

Medical devices manufactured from latex: European regulatory initiatives

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Abstract

In Europe the marketing of medical devices manufactured from latex is regulated by directives describing the essential (safety) requirements that products have to fulfill to obtain marketing approval. This paper describes the general requirements for marketing medical devices in Europe and, more specifically, the requirements for products manufactured from natural rubber latex. The requirements for marketing medical devices can be fulfilled by using the relevant harmonized European standards. These standards are regularly under revision to incorporate the latest scientific developments. For certain devices, for example, latex medical (examination and surgical) gloves, specific standards have been published. Medical devices manufactured from latex pose a serious problem because of the risk of induction of allergy both against the latex proteins inherently present (type I or immediate type allergy) and against chemicals added during processing (type IV or delayed type hypersensitivity) present as residues in the latex products. So, besides requirements for product quality in terms of barrier properties, strength, and sterility, the main focus consists of the allergy-inducing properties of the latex products. Recent developments have reopened the discussion on the value of total protein versus allergen determination in latex medical gloves. However, as long as minimal levels needed for both sensitization and elicitation have not been established, a safe maximum level for leachable proteins/allergens in latex products cannot be determined. A European Commission guidance document on the latex allergy problem is currently being drafted by experts from Competent Authorities. Published by Elsevier Science (USA).

1. Introduction

The legislative system of the European Union (EU) dealing with medical devices is based on a series of European directives. Countries of the EU are obliged to incorporate these directives into national law, which is binding within each country. European regulations are prepared in the context of the internal European market, which is an area without internal frontiers in which the free movement of goods, persons, services, and capital is ensured.

2. European directives

At the moment there are three directives dealing with medical devices, the Directive on Active Implantable

Medical Devices (AIMD, Directive 90/385/EEC) [1], the Medical Devices Directive (MDD, Directive 93/42/EEC) [2], and the In Vitro Diagnostic Medical Devices Directive (IVMDD, Directive 98/79/EC) [3]. For medical devices the U.S. approach and the EU approach differ considerably. In the United States, premarketing approval has to be obtained from the Food and Drug Administration (FDA, Rockville, MD; mostly by the Center for Devices and Radiological Health, some products by the Center for Biologics Evaluation and Research), very much like the system for medicinal products in Europe which are regulated by the European Agency for the Evaluation of Medicinal Products (EMA, London, UK) or by national pharmaceutical control bodies. In the EU, manufacturers are required to place a CE mark¹ on the medical device thereby

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¹ The letters “CE” are the abbreviation of the French phrase “Conformité Européenne,” which means “European Conformity.”

claiming that the device complies with the Essential Requirements, as they are listed in the directive. These Essential Requirements ensure the safety and performance of the products. CE-marked products are allowed to be marketed throughout the European Economic Area.

The MDD classifies products into four risk groups (Class I, Class IIa, Class IIb, and Class III). The manufacturer is required to follow certain CE conformity assessment procedures, the rigor of which depends on the risk class. These procedures are combinations of requirements for the product and the manufacturer. Depending on the classification of the product, more detailed information has to be provided. Products are categorized according to their risk for patients, with special emphasis on the nature and duration of patient contact.

Class I products are low-risk, generally noninvasive products, Class IIa and IIb products are medium-risk products, generally those with more intimate or invasive contact for longer periods (e.g., many implants are currently in Class IIb, although this is under review), Class III products are high-risk products, generally those intended for absorption or in contact with the central circulatory or central nervous systems. Most latex medical devices are in Class I or IIa but, as with any classification system, exceptions are mentioned in the MDD, such as the fact that barrier contraceptives are in Class IIb.

Although the Essential Requirements described in the MDD are the same for all products, the CE mark is obtained by different routes for each class. Products with low-risk are allowed on the market on the strength of a declaration of conformity by the manufacturer alone, with certification provided by a Notified Body with respect to products supplied sterile or with a measuring function. All products in the medium- or high-risk categories require Notified Body involvement in the CE marking process. Notified Bodies are commercial certification organizations, accredited by a Competent Authority (the government agency in each member state responsible for implementing the directives). Specific Notified Bodies are designated for specific product groups. In general, more detailed information is necessary to demonstrate conformity with the Essential Requirements, with increasing risk classification.

