## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

**[Docket No. 96N–0119]**

**RIN 0910–AA34**

### 21 CFR Part 801

### Latex-containing Devices; User Labeling

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Proposed rule.

**SUMMARY:** The Food and Drug Administration (FDA) is proposing to amend the regulations to require all medical devices containing natural rubber latex that may directly or indirectly contact living human tissue to be labeled with a statement identifying the product as one which contains natural rubber latex and which may cause allergic reactions. The agency is also amending the regulation to require that hypoallergenicity claims be removed from latex medical gloves and other natural rubber latex medical devices because the modified human Draize test currently used to support hypoallergenicity claims addresses only chemical sensitivity, and it is inappropriate for determining protein sensitivity in humans. These requirements are being proposed in response to numerous reports that have been received of severe allergic reactions to a wide range of medical devices containing natural rubber latex.

**DATES:** Comments by September 23, 1996. FDA is proposing that the final regulation based on this proposal be effective 180 days after the date of its publication in the Federal Register.

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

**FOR FURTHER INFORMATION CONTACT:** Donald E. Marlowe, Center for Devices and Radiological Health (HFZ–100), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–443–2444.

**SUPPLEMENTARY INFORMATION:**

## I. Background

Natural rubber latex is a milky fluid produced by the *Heavea brasiliensis* (rubber) tree. There is often confusion concerning the terminology used to describe the raw agricultural material derived from the rubber tree and the chemical nomenclature that refers to emulsions of synthetic rubbers and plastics to which natural rubber latex has been added.

Latex, either natural or synthetic, is a colloidal dispersion of a polymeric material in a liquid system mostly aqueous in nature (Ref. 1). ''Natural rubber latex,'' for the purpose of this proposed rule, means a milky fluid that consists of extremely small particles of rubber, obtained from the *H. brasiliensis* (rubber) tree, dispersed in an aqueous medium. It contains a variety of naturally occurring substances, including carbohydrates, lipids, phospholipids, proteins, minerals, small amounts of complex organic material, water, and cis–1,4 polyisoprene, in a colloidal suspension.

The phrase ''natural rubber latex'' refers to the raw material used in the manufacture of both natural rubber latex products and dry natural rubber products. These products are formed by two commonly employed manufacturing processes. One of these is the natural rubber latex manufacturing process (NRL process), which involves the use of natural latex in a concentrated liquid form. Products are formed from NRL processing by dipping, extruding, or coating, and are typically referred to as containing or made of ''natural rubber latex.'' Examples of devices manufactured by the NRL process include medical gloves, catheters, and condoms.

The dry natural rubber manufacturing process (DNR process) involves the use of coagulated natural latex in dried or milled sheets. Products are formed from the DNR process by compression molding, extrusion, or by converting the sheets into a solution for dipping. These products are typically referred to as containing or made of ''dry rubber.'' Examples of devices or device components containing dry rubber include syringes with dry rubber plungers, vial stoppers, and intravascular injection ports.

The phrase, ''contains natural rubber latex,'' as used herein, encompasses products made by either process, as well as products described as made of ''synthetic latex'' that include natural rubber latex in their formulations. This proposed rule would not apply to products made from synthetic latex, which do not include natural rubber latex in their formulation.

Since 1988, FDA has noted an increase in the number of reports submitted to its Medical Device Reporting (MDR) system regarding sensitivity to natural rubber latex proteins contained in medical devices. In May of 1990, FDA became aware of deaths associated with barium enema procedures. Further investigation of the problem revealed that these deaths were associated with anaphylactic reactions to the natural latex cuff on the tip of the barium enema catheters. In several hundred reports of adverse reactions to natural rubber latex that the agency has received since October 1988, 16 have involved deaths from anaphylactic shock. Furthermore, several scientific journals have reported incidents of sensitivity to natural rubber latex proteins in a wide range of medical devices. (See Refs. 2 through 18.)

Section 701(a) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 371(a)) authorizes FDA to issue substantive binding regulations for the efficient enforcement of the act. (*Weinberger* v. *Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609 (1973); see also *Weinberger* v. *Bentex Pharmaceuticals, Inc.*, 412 U.S. 645, 653 (1973); *National Ass'n of Pharmaceutical Manufacturers* v. *FDA*, 637 F.2d 877 (2d Cir. 1981); *National Confectioners Ass'n* v. *Califano*, 569 F.2d 690 (D.C. Cir. 1978); *National Nutritional Foods Ass'n* v. *Weinberger*, 512 F.2d 688 (2d Cir.), *cert. denied*, 423 U.S. 825 (1975).)

