THE JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE
REFERENCE LABORATORY FOR DERMATOLOGY, ALLERGY AND CLINICAL IMMUNOLOGY

January 26, 2000

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Dockets Management Branch
HFA-305
Department of Health and Human Services
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852
Tel: 301-827-4777

RE: Comments on "Surgeon and Patient Examination Gloves: Reclassification and Medical Glove Guidance Manual Availability; Proposed Rule and Notice; 21 CFR Parts 801, 878 and 880, Docket No. 98N-0313

Dear Drs. Henney and Shalala:

As an immunologist who has been working in the area of latex allergy since 1992, I believe that avoidance of natural rubber latex (NRL) allergen exposure is of vital interest to every American. Avoidance is in fact the only method we have that will both eliminate the risk for denovo sensitization to the potent allergenic proteins in NRL gloves and reduce the risk of allergic symptom induction in those individuals who have unfortunately already become sensitized (developed NRL-specific IgE antibody). I strongly support FDA's proposed ruling to reclassify all surgeon and examination gloves as class II devices because I believe it will lead to reduced allergenic content in NRL gloves and it will better insure their effective performance as a barrier by defining a shelf-life. My concern with this proposal rests in the details of the proposed target levels of allergenic protein and powder and the laboratory methods that have been proposed to assess these targets.

Extractable Protein versus Allergen Issue: I understand that the proposed level of 1200 micrograms of protein per glove is intended as a target that can be achieved by manufacturers and measured with the available ASTM Lowry assay. In our recent unpublished cross-sectional survey, we observed that the total protein level for 27 randomly selected brands of latex examination gloves ranged from 190 to 12,880 micrograms of protein per (10 gram) glove using the ASTM Lowry assay. More than 80% of these gloves had protein levels greater than this limit of 1200 micrograms of protein per glove. If you believe that there is a good correlation between the level of total protein and allergen content, then achieving the 1200 microgram per glove protein limit would represent a significant improvement over our current status. But, this level of protein still contains sufficient allergen to continue NRL sensitization and symptom induction in sensitized individuals. NRL preparations containing protein levels as low as 20 picograms (1 nanogram/ml x 0.02 ml) can produce a strongly positive reaction in the skin of 80% of latex allergic individuals (1). My major concern with this proposed ruling is that we will settle for NRL allergen targets that will not protect the user simply because they can be monitored with the ASTM D5712 Lowry assay that we all agree has an inadequate analytical sensitivity to meet our needs. Rather than just accepting assays that detect total protein, let us go into our best research laboratories where we have established RAST inhibition assays (2-3) and new immunoenzymetric assays (4) that detect NRL allergens in the nanogram per ml range. These assays exist now and they can be made rapidly available to manufacturers with carefully direct funding and joint scientific effort.

98N-0313 C54

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Particulate versus Insolubilized Allergen Issue: The 120 mg of powder per glove proposed limit for powdered gloves is a positive step because it defines a level, not because 120 mg per glove will guarantee no airborne allergen exposure. Total particulate is to be measured with an ASTM D6124-97 assay. Why not use immunoassays that exists in research laboratories in the USA to measure particle-bound NRL allergen rather than limit us to measuring total particulate. Together with the FDA, we published on such a competitive inhibition and direct binding immunoassay method in 1994 in which the allergens on the cornstarch are detected with latex allergen-specific IgE antibodies. We still use these assays to assess levels of allergen on glove cornstarch that is used in the diagnostic hooded chamber provocation procedure (6). Measurement of insolublized allergen rather than just particulate would provide a better assessment of the relative hazard that the product represents to exposed, at risk individuals.

References:

1. Hamilton RG, Adkinson NF. Natural rubber latex diagnostic skin testing reagents. Comparative performance of non-ammoniated latex, ammoniated latex and latex rubber glove extracts. J. Allergy Clin Immunol. 98:872-883, 1996.
2. Bronzert CT, Wisenauer JA, Adkinson NF, Hamilton RG: Quantitation of latex allergen in rubber gloves. J Allergy Clin Immunol 93:306 (1A), 1994.
3. Ownby D, Hamilton RG, Yunginger JW. An inter-laboratory comparison of assays used to estimate allergen content of latex products. Proceedings of Latex Allergy Symposium, Royal College of Physicians and Surgeons of Canada, Toronto, Sept. 14, 1994.
4. Hamilton RG, Yeang HY. Quantitation of Hev b 1 and Hev b 6 indicator allergens in prospective latex allergen preparations by polyclonal and monoclonal antibody-based immunoenzymetric assays. J. Allergy Clin. Immunol. (in press), AAAAI National Meeting Presentation, March 2000.
5. Tomazic VJ, Shampaine EL, Lamana A, Withrow TJ, Adkinson NF., Hamilton RG. Cornstarch powder on latex products is an allergen carrier. J Allergy Clin Immunol 93:751-758, 1994.
6. Kurtz, KM, Hamilton RG, Adkinson NF. Role and application of provocation in the diagnosis of occupational latex allergy. Ann Allergy Asthma Immunol 83:634-639, 1999.

