Guidance for Industry and FDA Reviewers/Staff

Premarket Notification [510(k)] Submissions for Testing for Skin Sensitization To Chemicals In Natural Rubber Products

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U.S. Department Of Health And Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Infection Control Devices Branch
Division of Dental, Infection Control, and General Hospital Devices
Office of Device Evaluation

Preface

Public Comment

Comments and suggestions may be submitted at any time for Agency consideration to Chiu S. Lin, Ph.D., CDRH, 9200 Corporate Blvd., Rockville, MD 20850. Comments may not be acted upon by the Agency until the document is next revised or updated. For questions regarding the use or interpretation of this guidance contact Chiu S. Lin, Ph.D., Chief at (301)-443-8913.

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PREMARKET NOTIFICATION [510(K)] SUBMISSIONS FOR TESTING FOR SKIN SENSITIZATION TO CHEMICALS IN NATURAL RUBBER PRODUCTS

GUIDANCE DOCUMENT

A. PURPOSE

This document is intended to provide to manufacturers and FDA personnel, guidance for the preparation and evaluation of 510(k) submissions of natural rubber (NR) medical devices with labeling claims for:

(a) reduced potential for sensitizing users to rubber chemical additives, or;

(b) reduced potential for causing reaction in individuals sensitized to rubber chemical additives.

In addition, this document describes testing recommended to support these claims.

B. BACKGROUND

The increased use of natural rubber (NR) medical gloves and other NR containing medical devices, which coincided with the emergence of HIV infection, resulted in the increased prevalence and intensity of adverse reactions to NR. There are three distinctive types of adverse reactions to NR that differ in their mechanisms of induction and resulting clinical manifestations. These reactions include irritation, delayed hypersensitivity (Type IV allergy) and immediate hypersensitivity (Type I allergy). The major distinctions between the three types are: a) irritation is a nonimmunologic response with symptoms described as irritant contact dermatitis; b) Type IV allergy is a cell-mediated immunological reaction resulting in allergic contact dermatitis that develops 1 to 4 days after the exposure; and c) Type I allergy is an antibody-mediated reaction occurring immediately, usually within minutes after the exposure. While clinical manifestations of irritation and Type IV allergy are limited to skin reactions, clinical symptoms of Type I allergic reactions may range in severity from local skin reactions, defined as contact urticaria, to life-threatening anaphylactic reactions. Irritation can be induced by water, powder and chemicals, while Type IV allergy is predominantly

induced by the residual chemical additives (thiazoles, thiurams and carbamates) on the finished NR containing medical devices. Type I allergy is primarily caused by NR proteins remaining on the finished products. Although the term Type IV allergy is synonymous to Type IV hypersensitivity, the term Type IV allergy will be used in this document. Both Type I and Type IV allergic reactions to NR containing medical devices represent serious problems as the exposure of sensitized individuals to natural rubber medical devices may be life-threatening (Type I) or career-threatening (Type I and IV). Although Type I allergy is presently an issue of major concern due to an increase in prevalence and severity of the reactions in the past few years, Type I allergy is not the subject of this document. This guidance document is focused **only** on Type IV allergy to residual chemicals (predominantly thiazoles, thiurams and carbamates) on the finished NR containing medical devices. It is important, however, for users of this document, when selecting the human test subject panel, to consider the possibility that some of the healthy test subjects and some of the individuals demonstrating Type IV allergy may also have Type I allergy. Irritation reaction, a nonimmunolgical response, is also not a subject of this document (Section E.2.1.).

Allergy to chemical additives in NR containing medical devices has been known for a long time. Efforts have been made by industry to alleviate the problem by manufacturing products with reduced levels of chemical additives which are known to have sensitizing potential. In the past, the label "hypoallergenic" was sometimes applied to distinguish such products from the rest of the marketed products. However, with the apparent recent increase in the prevalence and severity of Type I allergy to NR proteins, the term “hypoallergenic” has been frequently misinterpreted as being related to protein allergy. Such devices, despite being labeled hypoallergenic, can cause allergic reactions in individuals sensitized to NR proteins and should not be used by such individuals. FDA published in the Federal Register (FR, Vol.62, No. 189, September 30, 1997, pages 51021-51030, “Natural Rubber-Containing Devices; User Labeling”) a rule prohibiting the label claim of “hypoallergenic" on NR containing medical devices. This rule became effective on September 30, 1998.