Section 502(a) of the act (21 U.S.C. 352(a)) provides that a device is misbranded ''If its labeling is false or misleading in any particular.'' Section 201(n) of the act (21 U.S.C. 321(n)) provides that, in determining whether labeling of a regulated article (such as a device) is misleading

> * * * there shall be taken into account * * * not only representations made or suggested by statement, word, design, device, or any combination thereof, but also the extent to which the labeling * * * fails to reveal facts material in light of such representations * * * with respect to consequences which may result from the use of the article to which the labeling * * * relates under the conditions of use prescribed in the labeling or advertising thereof or under such conditions of use as are customary or usual.

The courts have upheld FDA's authority to prevent false or misleading labeling by issuing regulations requiring label warnings and other affirmative disclosures. (See, e.g., *Cosmetic, Toiletry, and Fragrance Association* v. *Schmidt*, 409 F. Supp. 57 (D.D.C. 1976), *aff'd without opinion*, Civil No. 75–1715 (D.C. Cir. August 19, 1977), even in the absence of a proven cause-and-effect relationship between product usage and harm; *Council for Responsible Nutrition* v. *Goyan*, Civil No. 80–1124 (D.D.C August 1, 1980).)

Section 502(f)(1) of the act provides that a device is also misbranded unless its labeling bears adequate directions for use. Adequate directions for use means

adequate directions under which a layperson can use a device safely and for the purpose for which it was intended. (See 21 CFR 801.5 and 801.6.)

II. Latex Labeling

FDA is proposing that medical devices containing natural rubber latex that may directly or indirectly contact living human tissue be labeled with a statement identifying the product as one which contains natural rubber latex, which may cause allergic reactions. Direct contact with living human tissue occurs when a natural rubber latex-containing medical device touches the skin, mucous, or serosal surfaces. Examples of indirect contact with living human tissue by a natural rubber latex-containing medical device include, but are not limited to, the following: Contact with natural rubber latex proteins that have become suspended in liquid, which can occur when injections are given through a natural rubber latex-containing injection port or a syringe with a natural rubber latex-containing plunger; contact with natural rubber latex protein that is airborne, often in conjunction with the use of glove dusting powder; and contact with natural latex residues that have been transferred to nonrubber latex-containing medical devices, or other objects or surfaces. Devices affected by this proposed rule would be required to be labeled with one of the following statements: ''This product contains natural rubber latex which may cause allergic reactions in some individuals''; ''This product has components that contain natural rubber latex which may cause allergic reactions in some individuals''; or ''This product is made from natural rubber latex which may cause allergic reactions in some individuals''.

The agency has provided three labeling options so that manufacturers may choose the language most appropriate for their products. The agency invites comments regarding whether FDA should require a single, uniform, labeling statement for all natural latex-containing medical devices, and the agency will consider comments recommending alternative language for the proposed labeling statements.

Representative examples of natural rubber latex-containing medical devices which would require such labels include, but are not limited to the following: Cuffed-barium enema tips and enteroclysis catheters; contraceptive devices such as condoms with or without spermicidal lubricant, cervical caps, diaphragms and accessories, and therapeutic douche apparati; airway and respiratory devices such as oxygen cannulas, nasopharyngeal airways, tracheal tubes and inflatable cuffs, tracheobronchial suction catheters, breathing bags and mouthpieces; dental and surgical equipment such as dental dams, orthodontic appliances and headgear, anaesthetic gas masks, epistaxis balloons, and endotracheal tubes; and frequently used hospital equipment such as urinary catheters and accessories, blood pressure cuffs, intravascular equipment with latex injection ports, electrode pads, tourniquets, enema bags, hot or cold water bottles, rubber sheets, stomach and intestinal tubes, hemodialysis equipment, wound drains, adhesive tape, elastic bandages, and medical gloves.

