Draft Guidance for Industry and Food and Drug Administration Staff - Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex

U.S. Food & Drug Administration

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1. Introduction

The purpose of this guidance is to make recommendations on the appropriate language to include in the labeling of a medical product to convey that natural rubber latex was not used as a material in the manufacture of the product or product container. FDA is concerned that statements submitted for inclusion in medical product labeling, such as “latex-free,” “does not contain natural rubber latex,” or “does not contain latex” are not accurate because it is not possible to reliably assure that there is an absence of the allergens associated with hypersensitivity reactions to natural rubber latex in the medical product. Use of these terms may give users allergic to natural rubber latex a false sense of security when using a medical product. FDA is recommending that a consistent, scientifically accurate statement be used by all manufacturers who wish to convey that natural rubber latex was not used as a material in the manufacture of a medical product or medical product container.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

2. Scope

This guidance document applies to all FDA regulated medical products (i.e., devices, drugs, biologics, and veterinary products) for which: (1) natural rubber latex or synthetic derivatives of natural rubber latex were not used as materials in their manufacture; and (2) any packaging or container was not made withnatural rubber latex or synthetic derivatives of natural rubber latex. This guidance contains labeling recommendations for manufacturers who wish to include a statement in medical product labeling indicating that natural rubber latex or synthetic derivatives of natural rubber latex were not used as manufacturing materials in the medical product or its container.

3. Background

Contact with devices containing natural rubber has been associated with anaphylaxis in individuals allergic to natural rubber latex proteins.[1] [7] Our medical device regulations include provisions that require certain labeling statements on medical devices if the device or device packaging is composed of or contains natural rubber that contacts humans. See 21 CFR 801.437. The biologics regulations (21 CFR 610.61(l)) require that the package label or package insert declare the presence of known sensitizing substances, but do not specifically mention natural rubber latex. Specific regulations for labeling of natural rubber latex content in medical products or their containers do not exist for drugs or veterinary products.

At this time there are no regulations requiring a company to state that natural rubber latex was not used as a material in the manufacture of a medical product or medical product container. However, some manufacturers have included the promotional statements “latex-free” or “does not contain latex” in medical product labeling to inform users that natural rubber latex, dry natural rubber or synthetic derivatives of natural rubber latex were not used. FDA believes that these labeling statements are not sufficiently specific, not necessarily scientifically accurate and may be misunderstood or applied too widely, and therefore, it is inappropriate to include such statements in medical product labeling.

First, the term “latex” in the labeling statements “latex-free” and “does not contain latex” could refer to natural rubber latex or synthetic latex (not derived from natural rubber latex). Labeling statements that do not clearly state the material of concern are not sufficiently specific and therefore should not be included in medical product labeling.

Second, users may consider the terms “free” and “does not contain” to mean that the medical product is completely devoid of natural rubber latex. However, there are no analytical methods currently available that can identify all proteins and components in natural rubber latex that may lead to allergic reactions in medical product users. In addition, the use of the term “free” or “does not contain” does not address the potential for accidental contamination of a medical product or medical product container with natural rubber latex during or after manufacturing.

Although there are a number of tests to measure the various compounds related to natural rubber latex allergies, FDA is aware of no test method or combination of test methods available at this time that can demonstrate the absence of proteins or components from natural rubber latex that may cause allergic reactions in susceptible individuals. A brief description of three currently available test methods used to assess levels of total protein or natural rubber latex proteins in medical products are provided below:

1. ASTM D5712 – Standard Test Method for Analysis of Aqueous Extractable Protein in Natural Rubber and its Products Using the Modified Lowry Method.

This is an FDA- recognized standard[2] [8]. The purpose of this test method is to determine the protein content in natural rubber latex materials. This test method does not specifically measure antigenic or allergenic natural rubber latex proteins, but rather the total aqueous extractable protein content in the sample.

2. ASTM D6499 – Standard Test Method for the Immunological Measurement of Antigenic Protein in Natural Rubber and its Products.

This is an FDA- recognized standard[2] [8]. The purpose of this test method is to determine the amount of antigenic protein in natural rubber and its

products using rabbit antisera specific for natural rubber latex proteins. However, the standard clearly states that “Although this method detects antigenic proteins, it should not be considered as a measure of allergenic proteins. Correlation of protein/antigen levels with the level of allergenic proteins has not been fully established.”

3. ASTM D7427 – Standard Test Method for Immunological Measurement of Four Principal Allergenic Proteins (Hev b 1, 3, 5 and 6.02) in Natural Rubber and its Products Derived from Latex.

