



A System In Need of Repair - Medical Device Regulation: The Example of Latex Medical Gloves

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Abstract

The process of regulating medical devices in the United States was developed and implemented 37 years ago and is currently in need of an overhaul. It has been recommended that a new integrated regulatory framework be established with a clear focus on safety, from the initiation of the approval process through the lifetime or existence of the medical product. Currently, there are numerous safety concerns within the system itself, from the premarket approval to postmarket surveillance issues, as well as questionable agency follow-through once a safety concern has been identified. The overall lack of regulatory response regarding latex medical gloves, for two decades, serves as an eye-opening example of a flawed system long in need of repair, and is herein addressed in detail, with emphasis upon, extant and continued areas in need of systematic remediation.

Keywords: medical device, policy, regulation, latex allergy

“The world is not dangerous because of those who do harm but because of those who look at it without doing anything.” - Albert Einstein

Introduction

As science and technology continue to rapidly advance in this modern era, it is becoming increasingly imperative that policy and regulation maintain a similar, if not equivalent pace. The unprecedented quantity of scientific and medical innovations may also require inclusive guidance and surveillance on an international scale, to meet professional and societal needs arising from these advances and their potential unknown risks. However, there is doubt that the current regulatory system is capable of effectively and safely meeting these fundamental requirements in a timely and collaborative manner.

The system has failed on a number of occasions as the quantity and complexity of medical devices and medications has steadily increased. Amplifying the issue are the significant delayed responses on either identifying, or

responding to, the numerous drug and device debacles in the recent past; Vioxx (Rofecoxib), metal-on-metal hip implants, as well as with something as seemingly simple as the regulation of powdered latex medical gloves. Even when other countries have banned, or identified dangerous medications and medical devices, several have remained on the market in the United States, often for years (1, 2). It seems as though in America, finances and politics carry a disproportionate amount of weight over health and safety, but to what extent will it be allowed to continue?

Federal agencies have had the vital responsibility of creating and implementing numerous safety systems to benefit the American public. Specifically, in the past century, the Food Drug Administration (FDA) has held an essential and prominent role in public health, by monitoring and regulating the safety of food products, medications, and medical devices, some more successfully than others.

Despite the vast accomplishments of the FDA, there have been many criticisms. A more recent concern is that there is a tremendous amount of financial and political pressure

originating from the industries which they are to be regulating. In 2012, the Union of Concerned Scientists revealed that drug, biotechnology and medical device companies spent over \$700 million dollars in lobbying efforts, and over \$6 million in campaign contributions between 2009 and 2011 (3). Politics should not be outweighing safety issues, nor should finances, yet, this undue corporate influence and the conflicts of interests are allowed to persist.

There are also concerns with both premarket and post-market framework issues regarding medical devices. The classification and approval process itself has come under scrutiny, as there has been much debate in recent years on the FDA premarket notification or 510(k) process used to clear many medical devices without requiring rigorous clinical studies, or any study, on individual products. The premise of gaining approval is based upon predicate; the supposition that there is 'substantial equivalence' among similar medical products previously approved for use (4, 5). Essentially, the process may only consist of an application form, a fee, and a claim that the product is equivalent to an approved device already on the market. The safety concern is that the claim of substantial equivalence to a product may indeed be to another device which also gained its approval through equivalence, and so on; the original device may not have even been clinically tested for safety, but rather grandfathered in prior to the 1976 Medical Device Amendments (4). Some feel the 510(k) process lacks the element of safety, while others declare that it is both slow and burdensome, which impedes the timely availability of new medical technologies for patient use (5). Either way, there is a need for the almost four-decade old regulatory framework to be updated, again, not only to detect problematic trends with postmarket surveillance, but equally important is to ensure that the policies and practices are appropriate, and that there are effective responses once a performance or safety issue is identified.

