time. Replacing the phrase ''immunologically-mediated (allergic) response'' with ''immunologically-mediated hypersensitivity,'' captures those substances that sensitize through atypical mechanisms, rather than by inducing an obvious ''immunologically-mediated response.'' The final rule also eliminates the last sentence of the current definition based on concerns that the sentence could be misinterpreted to include substances that cause an irritant response only [1] (the response that is noted after the first exposure to a substance is more frequently an irritant response and not an allergic response). Typically, allergic responses are the result of a two-step process: (1) induction (sensitization), which requires sufficient or cumulative exposure to induce an immune response with few or no symptoms; and (2) elicitation when an individual who has been sensitized demonstrates symptoms upon subsequent exposures. The final rule includes the phrase ''variable period of exposure'' to reflect the latency period that is a characteristic in the development of sensitization. This section of the final rule is the same as proposed.

2. Determination of Significant Potential for Causing Hypersensitivity (§ 500.3(c)(5)((ii))

The statutory definition of ''strong sensitizer'' requires that, before designating a substance as a strong sensitizer, the Commission ''upon consideration of the frequency of occurrence and severity of reaction, shall find that the substance has a significant potential for causing hypersensitivity.'' 15 U.S.C. 1261(k).

As discussed in the NPR, the proposed definition added qualifiers for susceptibility profiles—genetics, age, gender, and atopic status— to the information and data listed in the 1986 supplemental definition that may be considered in determining whether a substance has a significant potential for causing hypersensitivity. These characteristics are well-known modifiers in the development and exacerbation of allergic responses to chemical sensitizers. In response to a

[1] An ''irritant response'' is a nonimmune mediated response and one that results from direct injury to the tissue. An irritant is any agent that is capable of producing cell damage in any individual if applied for sufficient time and concentration.

comment, for the final rule, we have reordered the list as it appeared in the proposed definition so that the final definition presents the factors to be considered in determining whether a substance has a significant potential for causing hypersensitivity. This represents the same order as the factors to be considered in determining whether a substance is a ''strong'' sensitizer. This reordering results in ''chemical or functional properties of the substance'' becoming the last category on the list, and the references to *in vitro* and *in vivo* experimental studies are reversed.

As discussed in the NPR, the proposed definition also replaced the term ''normal'' with ''non-sensitized,'' which describes more accurately the general control population. This remains the same in the final rule.

As discussed in the NPR, the proposed definition incorporated the factors to be considered in determining whether a substance is a ''strong'' sensitizer into the subsection explaining ''significant potential for causing hypersensitivity.'' The 1986 supplemental definition of ''strong sensitizer'' contains a separate subsection that sets forth factors that should be considered in determining the strength of a sensitizer. (16 CFR 1500.3(c)(5)(ii)). This section of the 1986 supplemental definition includes several factors that are subjective rather than quantitative (*i.e.,* physical discomfort, distress, hardship) and allows for risk assessment considerations in connection with an analysis that should only be a hazard characterization step.

As discussed in the NPR, the proposed definition eliminated the ''quantitative or qualitative risk assessment factor. '' We believe this terminology is confusing because the language places a risk assessment step within the hazard identification step of the process of determining whether a product containing a strong sensitizer is a hazardous substance that requires labeling. The NPR proposed definition remains the same in the final rule, except for the reordering of certain factors in response to a comment.

As discussed in the NPR, the proposed definition makes clear that a weight-of-the-evidence approach is to be used in determining the strength of a sensitizer because of the imprecise nature of some of the current factors and the potential lack of information or data available to permit useful consideration of certain factors. Rather than allow an ''any or all'' approach to the factors that would be considered by the Commission in determining whether a sensitizer is strong, the revision ranks data sources in order of importance following the FHSA preference for human data over animal data and takes into consideration the value and relevance that certain data would provide in evaluating the potential of a substance to cause hypersensitivity. For example, the proposed definition expressed a preference for general population epidemiological studies over occupational studies because the degree of sensitization in the workplace is likely to be greater than that of the general population, due to greater exposure (both in time and concentration) to the sensitizing agent. The ranking of data sources remains the same in the final rule.