The manufacturers of NR containing medical devices can utilize this guidance document to address the labeling options presented below regarding Type IV allergy and to conduct appropriate testing to support these claims: a) reduced potential for sensitizing users to rubber chemical additives; and b) reduced potential for causing reaction in individuals sensitized to specific rubber chemical additives.

C. CLAIMS AND TESTING RECOMMENDATIONS

Firms wishing to make a claim regarding the reduced potential of chemical sensitization or reduced reaction-inducing potential of their products in allergic individuals should submit to FDA the recommended biocompatibility test data for each NR containing medical device as described in the FDA manual "Guidance for Medical Gloves: A Workshop Manual" (FDA 96-4257). These tests include skin irritation and dermal sensitization studies in animals. In addition to these basic biological tests, this guidance document should be followed to support the following claims:

Claim 1:

> **Low Dermatitis Potential**
> This product demonstrated reduced potential for sensitizing users to chemical additives.
> **Warning:** Do not use this product if you have a known allergy to natural rubber protein or chemical additives.

Supporting Test Data:

A negative skin sensitization test (Modified Draize-95 Test) on a minimum of 200 nonsensitized human subjects, as described in Section E.

Claim 2:

> **Low Thiuram, and/or Carbamate, and/or Thiazole**
> This product demonstrated reduced potential for causing reaction in individuals sensitized to (name of chemical)
> **Warning**: Do not use this product if you have a known natural rubber protein allergy.

Supporting Test Data:

a) A negative Modified Draize-95 test as recommended for claim 1 above;

b) A negative patch test on 25 individuals who are allergic to the defined major chemical sensitizers present in natural rubber products as described in Section F below.

D. ADDITIONAL REGULATORY INFORMATION REGARDING CLAIMS

1. The NR containing medical devices labeled "hypoallergenic" which are presently on the market may, upon removal of that claim from all labeling, remain on the market without the need to supply additional documentation to the FDA.

2. Manufacturers who intend to use labeling claim 1 to market a NR containing medical devices, previously labeled "hypoallergenic", do not need to submit a new 510(k) if they have the supporting test data described in this guidance. However, the test data described for claim 1 should be in compliance with this guidance document and kept on file to support the claim.

3. Manufacturers who intend to use claim 2 to market a NR containing medical devices, previously labeled "hypoallergenic", in addition to the requirements for claim 1, would have to submit a 510(k) with completed testing on the 25 sensitized subjects.

4. For new NR containing medical devices intended to bear the claims described in this document, a 510(k) should be submitted with data from testing described in this guidance document.

A list of testing laboratories equipped to perform the Modified Draize-95 test on normal subjects is available through the Office of Health and Industry Programs, Division of Small Manufacturers Assistance (DSMA) by telephone at #1-800-638-2041 or DSMA FAX ON DEMAND at #1-800-899-0381. A partial list of physicians and groups with access to sensitized individuals and equipped to perform testing on sensitized subjects can also be obtained from DSMA.

E. MODIFIED DRAIZE-95 TEST

The purpose of this test is to evaluate whether residual chemical additives at the level that may induce Type IV allergy in the unsensitized general user population are present in a finished natural rubber (NR) containing medical device. The original sensitization test was developed by John Draize for use with rabbits and later adopted for skin testing in humans. For the purpose of this guidance document, the Modified Draize-95 Test includes additional changes that specifically evaluate the sensitization potential of chemical compounds in finished NR containing medical devices. These changes were based on the existing data, past experience and recent knowledge from published literature. This test should be used for claim 1 and for initial testing to support claim 2.

E.1. Test Subjects:

The test should be completed on a minimum of 200 nonsensitized adult human subjects. This sample size, with all negative results, provides 95% confidence that the chemical sensitization potential of the NR containing medical device in the user population is expected to be less than 1.5%.

The criteria for selection of the test subjects should be as follows:

E.1.1. Inclusion

a. The test subjects should be normal volunteers who have documented informed consent and have not participated in other voluntary testing for at least 30 days.

b. Efforts should be made to provide racial and gender diversity of the test subjects that reasonably reflects the general user population in the U.S.

c. Age of the test subjects should range from 18 to 65 years.