Medical gloves include surgeon's gloves, as classified at 21 CFR 878.4460, and patient examination gloves, as classified at 21 CFR 880.6250. Some medical gloves are made of materials that may not contain natural rubber latex in their formulations and, therefore, would not be subject to this proposal. It should be further noted that the term ''medical gloves'' is used to distinguish them from nonmedical gloves that are not regulated by FDA. Nonmedical gloves, commonly referred to as utility, industrial, protective, or general purpose gloves, are not medical devices if they are not intended and/or labeled for a medical purpose, such as prevention of disease. Such products would not be subject to this proposed rule.

This rule is being proposed because medical devices that are composed of natural rubber latex, or which contain components formulated from natural latex, pose a significant health risk to some health care consumers and providers. A statement on the label of medical devices identifying the presence of natural latex, and its risks, is considered to be necessary for the safe and effective use of such devices. The primary purpose of such a statement is to inform health care professionals and consumers about the presence and risks of natural rubber latex, and to ensure a safe medical environment for persons who have been identified as sensitive to natural rubber latex.

The agency believes that a statement on the labeling of the devices stating that the product contains natural rubber latex, and that the presence of natural rubber latex may cause allergic reactions, is essential. The omission of such information from the labeling of such a device would constitute an omission of a material fact, and would render the device misbranded within the meaning of section 502(a) of the act (21 U.S.C. 352(a)). Moreover, because users need to be aware of safety problems that may be caused by natural rubber latex, FDA believes that a device containing natural rubber latex, which is not labeled with information regarding the presence of natural rubber latex and its potential risks, fails to bear adequate directions for use, and is, therefore, also misbranded under section 502(f)(1) of the act.

Section 502(c) of the act provides that a device is misbranded ''[i]f any word, statement, or other information required by or under authority of this Act to appear on the label or labeling is not prominently placed thereon with such conspicuousness (as compared with other words, statements, designs, or devices, in the labeling) and in such terms as to render it likely to be read and understood by the ordinary individual under customary conditions of purchase and use.'' Accordingly, the proposed regulation would require the rubber latex sensitivity statement to be displayed prominently and conspicuously on the device labeling. If the labeling statement is not prominently displayed, the product would be deemed misbranded under section 502(c) of the act.

Accordingly, under the proposed rule, any natural rubber latex-containing medical device that is not labeled as required, and that is initially introduced or initially delivered for introduction into interstate commerce after the effective date of the final rule, would be misbranded under sections 201(n) and 502(a), (c), and (f)(1) of the act.

FDA believes that it is also necessary to prohibit certain labeling statements on devices that contain natural rubber latex. FDA has received reports of sensitivity to medical gloves labeled as ''hypoallergenic.'' FDA believes that this term, traditionally used with cosmetics, erroneously implies that the user of products labeled as hypoallergenic is assured that the risk of an allergic reaction to the chemicals or other materials in the products would be minimal. In the past, use of the ''hypoallergenic'' label has been based on results of the modified (human) Draize test. While this test may be appropriate for detecting sensitivity to residual levels of processing chemicals, the test cannot accurately detect the presence or absence of natural latex protein levels. Furthermore, current manufacturing processes cannot remove from devices the natural latex proteins below the level to which some individuals may be sensitive. Thus the risk of allergic reaction remains.

Therefore, the agency believes that the presence of the term ''hypoallergenic''

on the labeling of a natural rubber latex-containing device is false and misleading because it incorrectly implies that the product labeled as ''hypoallergenic'' may be used safely by latex sensitive persons. FDA also believes that products with such labeling fail to bear adequate directions for use because they do not state that rubber latex-containing products labeled as hypoallergenic may still cause allergic reactions. For these reasons, FDA is proposing that the hypoallergenic claim be removed from the labeling of natural rubber latex-containing medical devices. Accordingly, under the proposed rule, FDA would consider natural rubber latex-containing medical devices labeled as hypoallergenic that are initially introduced or delivered for introduction after the effective date of the final rule, to be misbranded under section 502(a) and (f)(1) of the act. Although manufacturers would no longer be permitted to label their rubber latex-containing devices as ''hypoallergenic,'' persons wishing to make claims regarding the sensitizing potential of manufacturing chemical residues (MTB's, thiurams, and carbamates) in finished latex products should contact the Division of Small Manufacturers Assistance (1–800–638–2041) and request a copy of the guidance document entitled ''Testing for Skin Sensitization to Chemicals in Latex Products.''