In 2011, the Institute of Medicine recommended the FDA overhaul the flawed 510(k) system, to develop a new integrated regulatory framework that will screen for safety and effectiveness in premarket approval. Recommendations for postmarket improvements include a continual and more thorough monitoring of medical devices (4, 5). Fortunately, some change and improvement may be soon realized. Congress authorized the development of a tracking system back in 2007, and after years of delay, the FDA has recently proposed a rule to require certain manufacturers to apply a unique identifying code to the device

or package. The unique device identifier (UDI) would allow electronic tracking and early identification of adverse events, or quality performance issues, while also aiding in faster recalls if necessary (2). When the UDI system comes to fruition, it will serve as a good first-step toward a more thorough surveillance process, although it will not include all medical products.

Another cause for concern is the increasing importation of pharmaceuticals and medical products from other countries. Reportedly over 40% of drugs and 80% of active ingredients comprising drugs (6), as well as 50% of medical devices are imported for use in the United States (7). Understandably, the current regulatory framework does not require inspections of foreign manufacturing plants every two years as it does for the US manufacturing establishments. However, as an alternative, they are relying in part on the governments of other countries to ensure the safety of drugs and devices for the US market. A recent article in the *Texas International Law Journal* explained, "Essentially, the FDA is outsourcing its regulatory power to other countries, some of which are highly susceptible to corrupt regulatory practices and counterfeit production" (7). In response, Congress passed the Food and Drug Administration Safety and Innovation Act in 2012, in an attempt to expand the FDA's authority and to develop strategies to better protect the drug supply (6).

Many medical professionals have witnessed other weaknesses within our current system, creating an expanding rift between healthcare and regulation. Several key themes have emerged; namely a severe lag time in response, or even a lack of adequate response and subsequent policy and regulation. Much of the concern in the literature surrounds prescription drugs, or recalled medical devices. However, there are other situations where the deficiency and inadequacy of FDA response clearly illustrates some of the more problematic flaws within our current system and should be used as a catalyst for change. It is felt by many that there is a significant disconnect between the science and the implementation of adequate policy or regulation, and indeed these are intricately interconnected and need to be addressed as such. The use of current scientific data and knowledge is a necessary component in the development or improvement of any evidenced based regulatory policy (8). However, when the current scientific data is being communicated to those with the regulatory authority, and still there is an inadequate or absence of a response, we must look further into the issue, to determine other areas where the system is failing.

One example is the continued use of powdered latex gloves, which were known to be causing systemic reactions and illness among both health care workers and patients. Curiously, the FDA identified and reported on several of the first fatalities, as well as the widespread scope of the problem caused by these devices, but since has been seemingly hesitant to respond to their own reports. Although many Americans would assume that the United States requires high standards of regulatory control and that there are safeguards in place for substandard medical devices, the truth is that the US regulations on this issue continue to considerably lag behind. Especially when compared to other countries such as Germany and England, and particularly when taking into account the lack of action and follow-through by the FDA on addressing this safety concern.

The history of latex allergy and latex gloves

The sudden arrival of natural rubber latex allergy two decades ago has become a prevalent and serious healthcare issue, which has presented many complications to both the medical profession and public health. When universal precautions were enacted, gloves, specifically powdered latex gloves, became routinely supplied to health care workers to be used when treating all patients, in an effort to diminish the potential exposure of American workers to blood-borne pathogens. In the early 1990s, reports and scientific publications began to surface almost simultaneously in developed countries regarding patients and health care workers developing severe life-threatening reactions, and fatalities, to products containing natural rubber latex (NRL). With the abrupt onset and increase of incidence of latex allergy occurring among both patients and health care workers worldwide, educational efforts combined with regulatory measures would have been vital components to curb and even prevent the crisis. Yet, any attempts to truly regulate these medical devices have been so negligible in the US, that other occupations are also being impacted.