E.1.2. Exclusion

a. Potential test subjects with any visible skin disease that might be confused with skin reactions caused by the test material.

b. Potential test subjects with any knowledge or indication of existing Type IV allergy to natural rubber chemical additives.

c. Potential test subjects with any indication of existing Type I allergy to natural rubber proteins.

d. Potential test subjects with a history of frequent irritation.

e. Potential test subjects who have used corticosteroids either systemically or topically on the potential test site two weeks before testing.

f. Potential test subjects who have received endogenous or exogenous immunosuppressive treatment (or prolonged exposure to sun).

g. Potential subjects who are pregnant or become pregnant during the study.

h. All lactating women.

E.2. Procedure:

E.2.1. Induction Phase - A sample of the test article, minimum size 2cmx2cm, should be applied to each test subject in the study. The patch should be applied to upper back area and continuously secured on the edges with a nonreactive adhesive tape. Complete occlusion of the patch is essential.

The induction phase of the test includes application of ten patches of the test article on each Monday, Wednesday, and Friday. The test article is removed and replaced by a new one at the same site every 48 hours for a total of ten changes. The patches applied on Fridays are removed on Mondays.

Any and all skin reactions should be recorded during this induction phase. If a reaction to an initial

induction test patch is observed, the subject should be considered a presensitized individual. A reaction observed after placement of the second patch in the induction phase is generally considered an irritation. In each of these cases, the procedure described in section E.2.5. would apply. If a local irritation caused by the occlusion material occurs, occlusion tape should be replaced with the non-irritating one, and the induction patching could be continued.

E.2.2. Rest Period - At the end of the induction period, the test article is removed. No test articles are to be applied to the test subjects for the next three weeks, until the challenge patches are applied.

E.2.3. Challenge Phase - Two samples of the same test article, a minimum 2cm X 2cm in size are applied consecutively to a virgin site for 48 hours each. The test site is evaluated for reaction at the time of each patch removal and again two to four days after removal of the second patch.

E.2.4. Scoring Criteria - The intensity of reactions should be scored according to the following criteria:

Basic Score:		**Description:**
0	-	No visible reaction
0.5	-	Doubtful or negligible erythema reaction
1.0	-	Mild or just perceptible macular erythema reaction in a speckled/follicular, patchy or confluent pattern (slight pinking)
2.0	-	Moderate erythema reaction in a confluent pattern (definite redness)
3.0	-	Strong or brisk erythema reaction that may spread beyond the test site

Supplemental scores:	Description:	Label:
0.5	Edema	E
0.5	Papules	P
0.5	Vesicles	V
0.5	Bullae	B

The supplemental scores may be added to the basic score, if the reactions include described symptoms. The final score should be the sum of basic and supplemental score values.

E.2.5. General - With any NR containing medical devices evaluated according to this guidance document, the surface of the device that the user is mostly exposed to should be tested.
In the case of medical gloves, the inside of the glove should be tested. The study should be conducted in two stages. In the first stage, a population of 50 human subjects may be tested to evaluate product for the potential to cause irritation or sensitization. If the test product does not indicate a potential for inducing dermal irritation and does not show sensitization capability, the second stage can be initiated on the remaining 150 individuals.

During the induction phase of the study, if a subject develops a positive reaction(a score value of 1.5) to chemicals or shows signs of irritation after patch applications, further patching on those individuals should be stopped. After 3 weeks of rest, these individuals should receive a challenge patch to confirm observed reaction as either preexisting sensitivity or irritant reaction. All such cases should be recorded and reported in addition to the 200 subjects in the test panel group.

E.3. Data Presentation:

A detailed study report should be kept on file and/or submitted in a 510(k), which should include at a minimum such items as study protocol, test subject selection, scoring criteria, test results, and interpretation of results. In order to qualify for the claim of a reduced sensitization potential, all 200 individuals completing the study should

exhibit a score value of no more than 1.5 based on the scoring criteria described in section E.2.4. of this document. The individuals who were identified as either presensitized to natural rubber chemicals or presenting irritant reactions, would be excluded from the statistical evaluation. However, the data from each such case should be recorded and reported

in addition to the data for the 200 nonsensitized test individuals completing the test.