This standard has not been recognized by the FDA as of the time of issuance of this draft guidance. The purpose of this test method is to determine the amount of four specific known natural rubber latex allergenic proteins. (At least thirteen natural rubber latex allergens have been identified.) Per the test method, “the sum of the four allergen levels shall be viewed as an indicator of the allergen burden and not as a measure of the total allergen content that can be released from the product.”

The specificity and sensitivity of currently available analytical methods are not sufficient to demonstrate that a medical product is completely “free” of natural rubber latex proteins or antigens, which have primarily been associated with causing severe allergic reactions (Type I allergic reactions). FDA recognizes that the complete absence of all natural rubber latex allergens is unlikely to be necessary for the safe use of medical products by individuals with natural rubber latex allergies. Threshold allergen levels, exposure below which no adverse reaction occurs in the majority of sensitive individuals, have been identified for some non-natural rubber latex allergens (e.g., hymenoptera venoms and specific foods).

Threshold allergen levels are unavailable for natural rubber latex-allergic individuals. There are at least 13 distinct allergens identified for natural rubber latex allergy and the sensitivity to each varies, not only among individuals, but among groups of individuals (e.g., health care providers, industry workers, children with meningomyelocele). Furthermore, thresholds are likely to be route-specific and multiple routes of exposure (e.g., respiratory, percutaneous, oral, and parenteral) have been implicated in natural rubber latex sensitization and reactivity. There is no one threshold level of exposure that can be considered safe, but rather many levels that are a function of the allergen, the risk group, the exposure route, the immune status of the individual and, perhaps, other factors as yet unidentified. Therefore, any preventative strategy must address the possible different threshold levels for sensitization and for triggering a reaction in an at-risk individual.

Ideally, all threshold levels should be established for each allergen under all conditions, and the lowest threshold level identified for each. This information is unlikely to become available without a concerted scientific effort. Even if this is achieved, the correlation of data from ASTM methods D5712 (total protein), D6499 (overall allergen levels), and D7427 (four specific allergens) to the established minimum threshold levels would be uncertain.

For the reasons stated above, FDA finds that the use of statements, such as “latex-free,” “does not contain latex,” or other similar labeling statements are, at this time, not scientifically supportable.

FDA strongly recommends that these statements not be used in medical product labeling.

4. Recommended Labeling Statement

Currently, there are no regulations requiring a manufacturer to state that natural rubber latex was not used as a material in their medical product or medical product container. If a manufacturer elects to include a statement in medical product labeling indicating that natural rubber latex or synthetic derivatives of natural rubber latex were not used as materials in the manufacture of their medical product andcontainer, FDA recommends the use of the statement **“Not made with natural rubber latex.**” If this statement is made without any qualification, it must apply to the entire product and all of its packaging. For certain medical products, statements regarding “not made with natural rubber latex” may be appropriate only for certain components. In this case a manufacturer may elect to make a statement that the specific component isnot made with natural rubber latex. For example, if the particular presentation or part of the presentation (e.g., vial stopper or syringe) is not made with natural rubber latex, FDA recommends the statement “**The <vial stopper> is not made with natural rubber latex**.”

These statements **“Not made with natural rubber latex”** and **“The <vial stopper> is not made with natural rubber latex**” communicate that natural rubber latex was not used as a material in the finished product or as a material in the container. At the same time, the statement does not make the unsupportable claim that the medical product is “free” of or “does not contain” natural rubber latex (i.e., materials or contamination), which may promote a false sense of safety to users who are allergic to natural rubber latex. Finally, use of a consistent scientifically supportable labeling statement will reduce confusion among FDA staff, medical product manufacturers, and medical product users.

Manufacturers who currently include statements such as “latex-free” or “does not contain latex” in medical product labeling should update their medical product labeling to show the recommended labeling statement **“Not made with natural rubber latex”** or **“The <vial stopper> is not made with natural rubber latex**” as appropriate. Alternatively, manufacturers should consider removing “latex-free” type statements from medical products and medical product packaging. Manufacturers may contact the Center that regulates the medical product for guidance on the appropriate regulatory mechanism to update the labeling.

[1] Ahmed SM, Aw TC, and Adisesh A. Toxicological and immunological aspects of occupational latex allergy. Toxicol Rev 2004; 23(2):123-34

[2] FDA recognizes national and international consensus standards for use in development of medical products. A database of all recognized standards can be found at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm [9]. Please see the following site for more information: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Standards/default.htm [10].

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