A virtually unheard of phenomenon 25 years ago, it quickly affected up to 17% of health care workers, whom have been exposed and acquired the illness occupationally. In addition to health care workers across the domains of medical, surgical and dentistry, the other well-defined category at highest risk are individuals who have undergone multiple surgical procedures. Specifically, spina bifida patients were identified as having a very high prevalence of latex allergy, as high as 64-67% from the mu-

cosal exposure during their extensive surgical procedures (9, 10). Other professions including food service, law enforcement, hairdressers, and mechanics have also been affected. The source of the problem has been identified by numerous scientific studies as being highly antigenic powdered latex gloves.

The dramatic increases in glove use, combined with alterations in the manufacturing processes of powdered latex gloves are theorized to be two of the converging factors responsible for the sudden occurrence of this issue, which quickly reached epidemic proportions. Between 1991 and 1996 the number of medical gloves imported into the US had increased by 247% (11). This notable increase went from under 1 billion a year and would continue to rise annually, when in 1996 there were 20.8 billion medical gloves imported into the United States (12).

The rising usage is thought to have brought about changes in the manufacturing processing and procedures of latex gloves, "resulting in a poor-quality, highly allergenic product" (13). However, the manufacturer can reduce much of the proteins; the residual protein content of the gloves varies partly on the leaching process to remove the water-soluble proteins during the production of the gloves. One of the main, long-held theories is that some manufacturers in order to increase production, cut corners by decreasing the rinsing cycles of gloves, and/or failed to routinely change the water in the rinse and leaching cycles (14-16) leaving measurable amounts of leachable proteins remaining on the gloves (14).

According to a study by Yunginger et al. in 1994, toward the beginning of the epidemic, extractable latex proteins found in latex gloves varied considerably in concentration, up to 3000-fold differences were found from various glove manufacturers (17). Thus, the difference in protein content allows for substantial variations of aerosolization potential between individual brands of gloves. Unfortunately, there was no way for the worker or patient to know the quality of the glove they were using, or being exposed to. There is also no way to either prove or disprove this theory scientifically, since there are no known studies conducted on the allergenicity of gloves prior to the late 1980s (18), simply because there was not previously any need to do so.

Historically, natural rubber latex (NRL) was considered an innocuous material, with very few documented problems or drawbacks (19). However, a change occurred

with the exponential increase of exposure to NRL gloves. Numerous published studies provide significant evidence that NRL protein allergens bind to the cornstarch powder, the common lubricant used in manufacturing gloves. The exposure occurs from direct repeated contact with latex gloves, in addition to the inhalation of the aeroallergens (20-22), when the natural rubber latex proteins bind to the glove powder, and then become aerosolized throughout the environment (23).

Due to the ubiquity of natural rubber latex in our environment, numerous lifestyle changes occur once a person has acquired the condition. "Latex allergy" typically refers to a Type I (IgE) immediate hypersensitivity to the proteins or allergens in the natural rubber latex (11). The extent of exposure needed to cause the allergy to develop in individuals has not yet been determined, however, it is known that even very low levels can elicit systemic allergic reactions (16). Symptoms can range from shortness of breath, hives, flushing, chest tightness, coughing, wheezing, to edema, difficulty swallowing, rapid heart rate, hypotension, and anaphylactic shock. Whereas allergic contact dermatitis (Type IV), is a localized delayed hypersensitivity, a contact reaction to the numerous chemical additives and accelerants which are used in the manufacturing process of latex gloves (10, 24).

In response to the severity and the sheer numbers of people being affected and exposed, Germany enacted regulations banning the use of powdered latex gloves back in 1998; if latex gloves were purchased, they were only powder-free, low-protein (10). Subsequently, they noted a reduction in new onset allergy and occupational asthma cases by over 80% each. There was also a simultaneous large-scale educational effort initiated, where a semi-governmental insurance carrier distributed latex allergy information packages to all of their clients; including doctors' offices, dentists, and private and church run hospitals (25). This study and numerous others, all provide evidence which clearly demonstrates that latex allergy is highly preventable when proper precautionary measures are taken, such as purchasing only non-powdered, low-protein gloves or non-latex gloves. Unfortunately, unlike Germany, the US did not authorize a ban back in 1998, or in 1991 when they knew, they also did not mandate change. Americans continued to be unnecessarily exposed.