As discussed in the NPR, the proposed definition listed additional factors that the Commission can consider in determining a substance's sensitizing potential, for which validated methods currently do not exist but are in development, such as: Quantitative Structure-Activity Relationships (QSARs), and *in silico* [2] data, along with the caveat that using these techniques would be in addition to consideration of human and animal data. We have revised the definition in the final rule to reposition these factors from the end of Section 1500.3(c)(5)(ii) to follow immediately the listing of ranked factors that are to be considered in determining whether a substance is a ''strong'' sensitizer.

As discussed in the NPR, the proposed definition provided that for a substance to be considered a ''strong'' sensitizer, the substance must be found to produce a ''clinically important reaction,'' which is defined as a reaction with a significant impact on the quality of life. The Commission has revised the proposed definition in response to a comment to replace ''substantial physical effects'' with ''substantial physiological effects'' as a factor to be considered in determining whether a strong sensitizer produces ''substantial illness''; to replace ''chronic morbidity'' with ''persistent morbidity''; and to add ''or in rare cases, mortality'' to the end of section 1500.3(c)(5)(ii). The change from ''physical'' to ''physiological'' is intended to describe more accurately and broadly the body's response to exposure to a substance that could rise to the level of a clinically important reaction. The change from ''chronic'' to ''persistent,'' also made in response to a comment, is intended to convey more clearly that a substantial illness may be one that endures for an extended period of time.

As discussed in the NPR, the proposed definition also directed the Commission to consider the location of the hypersensitivity response, such as the face, hands, and feet, and the persistence of clinical manifestations in determining whether the substance produces a ''clinically important reaction.'' This aspect of the NPR remains the same in the final rule.

3. Definition of Normal Living Tissue (§ 1500.3(c)(5)(iii))

The statutory definition of ''strong sensitizer'' specifies that a strong sensitizer is a substance that will cause hypersensitivity on ''normal living tissue.'' The 1986 supplemental definition identifies skin and other organ systems, such as the respiratory or gastrointestinal tract, as types of ''normal living tissue'' in which the allergic hypersensitivity reaction can occur. The proposed definition adds a specific reference to mucous membranes, such as ocular and oral systems, as additional types of normal living tissue upon which a substance can cause a hypersensitivity that warrants a determination that a substance is a ''strong sensitizer.'' This remains the same in the final rule.

D. Staff Guidance and Notice of Availability

Commission staff developed a guidance document that is intended to clarify the ''strong sensitizer'' definition and assist manufacturers in understanding how CPSC staff would assess whether a substance and/or product containing that substance should be considered a ''strong sensitizer.'' A Notice of Availability was published in the **Federal Register** on March 12, 2013 (78 FR 15710), which provided a link to the location on the Commission's Web site where the staff guidance document can be found. Several commenters included questions and observations regarding the guidance document in their submissions addressing the proposed revision to the definition of ''strong sensitizer.'' Commission staff will review these comments, and where appropriate, will revise the guidance document.

E. Impact on Small Businesses

The Commission certifies that this rule will not a have a significant impact on a substantial number of small entities

[2] QSARs are mathematical models that relate a quantitative measure of chemical structure to biological activity. *In silico* data is a computational approach using sophisticated computer models for the determination of a sensitizing potential. Both of these approaches are evolving methodologies that have not yet been validated, but are being pursued as testing options that would reduce the numbers of expensive laboratory and animal experiments being carried out.

under section 605(b) of the Regulatory Flexibility Act (RFA), 5 U.S.C. 605(b). For the NPR, the Commission's Directorate for Economic Analysis prepared an assessment of the impact of the proposed definition of ''strong sensitizer.'' That assessment found that there would be little or no effect on small businesses and other entities because the amendment, which simply modifies the existing supplemental definition of ''strong sensitizer,'' will not result in compliance actions. Products will not need to be modified to comply with the revised supplemental definition, nor will the revised supplemental definition impose any additional testing or recordkeeping burdens. The obligation to label a product as a strong sensitizer and any costs associated with that obligation will not arise until the Commission has designated a particular substance contained in the product as a strong sensitizer, which would occur only in connection with a separate process. Thereafter, we would assess the potential small business impact of designating the particular substance as a strong sensitizer. Whether the final rule would impose any indirect burden on small businesses or other entities is unknown because the impact of the changes to the supplemental definition of strong sensitizer on future strong sensitizer designation proceedings is not known. The Commission did not receive any comments concerning the impact the rule would have on small businesses and is not aware of any information that would alter the assessment stated in the NPR.