These are my thoughts on the Notice's specific request for comments on page 41716 (section VI):

Question 1: I would encourage a 1-year rather than 2 year time frame for implementation. As nicely stated in the Notice, 1 year represents a significant number of reactions and new cases of sensitization that could have been avoided if 1 rather than 2 years was adopted as the time frame.

Questions 2-4: I defer response to these questions to others with more practical experience in applying glove powder. Regarding question 3, I will suggest that knowledge is power for the consumer and thus I support extended labeling to include the source and ingredients (e.g. protein content of powder) in glove powder as part of the labeling.

Question 5: There are some surgeons at Johns Hopkins Hospital that double glove. The powder they indicate facilitates the putting on of the second glove. We are trying to discourage double gloving at the Hospital and we have been able to identify non-powdered alternatives that appear

satisfactory for these surgeons. It is therefore my opinion that powdered surgeon gloves are not needed.

Question 6: In a perfect world, the total elimination of the powdered latex surgeon and examination gloves would be preferred as they represent the highest source of NLR allergen exposure for healthcare workers and patients. As the practical minimum, I support a restricted sale, distribution and use of powdered surgeon and patient examination gloves

Question 7: The 1200 microgram per glove limit for protein is a positive step. If the only reason for selecting this level is the analytical sensitivity limit of the ASTM Lowry assay, then this is not an acceptable limit. We know that protein (allergen) levels well below 50 micrograms (the analytical sensitivity of the Lowry) can induce marked wheal and flare reactions in the skin of latex allergic individuals (1). I would encourage the adoption of more sensitive assays for allergen that would allow the assignment of a lower allergen level that maximizes safety for the user. (please see comments in paragraph 2 above).

Question 8: I am not aware of any alternative feasible methods for accomplishing the goal of reducing adverse health effects from allergic and foreign body reactions other than controlling the levels of allergen (protein) and particulate (glove powder). Use of a force air protection hood or a gas mask by healthcare workers are impractical and not satisfactory alternatives.

Question 9: These limits if adopted should be a requirement not a recommendation. If the limits were not required, then the FDA would be letting the marketplace dictate safety. This would be fine except that many healthcare providers (HMOs, managers) who work on a profit margin or who must show a profit are interested in the cheapest and not necessarily the safest gloves for their workers and patients. Assigning these limits as recommendations would simply not work.

Question 10: I defer on the issue of accelerated stability protocols to others who have more experience.

Question 11: The use of glove boxes or special room HEPA filters simply will not protect the healthcare worker or patient. These are expensive devices. It would be more efficient and cost effective to control the exposure risk at the source rather than attempt to remove it from the environment once the gloves were worn. One study by the Mayo group has shown that glove boxes do not work as they are not used, even with the best of intentions.

Question 12: The definition of "affected persons" is vague. Are these "small" manufacturers of gloves? I would discourage any "loop holes" that allow for by passing this rule.

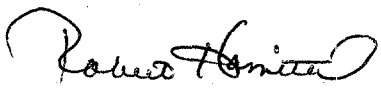
Finally, I would like to offer several suggestions to improve the accuracy of the terminology used in the "Proposed Rule and Notice" and any future documents related to this issue.

1. The proposed rule as written uses the acronyms NL (natural latex) and NRL (natural rubber latex) interchangeably. It is unclear why NL is used at all in the document, as natural rubber latex is the substance discussed in the document. I suggest that the term "NL" be replaced by "NRL" throughout Docket No 98N-0313 and any future documents relating to this topic to make them internally consistent and clearer to the reader.
2. Section I, para 2. (Background): *Hevea brasiliensis* is misspelled.

3. Section I, para 3. (Background): The distinction between donning and dusting powder is not clear. My understanding is that donning and dusting powder are the same and yet the way it is written, it appears to be two separate things. This needs to be clarified.
4. On pg 41740 of the Notice, the (ASTM D5712) Lowry is misspelled and on page 41741, the Lowry and glove powder (ASTM D6124-97) assays got mixed up.

I appreciate the opportunity to share my thoughts on the FDA's proposed ruling and notice regarding the reclassification of surgeon and patient examination gloves.

Respectfully submitted:



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