Since universal precautions were established to ensure safety, then universal standards for quality control also needed to be established to regulate the medical devices

used to do so, especially when they are known to be causing illness. Yet, aside from issuing several draft guidance documents and recommendations, there has been virtually little regulatory response.

US agency responses

On March 29, 1991 the Food and Drug Administration issued a medical alert "Allergic Reactions to Latex-Containing Devices," in response to the surprising and unexpected reactions reported to latex-containing medical products, including several patient fatalities during medical procedures from latex-cuffed barium enema tips. The letter stated, "Proteins in the latex itself appear to be the primary source of the allergic reactions..." and also that the FDA is working with manufacturers of latex devices to make the protein levels in their products as low as possible (26). On May 1, 1991 the FDA sent a letter to all manufacturers of latex devices warning that they had concerns, "...that deficiencies in the manufacturing process for latex devices could be a contributing factor for some of these adverse events. That is, insufficient leaching or insufficient surface treatment by some manufacturers will not remove leachable proteins that are associated with these reactions" (14). The letter urges manufacturers to reduce the protein levels. Meanwhile, billions of these hazardous gloves continued to be imported into the US.

Six years later in September of 1997, the FDA formulated the Medical Glove Powder Report, in response to requests to ban the use of powder on gloves. The issue was posed as a question: "Do the current Center (Center for Devices and Radiological Health) policies adequately address potential adverse health effects of medical glove powder?" The draft conclusions included: "The major adverse impact of glove powder appears to be its contributing role in natural rubber latex allergies; glove powder acts as an airborne carrier of natural latex proteins, exposure to airborne natural rubber latex allergens can be most effectively reduced by considering both the level of natural latex proteins and the amount of glove powder on medical gloves" (12). Some of the recommendations included: to establish and standardize maximum allowable powder levels for powdered gloves; to establish a maximum allowable glove protein level; require manufacturers to label all medical gloves with glove powder content unless < 2 mg per glove; also label total quantity of water soluble proteins remaining on gloves (12). As of this writing, there continues to be no label requirement indicating latex protein or powder content.

On January 7, 1998, a petition was submitted to the FDA to “Ban Cornstarch Powder on Latex Gloves.” Despite the urgency this petition warranted, it would be a year and a half before a reply came, when the FDA published the July 30, 1999 Federal Register notice. The FDA only addressed alternatives to the proposed regulation and petition by stating:

“A ban of all powdered medical gloves has been requested in a citizen petition submitted to FDA. FDA considered banning powdered gloves because that action would meet the stated objective of eliminating airborne powder and greatly reducing exposures to airborne allergens associated with the use of medical gloves. However, FDA did not select this alternative because a ban would not address exposure to NL [natural latex rubber] allergens from medical gloves with high levels of NL proteins. Moreover, such a ban of powdered gloves might compromise the availability of high quality medical gloves and greatly increase the annual costs by almost as much as \$64 million over the selected alternative” (27).

Instead of attending to the powder and/or latex protein issues, they proposed the reclassification of surgical and medical exam gloves. The FDA felt that a reclassification was needed, which would allow the agency more regulatory control over the gloves subjecting them to additional testing and special controls. The FDA categorizes medical devices into one of three regulatory classes, each of which differentiates the level of regulatory control necessary to ensure safety. Medical gloves are currently in Class I, with the least regulatory control (28), other items in this Class include tongue depressors. The FDA indicated that the controls of Class I are “insufficient to provide reasonable assurance of safety and effectiveness” for medical gloves (29). A classification change if enacted would include limits on powder and protein content, as well as a caution statement and labeling of the actual levels of powder and protein. The current standards and guidance are voluntary; they are derived from the American Society for Testing and Materials (28). Yet, the FDA has specific acceptable quality levels allowed for defects for medical gloves, such as size, and rates for leakage, tears, etc. but it does not mandate barrier testing, or minimum requirements for protein or powder levels (8). However, to date, fourteen years later, they have yet to follow through with the reclassification.