F. Environmental Considerations

Generally, CPSC rules are considered to ''have little or no potential for affecting the human environment,'' and environmental assessments and environmental impact statements are not usually prepared for these rules (see 16 CFR 1021.5(c)(1)). The Commission does not expect the rule to have any adverse impact on the environment under this categorical exclusion.

G. Executive Orders

According to Executive Order 12988 (February 5, 1996), agencies must state in clear language the preemptive effect, if any, of new regulations. Section 18 of the FHSA addresses the preemptive effect of certain rules issued under the FHSA. 15 U.S.C. 1261n. Because this rulemaking would revise a regulatory definition, rather than issue a labeling or banning requirement, section 18 of the FHSA does not provide for the rule to have preemptive effect.

H. Paperwork Reduction Act

This rule would not impose any information collection requirements. Accordingly, this rule is not subject to the Paperwork Reduction Act, 44 U.S.C. 3501–3520.

I. Effective Date

The Administrative Procedure Act generally requires that a substantive rule be published not less than 30 days before its effective date, unless the agency finds, for good cause shown, that a lesser time period is required. 5 U.S.C. 553(d)(3). The final rule will take effect March 17, 2014.

List of Subjects in 16 CFR Part 1500

Consumer protection, Hazardous substances, Imports, Infants and children, Labeling, Law enforcement, Reporting and recordkeeping requirements, and Toys.

Accordingly, 16 CFR part 1500 is amended as follows:

PART 1500—[AMENDED]

■ 1. The authority citation for part 1500 continues to read as follows:

Authority: 15 U.S.C. 1261–1278.

■ 2. Revise paragraph (c)(5) of § 1500.3 to read as follows:

§ 1500.3 Definitions

* * * * *

(c) * * *

(5) The definition of *strong sensitizer* in section 2(k) of the Federal Hazardous Substances Act (restated in paragraph (b)(9) of this section) is supplemented by the following definitions:

(i) *Sensitizer.* A sensitizer is a substance that is capable of inducing a state of immunologically mediated hypersensitivity (including allergic photosensitivity) following a variable period of exposure to that substance. Hypersensitivity to a substance will become evident by an allergic reaction elicited upon reexposure to the same substance.

(ii) *Significant potential for causing hypersensitivity.* (A) Before designating any substance a ''strong sensitizer,'' the Commission shall find that the substance has significant potential for causing hypersensitivity. *Significant potential for causing hypersensitivity* is a relative determination that must be made separately for each substance. The determination may be based on documented medical evidence of hypersensitivity reactions upon subsequent exposure to the same substance obtained from epidemiological surveys or case histories; controlled *in vivo* or *in vitro* experimental studies; susceptibility profiles (*e.g.,* genetics, age, gender, atopic status) in non-sensitized or allergic subjects; and chemical or functional properties of the substance.

(B) In determining whether a substance is a ''strong'' sensitizer, the Commission shall consider the available data for a number of factors, following a weight-of-evidence approach. The following factors (if available), ranked in descending order of importance, should be considered: well-conducted clinical and diagnostic studies, epidemiological studies, with a preference for general population studies over occupational studies, well-conducted animal studies, well-conducted *in vitro* test studies, cross-reactivity data, and case histories.

(C) Additional consideration may be given to Quantitative Structure-Activity Relationships (QSARs), *in silico* data, specific human sensitization threshold values, other data on potency and sensitizer bioavailability, if data are available and the methods validated. Bioavailability is the dose of the allergen available to interact with a tissue. Bioavailability is a reflection of how well the skin or another organ can absorb the allergen and the actual penetrating ability of the allergen, including factors such as size and composition of the chemical.

(D) Criteria for a ''well-conducted'' study would include: validated outcomes, relevant dosing, route of administration, and use of appropriate controls. Studies should be carried out according to national and/or international test guidelines and according to good laboratory practice (GLP), compliance with good clinical practice (GCP), and good epidemiological practice (GEP).