FDA does not intend to require a new submission under section 510(k) of the act (21 U.S.C. 360) (510(k) submission) based upon labeling changes made to comply with this proposed regulation, provided that no other changes requiring a new 510(k) submission under 21 CFR 807.81 are made to the device. FDA does not intend to require manufacturers of devices subject to an approved premarket approval (PMA) application to submit a PMA supplement under 21 CFR 814.39(d), for any change to the product labeling that would be required by this regulation. FDA intends, instead, to require manufacturers to submit an annual report under 21 CFR 814.39(e) for such changes.

## III. Request for Comments

FDA recognizes that this regulation applies to an array of devices that vary widely in their manufacture and use. FDA welcomes comments on all aspects of the regulation, but particularly invites comments on the following areas:

1. Some of the devices to which this regulation applies may be sold in bulk packages which are then divided up and used individually. How can FDA best ensure that the message that the regulation is intended to convey reaches the ultimate user?

2. It has been suggested that the message could be conveyed by using a symbol, especially on smaller devices. FDA invites comments on whether using a symbol would be useful, and, if so, what would be an appropriate symbol?

## IV. Exemptions and Variances

Affected persons may request an exemption or variance from the requirements of this regulation, if they believe that full compliance with the regulation is not necessary for the safe and effective use of the device. Requests for exemption or variance must be submitted in accordance with the requirements for a citizen petition set forth in 21 CFR 10.30.

## V. Environmental Impact

The agency has determined under 21 CFR 25.24(e)(2) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

## VI. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (Pub. L. 96–354). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the proposed rule is not a significant regulatory action as defined by the Executive Order and so is not subject to review under the Executive Order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. This proposed rule primarily requires a labeling change which would not have a significant economic impact on small entities, because the 180 days before the final rule based upon this proposal would become effective will allow most manufacturers to exhaust their existing supply of labels. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

## VII. Paperwork Reduction Act of 1995

FDA tentatively concludes that the labeling requirements in this proposed rule are not subject to review by the Office of Management and Budget because they do not constitute a ''collection of information'' under the Paperwork Reduction Act of 1995 (Pub. L. 104–13). Rather, the proposed warning statements are ''public disclosure of information originally supplied by the Federal Government to the recipient for the purpose of disclosure to the public'' (5 CFR 1320.3(c)(2)).

## VIII. Comments

Interested persons may submit written comments regarding this proposed rule, by September 23, 1996, to the Dockets Management Branch (address above). Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

## IX. References

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

1. ''Introduction to Latex Compounding and Processing,'' *The Vanderbilt Latex Handbook,* 3d edition, 1987.

2. Turjanmaa, K., ''Incidence of Immediate Allergy to Latex Gloves in Hospital Personnel,'' *Contact Dermatitis,* 17: 27–275, 1987.

3. Turjanmaa, K., K. Laurila, S. Makinen-Kiljunen, and T. Reunala, ''Rubber Contact Urticaria-Allergenic Properties of 19 Brands of Latex Gloves,'' *Contact Dermatitis,* 19: 362–364, 1989.

4. Turjanmaa, K. and T. Reunala, ''Condoms as a Source of Latex Allergen and Cause of Contact Urticaria,'' *Contact Dermatitis,* 20: 360–364, 1989.

5. FDA medical alert—allergenic reactions to latex-containing medical devices, March 29, 1991.

6. Heese, A., J. Hintzenstern, K–P Peters, H. Koch, and O. Hornstein, ''Allergic and Irritant Reactions to Rubber Gloves in Medical Health Services,'' *Journal of the American Academy of Dermatology,* No. 5 (part 1): 831–839, November, 1991.

7. Hintzenstern, J., A. Heese, H. Koch, K–P Peters, and O. Hornstein, ''Frequency, Spectrum and Occupational Relevance of Type IV Allergies to Rubber Chemicals,'' *Contact Dermatitis,* 24: 244–252, 1991.

8. Tomazic, V., T. Withrow, B. Fisher, and S. Dillard, ''Short Analytical Review-Latex-Associated

Allergies and Anaphylactic Reactions,'' *Clinical Immunology and Immunopathology,* 64: 89–97, 1992.