In May of 1998, federal agencies organized and held a teleconference on latex allergy, which numerous organizations and industry participated in (28, 30). Unfortunately, at that time, many of the health care workers who were being exposed daily had yet to hear that this problem even existed.

It would be seven years after issuing the letter to manufacturers to decrease protein levels before the FDA enacted a labeling mandate for NRL medical devices. The regulation titled, “Natural Rubber-Containing Medical Devices; User Labeling” became effective September 30, 1998. This regulation was a significant step forward for safety purposes, and included two main issues- an identifying warning statement, and the prohibition of the use of the term hypoallergenic. These requirements apply to all medical devices as well as the packaging of devices that are composed of or contain natural rubber latex which will come in contact with humans (32). It is important to note that these regulations do not apply to any non-medical devices, including gloves which are routinely used by the public for “non-medical” purposes (33).

In response to this escalating health threat, the National Institute for Occupational Safety and Health (NIOSH) released an Alert in 1997, *Preventing Allergic Reactions to Natural Rubber Latex in the Workplace* to serve as a warning and source of information to exposed workers. According to the NIOSH Alert, “When powdered gloves are worn, more latex protein reaches the skin. Also, when gloves are changed, latex protein/powder particles get into the air, where they can be inhaled and contact body membranes” (16). NIOSH then released the “Latex Allergy Prevention Guide” a smaller packet similar to the Alert.

The Occupational Safety and Health Administration (OSHA) published the Technical Information Bulletin: *Potential for Allergy to Natural Rubber Latex Gloves and Other Natural Rubber Products*, in April of 1999 (33). The purpose was “intended to alert [their] field personnel to the potential for allergic reactions in some individuals using natural rubber latex (NRL) products, particularly gloves in the workplace setting.” It was the topic of a congressional hearing, to determine if OSHA should be “stepping into this arena” and if OSHA’s actions will clarify or confuse people on the topic of latex allergies in the health care industry (33). With up to 17% of health care workers afflicted, it seems that OSHA was certainly justified, if not obligated to “step in”.

In September of 2008, a Citizens Petition was submitted to the Food and Drug Administration, *Ban Cornstarch Powder on Medical Gloves: Maltese Cross Birefringence*. The well-argued six-page document cites numerous peer-reviewed scientific studies on the dangers of cornstarch powder in the medical field including issues with wound infections, peritoneal adhesion formation, cornstarch-induced granulomatous peritonitis, and latex allergy. The authors warn that, "Evidence of harm to health care workers and their patients by cornstarch glove powder is overwhelming and ignoring it is unjustifiable..." (28). They request that the FDA use their legal authorization under the Food Drug and Cosmetic Act to take action and impose a ban eliminating the use and manufacture of cornstarch powder on medical gloves. A separate petition was filed on February 24, 2009, also requesting the FDA to ban cornstarch powder on all latex medical gloves (35).

The response took another two and a half years, when on February 7, 2011 in the Federal Register Notice, the FDA asked for feedback from health care workers to determine if there were any "potential benefits" of powdered gloves, so they could proceed with how to "best address the risk in light of any benefits" there may be (36). Furthermore, again without addressing the ban or regulation on the cornstarch powder, the FDA considers a warning label to be applied to both surgical and medical exam gloves. This warning, the FDA feels, will be sufficient to inform health care providers and consumers of the risks of powder on gloves (37).

