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Dockets Management Branch (HFA - 305)
Food and Drug Administration
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RE: Comments regarding Docket No. 99D-2335

October 28, 1999

1. FDA requests comments on the timeframe for implementation of the proposed rule considering the need for changes in production, technology, and labeling, as well as the immediate need to address adverse health concerns associated with medical gloves. Although FDA prefers a 1-year effective date, FDA is proposing a 2-year effective date based on indications from industry that the necessary changes could not be made in 1 year and that a shortage of medical gloves could result.

March 29, 1991 - The FDA issued a Medical Alert, informing health care providers of severe allergic, anaphylaxis and deaths associated with medical devices containing natural rubber latex and requested their assistance in reporting latex allergic reactions.

May 1, 1999 - In response to an increase in the number of reported severe allergic reactions and deaths associated with products containing or made from natural latex rubber, the FDA issued a correspondence to "All Manufacturers of Latex Devices" in which companies were advised to remove as much of the water soluble proteins as possible from latex devices. On-line production recommendations were communicated, specifically leaching process controls. In addition, recommendations for production technique which would achieve this goal included "post-cure processing" measures including off-line washing and surface treatment with chlorine or other agents to denature surface water soluble proteins.

Nine and a half years have elapsed since the issue of the FDA Medical Alert and the communication to latex manufacturers. Based on this fact - the timeframe for implementation of the proposed rule considering the need for changes in production, technology, and labeling, as well as the immediate need to address adverse health concerns associated with medical gloves should be as brief as possible. Prompt action must be taken for the thousands of patients and healthcare workers already sensitized to reduce the risk of serious reactions in the event of inadvertent exposure. Expedient measures must be taken for the thousands of latex allergic people who will certainly add to the already exploding population of sensitized individuals. Indeed, many companies have been gradually reducing protein content and reducing or eliminating glove powder over the past five years - a fact reflected in product advertising, industrial publications and media interviews. Two years ago, there may have been a threat of a glove shortage - in 1999, this is far less likely.

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In addition – the FDA would be wise to issue a latex allergy medical alert update along with adverse event reporting information. This should be distributed in a manner, which would insure all health care personnel would receive it – not just administrators. Some medical facilities have successfully incorporated latex allergy education into their annual safety reviews to insure all personnel receive information and updates.

Rationale: The vast majority of latex allergic individuals develop the disease from medical and surgical exposure as patients and from occupational exposure, primarily by wearing latex gloves.

Spina bifida is the most frequently occurring permanently disabling birth defect. It affects approximately one out of every 1,000 newborns in the United States. Studies indicate that up to 73% of this patient population develop latex allergy. According to the National Vital Statistics Reports, Vol. 47, No. 1 to Present, approximately 3,947,000 children were born in the U.S. last year. Using this data and incidence data from the Spina Bifida Association, one can assume an estimated 3,947 children were born with spina bifida in 1998, nearly 4000 children at extremely high risk for developing latex allergy. This does not include patient populations with other types of medical conditions requiring multiple surgeries, instrumentation's, invasive procedures and hospitalizations. These children are born with difficult medical conditions, however, they are not born with latex allergy – it is an iatrogenic disease caused by frequent and significant exposure to latex medical gloves and other products. To safeguard against future sensitization's, to protect to these children, all strategies to reduce overall medical exposure to latex allergens must be employed routinely and swiftly.

Excerpt from Occupational Latex Allergy – The End of Innocence (Holtzman R.S. and Katz J.D., Anesthesiology – 1998;89(2):287-9)

"In this issue of Anesthesiology, Brown et al. Report their findings with regard to latex sensitivity among members of the Johns Hopkins Department of Anesthesiology and Critical Care Medicine. Although a 24% incidence of irritant or contact dermatitis and a 12.5% incidence of latex-specific IgE positivity are sobering, it is hardly surprising in 1998. Perhaps more significant is the observation that 10% were clinically symptomatic although IgE positive.

The essence of the authors' message about the 10% of their colleagues who have latex-specific IgE but are asymptomatic is embedded within their statement 'we believe that these individuals are in early stages of sensitization and perhaps, by avoiding latex exposure, we can prevent their progression to symptomatic disease.'

There are some 38,000 anesthesiologists and 30,000 nurse anesthetists practicing in the United States today. Can we really assume that approximately 6,800 anesthesia personnel are sensitized and more than 1,700 are overtly allergic to latex? The clinical experience and the science is remarkably consistent over the past 10 years, and suggests the answer is yes. Should one continue workings in an environment with powdered, high antigen gloves capable of sensitizing those exposed with a prevalence of 12.5% and a clinically allergic prevalence of 2.5%? Don't bet your life on it."