9. Slater, J. and S. Chhabra, ''Latex Antigens,'' *Journal of Allergy and Clinical Immunology,* 89: 673–678, 1992.

10. Lahti, A. and K. Turjanmaa, ''Prick and Use Tests with 6 Globe Brands in Patients with Immediated Allergy to Rubber Proteins,'' *Contact Dermatitis,* 26: 259–262, 1992.

11. Jaeger, D., D. Kleinhans, A. Czuppon, and X. Baur, ''Latex-Specific Proteins Causing Immediate-Type Cutaneous, Nasal, Bronchial, and Systemic Reactions,'' *Journal of Allergy and Clinical Immunology,* 89: 759–768, 1992.

12. Berky, Z., J. Luciano, and W. James, ''Latex Glove Allergy--A Survey of the US Army Dental Corps,'' *Journal of the American Medical Association,* 268: 2695–2697, 1992.

13. Gonzalez, E., ''Latex Hypersensitivity: A New and Unexpected Problem,'' *Hospital Practice,* pp. 137–151, February 15, 1996.

14. Stehlin, D., ''Latex Allergies: When Rubber Rubs the Wrong Way,'' *FDA Consumer,* pp. 16–21, September 1992.

15. ACAI (American College of Allergy & Immunology), Interim Recommendations to Health Professionals & Organizations Regarding Latex Allergy Precautions, March, 1992.

16. Young, M., M. Meyers, L. McCulloch, and L. Brown, ''Latex Allergy-A guideline for perioperative nurses,'' *AORN Journal,* 56: 488–502, 1992.

17. Hamann, C. P., ''Natural Rubber Latex Protein Sensitivity in Review,'' *American Journal of Contact Dermatitis,* 4:1. March 1993, 4–21.

18. Marzulli, F. N., and H. I. Maibach, ''The Use of Graded Concentrations in Studying Skin Sensitizers: Experimental Contact Sensitization in Man,'' *Food, Cosmetics, and Toxicology,* 12:219–227, 1974.

19. USDHHS/PHS/FDA/CDRH, *Regulatory Requirements for Medical Gloves—A Workshop Manual,* FDA 93–4257, as amended May, 1993.

List of Subjects in 21 CFR Part 801

Labeling, Medical devices, and Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act, and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 801 is amended as follows:

## PART 801—LABELING

1. The authority citation for 21 CFR Part 801 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 507, 519, 520, 701, 704 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 357, 360i, 360j, 371, 374).

2. New § 801.437 is added to subpart H to read as follows:

### § 801.437 User labeling for rubber latex-containing medical devices.

(a) This section applies to all medical device products composed of or containing, or having components which are composed of or contain, natural rubber latex that may directly or indirectly contact living human tissue. The term ''natural rubber latex'' includes natural rubber latex, dry rubber, and synthetic latex which contains natural rubber latex in its formulation.

(b) Data in the Medical Device Reporting System and scientific literature indicate that some individuals may be at risk of a severe anaphylactic reaction to natural rubber latex proteins. In order to protect the public health and minimize the risk to rubber latex sensitive individuals, medical devices containing natural rubber latex shall be labeled as set forth in paragraphs (c) and (d) of this section.

(c) Natural rubber latex-containing medical devices shall prominently and legibly bear one of the following statements on the device labeling, in conformance with section 502(c) of the act: ''This product contains natural rubber latex which may cause allergic reactions in some individuals''; ''This product has components that contain natural rubber latex which may cause allergic reactions in some individuals''; or ''This product is made from natural rubber latex which may cause allergic reactions in some individuals''.

(d) Because the natural rubber latex proteins to which some individuals are sensitive cannot be completely removed from latex gloves, the term ''hypoallergenic'' is inappropriate. Therefore, rubber latex gloves and other natural rubber latex-containing medical devices shall not contain the term ''hypoallergenic'' on their labeling.

(e) Any affected person may request an exemption or variance from the requirements of this section by submitting a citizen petition in accordance with § 10.30 of this chapter.

(f) Any device subject to this section that is not labeled in accordance with paragraphs (c) and (d) of this section, and that is initially introduced or initially delivered for introduction into interstate commerce after the effective date of this final regulation, is misbranded under sections 201(n) and 502(a) and (f)(1) of the act. Any such device that is not labeled in accordance with paragraph (c) of this section, is also misbranded under section 502(c) of the act.

Dated: June 17, 1996.

William K. Hubbard,

*Associate Commissioner for Policy Coordination.*

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