On April 25, 2011, Public Citizens again submitted a petition to the FDA to immediately ban the use of cornstarch powder on both surgeons and medical exam gloves, and ban the use of natural latex rubber surgical and medical exam gloves. They state the rationale is due to the serious threat and widespread dangers they pose to both patients and health care workers, and the ample supply and availability of safer alternatives. In the petition and in a press statement, Dr. Michael Carome, the deputy director of Public Citizen's Health Research Group said, "The FDA's prolonged failure to take action eliminating the dangers posed by powdered surgical and patient examination gloves demonstrates an astonishing reckless and inexcusable disregard for the health and safety of patients and health care workers" (38).

There is overwhelming documented scientific evidence on the dangers of cornstarch powder in medical gloves and its clinical disease causing capabilities. How and why

the FDA is not taking regulatory action to protect the public is both disconcerting and perplexing.

Evidence that the FDA at times evades their regulatory duties is readily apparent, and continues to mount. Their own reports provide substantive evidence of the lack of follow-through on this topic. The FDA has been well aware of this issue since at least 1990, when they conveyed they had identified highly allergenic NRL medical products as the cause of what would become an epidemic of disease in health care workers. The FDA indicated that their general controls of gloves are "insufficient to provide reasonable assurance of safety and effectiveness" (29), but have yet to change them to a Class II device. They admitted that the deficiencies in the manufacturing processes of these medical products are causing the problem to occur. These are the medical devices they are supposed to be regulating, yet, their response is to ask, and not require the manufacturers to reduce the protein levels. They conclude that maximum limits should be set on both powder and protein levels, and then essentially do nothing to require such regulations. The US still has no FDA approved reagent to use for latex skin-prick testing, although they were asked in the early 1990s to "fast-track" the evaluation process, as well as allow reagents to be permitted from other countries to be used in the interim (39) neither of which seems to have occurred. This is perceived by many as an unacceptable level of inactivity and accountability.

The extensive science and research in this area is conclusive. Countless studies have shown a causative relationship between exposure and disease. Other countries, namely Germany addressed this back in 1998, removing not only all powdered gloves, but also all high protein latex gloves; the common sense, responsible resolution, which is prevention.

Since the American public has exposures via medical and dental care, as well as in food service, this issue should be the focus of public health, occupational health, and patient safety, but in the United States, it is more of a silent epidemic, seemingly un-newsworthy. Unfortunately, the needless exposure causing the sensitization to latex still occurs, albeit on a reduced scale, and to this day, latex allergy remains an ongoing issue being battled in the courts, the legislature, and within government agencies. Americans, consumers, health care workers, and patients should not have to make a sacrifice between the safety of, and the protection from, medical devices.

Conclusions

Over the years there have been numerous public health concerns identified over various medical devices. Latex allergy is a more recent one, which in an enlightened society should be totally preventable. It is a problem that could have been largely avoided if the proper precautions and regulatory measures had been enacted in a timely fashion. Undeniably, the FDA's evasive sidestepping and inadequacy in regulation for two decades, has significantly contributed to the life-long illnesses of hundreds of thousands of medical professionals, patients and others occupationally exposed.

If the current regulatory framework allows health and safety issues such as this to occur not only for years, but for decades, one must wonder what will be deemed an acceptable risk in the future, especially considering the potential unknown risks arising from the endless biotechnologies, nanotechnologies and the scientific advances yet to be developed. The time has come to return to focusing on safety in our regulation, without the financial and political influence tipping the scale and influencing critical decisions.

We must look internationally to other regulatory systems which have demonstrated effectiveness, and then seek to improve and implement them in the United States. Overhauling and updating the premarket approval and post-market monitoring are necessary; closing the loopholes which were created by grandfathered medical devices and substantial equivalence, as well as relying on voluntary reports for surveillance of adverse events. A thorough review and reevaluation of all devices which currently have a Class I rating, such as medical gloves, should also be encouraged. Of utmost importance is requiring the timely action and response, which is a requisite element that needs to be incorporated into all future FDA policy.

Fortunately, some change and improvements are currently underway, or are being considered. Nevertheless, it is imperative that this flawed framework be addressed, soon, before more potentially dangerous or complex scientific advances and devices are developed, marketed, and used on the public.

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