This article written by medical professionals portrays a vivid and frightening reality. How many more highly trained health care professionals must needlessly become sensitized, suffer serious

allergic reactions, asthma and other deleterious health effects associated with latex allergy? How many more must unnecessarily relinquish their careers because of the prevalence of latex gloves and other products as well as the presence of ambient latex allergens from powdered latex gloves use in health care settings? Five deaths associated with latex gloves, all health care workers, were reported to FDA MedWatch in the past year. How many more must die before this needless process of sensitization and disease is halted? Every effort must be made to protect our nation's workers.

Comment for #2 & #6 -

2. In the proposed guidance document, FDA recommends a limit of no more than 120 mg powder per powdered glove, regardless of size, as the maximum level in order to reduce exposure to particulates and airborne allergens. FDA requests comments on the recommended limit with regard to the minimum level of powder needed for adequate donning of gloves.
6. FDA considered restrictions on the sale (advertising), distribution, and use of powdered surgeon's and patient examination gloves. FDA is seeking comments on the feasibility of such restrictions.

Lauran Neergaard (Associated Press) - San Diego Daily Transcript Jan 07 1998 -

The FDA has studied the problem for two years and encouraged glove makers to go powder-free, said medical device chief Dr. Bruce Burlington. But he said the FDA would not ban powdered gloves because so few alternatives are sold today that hospitals would face serious shortages.

"We recognize the severity of the problem," Burlington said. "We need to move on it, but in a way that doesn't leave the vast majority of health care workers without the protection they need."

1997 FDA Medical Glove Powder Report - It has been suggested that experimental and clinical studies demonstrate that glove powder on medical gloves can enhance foreign body reactions, increase infections and act as a carrier of natural latex allergens.

A literature search using the term "glove powder" revealed many, many articles supporting this statement by the FDA. All articles acknowledged the presence of glove powder as a lubricant to facilitate glove donning. However, the overwhelming consensus of the reviewed information was to eliminate powdered gloves altogether in an effort to safeguard both patients and workers.

Recommendation - 1 to 2 year phase out of all powdered glove products.

A recommendation for FDA proposals in this direction might include:

An immediate maximum powder limit to be set at 120 mg per exam glove - regardless of glove material, (suggest an appropriate manufacturing compliance time frame - perhaps 12-24 months) with a stepwise powder reduction plan that would ultimately result in a phase-out of powdered gloves. (Powder-free criteria may be applied at this point)

An immediate maximum powder limit to be set at 250 mg per surgical glove - regardless of glove material, (suggest an appropriate manufacturing compliance time frame - perhaps 12-24 months) with a stepwise powder reduction plan that would ultimately result in a phase-out of powdered gloves. (Powder-free criteria may be applied at this point)

Rationale –

When powdered products are used, everyone in the environment is subjected to, among other powder contaminants (including residual processing chemicals and bacterial endotoxins), second-hand latex. This issue, parallels that of the hazards associated with another environmental contaminant - second-hand tobacco smoke, and should be addressed accordingly.

Glove powder is a matter of the patient's Right to Know - To my knowledge, at no point is glove powder in itself communicated to the patient as a specific cause of possible surgical or procedural complications – the risk is simply related as a potential for post-operative adhesions and other adverse consequences. Patients are exposed to this known biohazard without their knowledge, in other words, they are not given a choice of powdered or powder-free gloves to be worn by the surgical staff.

In addition – I believe the use of the term mg per square decimeter continues to leave the end-user in the dark. Health care providers do not usually have the time, or the inclination, to figure out mathematically what this means in terms of allergen content, protein content or powder levels per glove. Workers wear gloves, not units of surface area. Per glove is a unit description that everyone can identify with and will encourage end-user education and more informed user populations.

Enclosed with this comment, is a small sample of literature abstracts, available through a simple Medline search, which reflect the hazardous nature of glove powder. It's continued use implies a troubling lack of concern for both patients and workers alike.

J Long Term Eff Med Implants 1997;7(3-4):215-8

Surgical glove hazards: a commentary.

Ellis H - Department of Anatomy, United Medical and Dental School (Guy's Hospital), London, England.

Surgical contaminants of many kinds, including glove powder, cause granuloma formation. This is particularly well documented in the peritoneal cavity, but has been demonstrated in most anatomic sites. In addition, systemic manifestations result from the absorption of the latex protein antigens onto the starch powder on the surgical gloves, which is aerosolized when the gloves are donned or removed.

J Hosp Infect 1999 Aug;42(4):283-5

Glove powder: implications for infection control.