F. PATCH TEST ON SENSITIZED INDIVIDUALS

The purpose of this test is to determine whether a finished natural rubber containing medical device contains residual chemicals which might cause a skin reaction in individuals who are already allergic to one or more of the following classes of chemicals: thiazoles, thiurams and carbamates. These test data combined with the data from the Modified Draize-95 test described for claim 1, should be completed to support claim 2.

The test subjects with a prediagnosed allergy of a minimum grade of 1.5 according to the standard scoring of the North American Contact Dermatitis Research Group (NACDRG) (“Am. J. Contact Dermatitis” 2:122-129,1991) should be selected for this study. The diagnostic test determining the sensitivity level of the test subjects should be completed one month prior to the date that the subject is being included in this study.

F.1. Test Subjects:

The study should include a minimum of 25 individuals who were positively diagnosed to be allergic to one or more of the above classes of chemical sensitizers in NR containing medical devices. This sample size, with all negative results, provides 95% confidence that chemicals on the tested natural rubber medical products would be expected to cause reactions in less than 11.3% of sensitized individuals.

The criteria for selection of the test subjects should be as follows:

F.1.1. Inclusion

a. Individuals who have a prediagnosed allergy to NR chemicals of a minimum of 1+ reaction according to the NACDRG standard.

b. The test subjects with documented informed consent.

c. Efforts should be made to provide racial and gender diversity of the test subjects that reasonably reflects the general user population in the U.S.

d. Age of the test subjects should range from 18 to 65 years.

F.1.2 Exclusion

a. The test subjects with any visible skin disease that might be confused with skin reactions caused by the test material.

b. The test subjects with any indication of existing Type I allergy to natural rubber proteins.

c. The test subjects who have used corticosteroids either systemically or topically on the potential test site two weeks before testing.

d. Test subjects who have received endogenous or exogenous immunosuppressive treatment(or prolonged sun exposure).

e. All subjects who are pregnant or become pregnant during the study.

f. All lactating women.

F.2. Test Procedure:

A minimum 2cm x 2cm sample of the test article is applied to each of the 25 human subjects who were previously diagnosed to be allergic to one or more of the three classes of known chemical sensitizer(s) in NR containing medical devices; thiurams, carbamates and thiazoles.

In this test procedure the patch is applied with all edges continuously secured with non-reactive adhesive tape for 48 hours. Complete occlusion of the patch is essential. If the test article causes discomfort to the individual, it should be removed earlier. The test sites are evaluated at the time of the patch removal and again two to four days later.

F.3. Data Presentation:

A detailed study report should be submitted in a 510(k), which at a minimum should include such items as study protocol, test subject selection, scoring criteria, test results, and interpretation of results. The sensitivity level score for

each allergic subject before involvement in the testing should be recorded and reported with the test results. In case of allergy to more than one chemical, the score should be reported for each chemical. All tested individuals in this group should present negative results (a score of less than 1.0 based on the scoring criteria in section E.2.4. of this document) as a prerequisite for the claim of reduced reaction-inducing potential.

G. INVESTIGATIONAL DEVICE REQUIREMENTS:

This guidance document applies to the NR containing medical devices which have gone through additional manufacturing processes to reduce levels of residual chemical additives, and which have shown negative results in the irritation and dermal sensitization studies in animals. Therefore, the level of risk to the nonsensitized subject during a skin patch test would be considered nonsignificant risk. In addition, the studies performed on sensitized subjects with a patch test of NR containing medical devices should be nonsignificant risk studies because the products should, as a prerequisite, have passed the Modified Draize-95 test.

A nonsignificant risk device study, under IDE regulations (CFR 812), requires an institutional review board approval and affords the patient informed consent. Studies conducted in foreign countries are not subject to the IDE regulations, although FDA recommends that they be conducted according to the IDE provisions. At a minimum, they need to be conducted in compliance with the Helsinki Declaration.

H. FOR FURTHER INFORMATION OR QUESTIONS REGARDING THIS GUIDANCE PLEASE CONTACT:

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