(E) Before the Commission designates any substance as a ''strong'' sensitizer, frequency of occurrence and range of severity of reactions in exposed subpopulations having average or high susceptibility will be considered. The minimal severity of a reaction for the purpose of designating a material as a ''strong sensitizer'' is a clinically important reaction. A clinically important reaction would be considered one with a significant impact on quality of life. Consideration should be given to the location of the hypersensitivity response, such as the face, hands, and feet as well as persistence of clinical manifestations. For example, strong sensitizers may produce substantial illness, including any or all of the following: substantial physiological effects, such as discomfort and distress, substantial hardship, functional or structural impairment, persistent morbidity, or in rare cases, mortality.

(iii) *Normal living tissue.* The allergic hypersensitivity reaction occurs in normal living tissues, including the skin, mucous membranes (*e.g.,* ocular, oral), and other organ systems, such as the respiratory tract and gastrointestinal tract, either singularly or in combination, following sensitization by contact, ingestion, or inhalation.

* * * * *

Dated: February 11, 2014.

Todd A. Stevenson,

Secretary, U.S. Consumer Product Safety Commission.

[FR Doc. 2014–03260 Filed 2–13–14; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 803

[Docket No. FDA–2008–N–0393]

RIN 0910–AF86

Medical Device Reporting: Electronic Submission Requirements

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is revising its postmarket medical device reporting regulation and making technical corrections. This final rule requires device manufacturers and importers to submit mandatory reports of individual medical device adverse events, also known as medical device reports (MDRs), to the Agency in an electronic format that FDA can process, review, and archive. Mandatory electronic reporting will improve the Agency's process for collecting and analyzing postmarket medical device adverse event information. Electronic reporting is also available to user facilities, but this rule permits user facilities to continue to submit written reports to FDA. This final rule also identifies changes to the content of required MDRs to reflect reprocessor information collected on the Form FDA 3500A as required by the Medical Device User Fee and Modernization Act of 2002 (MDUFMA).

DATES: This final rule is effective August 14, 2015 (see also section IX of this document).

FOR FURTHER INFORMATION CONTACT: Sharon E. Kapsch, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 3208, Silver Spring, MD 20993–0002, 301–796–6104.

SUPPLEMENTARY INFORMATION:

Table of Contents

I. History of the Medical Device Reporting Regulation

The MDR regulation was first published on September 14, 1984 (49 FR 36326), with requirements for manufacturer and importer reporting of deaths, serious injuries, and malfunctions effective December 13, 1984.[1] FDA's regulations governing medical device adverse event reporting implement section 519 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 360i). Section 519 of the FD&C Act has undergone several changes since its enactment as part of the Medical Device Amendments of 1976 (Pub. L. 94–295). As a result, FDA's regulations at part 803 (21 CFR part 803) have also undergone multiple revisions. The Safe Medical Devices Act of 1990 (SMDA) (Pub. L. 101–629) amended the FD&C Act to require mandatory reporting of device adverse events by user facilities (deaths reported to FDA and the manufacturer, and serious injuries or illnesses reported to the manufacturer) and domestic distributors (deaths and serious injuries or illnesses reported to FDA and the manufacturer, and certain malfunctions reported to the manufacturer). The SMDA also amended the FD&C Act to require manufacturers and distributors (including importers) to certify the number of MDRs submitted to the Agency each year and to require user facilities to submit a semiannual report summarizing reportable events. FDA published a tentative final rule on November 26, 1991 (56 FR 60024), to implement the SMDA requirements for reporting for device manufacturers, user facilities, and distributors, including importers (the 1991 tentative final rule). By statute, user facility reporting became effective on November 28, 1991, and distributor reporting became effective on May 28, 1992.

On June 16, 1992, the Medical Device Amendments of 1992 (the 1992 amendments) (Pub. L. 102–300) further amended certain provisions of section 519 of the FD&C Act relating to reporting of adverse device events. The amendments adopted a single reporting standard and definition for serious injury/serious illness for manufacturers, importers, distributors, and user facilities. The changes under the 1992 amendments were effective on June 16, 1993.

On September 1, 1993, FDA published a final rule (58 FR 46514) that collected the requirements for all wholesale distributors, importers as well as domestic, under a new part 804 (21 CFR part 804).

On December 11, 1995 (60 FR 63578), FDA published a final rule for manufacturers and user facilities (the 1995 final rule), with changes from the 1991 tentative final rule, including a requirement for the use of the Form

[1] See 49 FR 36644, September 19, 1984 (correcting the effective date).