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Gloves are increasingly promoted for use by healthcare workers, but this use is not without risk. Data associating powdered gloves with an increased risk of latex allergy is available and there is circumstantial evidence that the powder used may increase bacterial environmental contamination. In animal models, corn starch, the material used as glove powder, promotes wound infection. Infection control teams need to be aware of this evidence and should support switching from use of powdered to powder free gloves.

Eur J Surg 1999 Jul;165(7):698-704

Postoperative exposure to glove powders modulates production of peritoneal eicosanoids during peritoneal wound healing.

Chegini N, Rong H - Department of Obstetrics and Gynecology, Institute for Wound Research, University of Florida, Gainesville 32610, USA.

OBJECTIVE: To assess the effect of postsurgical exposure of peritoneal cavity to glove powders, Hydrocote, latex proteins, and lipopolysaccharide (LPS) on eicosanoid production in peritoneal fluid and cellular distribution of eicosanoid enzymes in peritoneal wound during healing. **DESIGN:** Randomised experimental study. **SETTING:** Institute for Wound Research, USA. **ANIMALS:** 360 mice randomised into six groups of 60 each. **INTERVENTION:** Abrasion of peritoneal cavity followed by instillation of 500 microl of sterile phosphate buffered saline (PBS) alone (Control) or containing 100 microg/ml of Biosorb, Keoflo, Hydrocote, 1 mg/ml of latex proteins, or 12.5 microg/ml of LPS. Mice were killed at 1, 2, 4, 7, 14 and 28 days, and the peritoneal washing obtained from each animal and concentration of eicosanoids measured. Tissue were immunostained for cyclooxygenases and 5-lipoxygenase and thromboxane A2 (TXA2) synthetase. **RESULTS:** Peritoneal fluid from uninjured controls contained 3.9 (0.8), 5.2 (0.3) and 0.2 (0.02) ng/ml of thromboxane B2 (TXB2), prostaglandin E2 (PGE2) and leukotriene B4 (LTB4), respectively. These increased significantly during the first week to 6.3 (0.3), 11.7 (0.8) and 2.6 (0.1) ng/ml, $p < 0.05$, before returning to baseline by day 14. In all the treated groups the values were significantly higher than in controls ($p < 0.05$). Immunoreactive cyclo-oxygenases, 5-lipoxygenase and TXA2 synthetase proteins were present in various cell types in uninjured skin and peritoneum, incisional and peritoneal wounds and adhesion tissues. Staining was more intense at the site of wounds and paralleled eicosanoid concentrations during healing. There was no difference between exposed and unexposed groups. **CONCLUSION:** The presence of glove powders, latex proteins and LPS in peritoneal cavity cause increased eicosanoid production and aggravate the normal inflammatory reaction to tissue injury. This may contribute to the inflammatory or immune reactions and development of adhesions caused by glove powders.

Inflammation 1997 Oct;21(5):489-99

Retrograde migration of starch in the genital tract of rabbits.

Edelstam GA, Sjosten AC, Ellis H - Department of Obstetrics and Gynaecology, SOS, Karolinska Institute, Sweden.

This study in a rabbit model simulates contamination with glove powder in association with a routine gynaecological examination. Large individual variations of powder contamination were found and there were no overall statistically significant differences between the control and experimental animals. The findings are supported by the observation that some but not all women develop adhesions after gynaecological surgery. Analyses of variances indicate differences in the migration of starch particles in the genital tract with the highest amount of particles found three days after starch contamination of the vagina. Since no adhesions were observed, there would probably need to be an ongoing post surgical or post infectious inflammation in the tissue, when the starch particles are added. Starch powder from latex gloves can cause adhesions and increase the risk of latex allergy in healthcare workers. Retrograde migration in the genital tract cannot be excluded, powdered examination products should be eliminated from the gynecologicla examination room.

Korean J Ophthalmol 1997 Jun;11(1):51-9

The inflammatory potential of surgical glove lubricants: Biosorb, Keoflo, calcium carbonate and Hydrocote after intravitreal injection.

Park HS, Kim MS - Department of Ophthalmology, Kangnam St. Mary's Hospital, Catholic University of Korea, Medical College, Seoul, Korea.

Surgical glove powders have been implicated in serious postoperative foreign body reactions due to contamination of the operative field. Inflammatory responses to glove lubricants or mold release agents have to date been studied to a lesser extent in ocular tissues than other body tissues, although powder contamination of intraocular lenses, with severe postoperative anterior chamber inflammatory responses, have been reported. The object of this study was to grade and quantitate the inflammatory response of

surgical glove lubricants, namely Biosorb, Keoflo, calcium carbonate and Hydrocote (a hydrogel polymer film used in powderless gloves), as introduced into the posterior chamber on New Zealand white rabbits. In a double masked GLP study, a total of 150 eyes were evaluated. For each of the four test samples, a dose response curve was obtained at 10 micrograms (Keoflo only), 125 micrograms, 250 micrograms, 500 micrograms, 1000 micrograms, and 1500 micrograms. Study parameters were the quantitation of inflammatory cells in the aqueous and vitreous, and ocular irritation and inflammation, as graded by the rabbit inflammation score system, at 0 and 48 hours post-injection. A Wilcoxon signed-rank test used to evaluate statistical significance ($p < 0.05$). A test vitreal cell count was less than 50 cells/mm³ and the overall mean clinical response was less than 2.0. This study established that Keoflo at all concentrations 10 micrograms-1000 micrograms, and Biosorb at concentrations greater than 1000 micrograms were inflammatory. Calcium carbonate and Hydrocote were non-inflammatory at concentration of 125 micrograms-1500 micrograms. The unoperated, sham, vehicle and Ocugel controls were all non-inflammatory. The positive Zymoan A controls were defined as inflammatory. In conclusion, no glove powder is totally safe, even small amounts of glove powder (10 micrograms) can elicit an inflammatory immune response. If all glove powder averages 700mg/pair, this should be removed prior to contact with a patients tissue. Powder-free gloves and greatly reduce the potential inflammatory risk associated with powdered gloves.

J Emerg Med 1997 Mar-Apr;15(2):209-20

Surgical glove lubricants: from toxicity to opportunity.

Woods JA, Morgan RF, Watkins FH, Edlich RF - Department of Plastic Surgery, University of Virginia School of Medicine, Charlottesville 22908, USA.

In most emergency departments, surgical gloves are coated with surface powders that act as lubricants to facilitate donning. Cornstarch powder is an absorbable powder employed as a donning agent on most powdered gloves. Talcum powder, a nonabsorbable powder, is used as a mold release agent in glove manufacture and is still commonly found on the surfaces of modern surgical gloves. These powders are foreign bodies that elicit inflammatory responses, leading to a wide number of symptoms and complications. The best method of preventing clinical complications from glove powder is to use powder-free gloves.

Eur J Surg Suppl 1997;(579):35-8

Effects of powder on infection risks and associated mechanisms.

Renz H, Gemsa D - Laboratory Medicine and Immunopathology, Humboldt University of Berlin, Germany.

This paper examines the release of Tumour necrosis factor alpha, (TNF α) interleukin 1, eicosanoids, and hydrogen peroxide from macrophages exposed to glove starch particles. Studies are described which show that T-cell responses are potently activated by glove powder products leading to the release and formation of high amounts of pro-inflammatory mediators, ultimately resulting in adverse clinical consequences such as starch peritonitis or adhesions.

J Long Term Eff Med Implants 1997;7(3-4):225-34

Endotoxin and particulate matter on surgical gloves.

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Department of Surgery, Ostra Hospital, University of Goteborg, Sweden.

Because of the continual need to protect of health care workers, gloves are increasingly used. Most gloves purchased are powdered. Besides having deleterious effects on wound healing, glove powder can act as a vehicle for latex allergens, endotoxin, and possibly bacteria. Few tested gloves had undetectable levels of endotoxin, and only one was free from particulate matter. Since powder particles can become airborne and are thus easily spread, concerns for health care professionals and patients arise. To reduce risks

for exposure, glove-selection criteria must include low or undetectable levels of latex allergens, endotoxin, and particulate matter.

Allergy 1995 Apr;50(4):378-80

Latex allergens in glove-powdering slurries.

Lundberg M, Wrangsjö K, Johansson SG - MIAB, Knivsta, Sweden.

Exposure to airborne glove powder contaminated with latex allergens is known to provoke respiratory symptoms in latex-sensitized individuals. In the commonly used wet-powdering process in glove manufacturing, powder is applied by dipping gloves in a cornstarch suspension, a slurry. The slurry is a potential source of allergen contamination of the powder. The protein and latex allergen contents in five different slurries and in extracts from the corresponding latex gloves were measured using the BCA assay and the IgE antibody inhibition assay (EAI assay). Latex allergens were found in all slurries and gloves. No correlation between the values of protein contents and allergen contents was found. Wet powdering of gloves induces a risk of latex protein contamination of the cornstarch.

J Appl Toxicol 1992 Dec;12(6):443-9

The pathological effects of glove and condom dusting powders.

Kang N, Griffin D, Ellis H - Department of Anatomy, University of Cambridge, U.K.

Dusting powders are used on latex gloves and condoms. They help to release these products from their moulds during manufacture and facilitate processing and donning. Dusting powders are also used on contraceptive diaphragms, sanitary napkins and in toiletries. There are numerous dusting powders in current use around the world. At present a consensus exists about the best dusting powder to use on surgical gloves, based on data about the safety of these agents in humans, as well as their manufacturing qualities. No such consensus exists for the use of dusting powders in other situations. However, there is uncertainty about whether dusting powders used in situations other than on surgical gloves are responsible for harmful effects. This study uses intraperitoneal injections in rats to examine the pathological effects of dusting powders that are in current use on surgical gloves and condoms. We suggest that dusting powders may be a source of morbidity when used in situations other than on surgical gloves and confirm the findings of previous investigators that the dusting powders we tested differ in their ability to produce pathological effects.

Transfusion 1992 Jan;32(1):83-5

False-negative results by polymerase chain reaction due to contamination by glove powder.

de Lomas JG, Sunzeri FJ, Busch MP - Irwin Memorial Blood Centers, San Francisco, California.

The polymerase chain reaction (PCR) technique has become an important, widely employed method for the detection and quantitation of the nucleic acid sequences used in the diagnosis and monitoring of genetic and infectious diseases. Much attention has been directed at the problem of false-positive PCR results, which are generally attributed to low-level laboratory contamination of amplified sequences ("carryover"). In contrast, few investigators have commented on the somewhat less frequent, but equally problematic, false-negative PCR results. Investigation of the source of sporadic false-negative PCR reactions found that glove powder, inadvertently introduced into tubes when gloves are changed in an effort to reduce false-positive results, can nonspecifically inhibit each of the major steps in the PCR detection process. Methodologic precautions are recommended to minimize this problem.

Am J Clin Pathol 1988 Jul;90(1):81-4

Contamination of perfused donor kidneys by starch from surgical gloves.

Moriber-Katz S, Goldstein S, Ferluga D, Greenstein SM, Miller AS, Schwartz AB, Simonian S - Department of Pathology and Laboratory Medicine, Hahnemann University School of Medicine, Philadelphia, Pennsylvania 19102.

Starch induces a variety of inflammatory reactions in humans and may contaminate surgical procedures from surgical gloves. Using polarized microscopy and electron microscopy, the authors observed starch particles in renal perfusate and in glomeruli of perfused donor kidneys. Group 1 consisted of 10 unusable kidneys handled with standard concern of glove sterility. Eight other kidneys (Group 2) were perfused with particular attention toward avoidance of starch contamination. The gloves were rinsed five times, and the cuffs were not dipped into the perfusate. Two kidneys (Group 3), deemed unsuitable for transplantation, were perfused for 24 hours with perfusate swished with unwashed sterile gloves. Group 4 consisted of five transplant biopsies performed within one week after transplantation. Perfusates alone were also circulated through the Waters Perfusion Machine continuously for 24, 72, and 188 hours with and without the use of gloves. The number of birefringent crosses were counted in each of 25 glomeruli per specimen. Group 1 displayed a mean of 1.8 birefringent crosses per glomerulus; Group 2, 0; Group 3, 5.3; and Group 4, 4.4. Groups 1 and 3 also exhibited birefringent crosses in peripheral renal vessels. Perfusate alone, handled without gloves, showed no birefringent crosses; by contrast, perfusate handled with gloves showed numerous birefringent crosses. The authors conclude that starch from surgical gloves can enter the perfusate and lodge in glomeruli and other sites of donor kidneys. Rinsing gloves five times and avoiding contact of the perfusate with the glove cuff effectively eliminates the contamination.

7. In the proposed guidance document, FDA is recommending an upper limit of no more than 1,200 micrograms protein per NL glove, regardless of size, as the maximum level for NL surgeon's and patient examination gloves. FDA is seeking comments on the proposed recommended limit.

It is important to use terminology that will encourage end-user recognition and intelligent glove selection. I believe the upper limit of no more than 1,200 micrograms protein per NL glove is appropriate and hope that the FDA will retain the term "per glove".

9. FDA also invites comments on the issue of whether the recommended limits on powder and protein proposed in this rule should be recommended limits or required limits.

It is my opinion that the recommended limits proposed in this rule, should be required. While many manufacturers work diligently to comply with FDA recommendations, this is not true with all companies. To reduce the risk to patients and workers, product standards must be maintained. Prescription and over the counter medication must identify and indicate amounts of "active ingredients", in other words - those ingredients which cause a sensitivity or allergic reaction and which may be toxic at higher doses. To date, there is no determination for "safe" levels of NRL, but maximum limit requirements may provide future insights for latex allergy prevention and management strategies.