When medical devices form intrinsic combinations with medicinal products or stable derivatives of human blood or human plasma, they are classified as Class III products and the nondevice constituents must be reviewed according to regulations for medicinal products (93/42/EC, 2000/70/EC) [2,4]. Antibacterial-coated urinary catheters and condoms containing spermicide are among the few examples of latex products in this category.

3. Conformity assessment

To prove that their products comply with the Essential Requirements, which are formulated in the directives in general and sometimes abstract wording, manufacturers can make use of standards. The European Committee for Standardization (Comité Européen de Normalization, CEN, Brussels, Belgium) develops European standards for medical devices. Part of this work is carried out under mandates from the European Commission (EC). A mandate is given if the EC decides that specific measures are necessary on a specific subject to indicate how conformity with the Essential Requirements can be demonstrated. After their completion European Standards can be submitted for harmonization by the EC. In this context a harmonized standard is a standard that is recognized by the EC as sufficient to prove that a product or process complies with the Essential Requirements. If a product complies with a harmonized standard, it is deemed also to conform to the Essential Requirements. There is no such presumption of conformity if other standards are used, even if these standards are widely recognized in their particular field of application such as ISO standards (International Organization for Standardization, Geneva, Switzerland) or ASTM standards (American Society for Testing and Materials, West Conshohocken, PA, USA).

In the MDD a “safeguard clause” exists allowing a Competent Authority to remove a product from its national market if it considers that the product may compromise the health and/or safety of patients, users, or other persons. This safeguard clause is not used lightly in view of the basic principle of an open European market, although it is expected that member states will take action on the basis of the precautionary principle [5]. Any use of the safeguard clause attracts an official investigation by the European Commission.

4. Latex² Products

Depending on the product and its use, latex products can belong to any of the risk classes but, in practice, no latex products would be expected in Class III (apart from drug–device combinations). Many medical devices are manufactured from latex. However, the major focus of concern has been medical gloves for single use, since exposure to these products is by far the most extensive. This paper therefore focuses on that product group. Medical gloves can be divided into examination gloves and (sterile) surgical gloves. Examination gloves are Class I medical devices and surgical gloves are Class IIa

² In this text, whenever the term “latex” is used, this refers specifically to natural rubber latex derived from the tree *Hevea brasiliensis*.

devices. This means that a manufacturer can affix a CE mark on examination gloves on his or her own responsibility. For surgical gloves a Notified Body must be involved in the CE marking process. In both cases, however, the manufacturer is obliged to have a complete technical dossier showing that the product complies with the Essential Requirements of the MDD. As explained above, the most straightforward way to do this is to show compliance with the harmonized European standards that are applicable.

For medical gloves a series of harmonized standards exist:

- EN 455-1 Medical gloves for single use—Part 1: Requirements and testing for freedom from holes [6].
- EN 455-2 Medical gloves for single use—Part 2: Requirements and testing for physical properties [7].
- EN 455-3 Medical gloves for single use—Part 3: Requirements and testing for biological evaluation [8].

These standards cover both examination gloves and surgical gloves manufactured from any material. Part 1 requires that medical gloves for single use shall not leak when tested in accordance with the watertightness test that is described in the standard. Part 2 specifies requirements and gives test methods for the dimensions (length and width) and the strength (force at break before and after accelerated aging) of single-use medical gloves. Different requirements are made for seamed gloves and unseamed gloves and for gloves manufactured from different materials. A detailed description of Parts 1 and 2 is considered to be outside the scope of this article.

Part 3 of the standard, however, is very relevant in the context of latex allergy [8]. It contains the general requirement that medical gloves should be examined as described in the EN ISO 10993 series [9], the horizontal standard for Biological Evaluation of Medical Devices. In addition to this, there are specific requirements related to latex allergy. During the development of this standard great effort was put into attempts to align it with the parallel ASTM standards for gloves [10]. Although this has resulted in a similar approach and an equivalent test method for protein determination, the CEN and ASTM standards still differ on certain aspects.

The first specific requirement of EN 455-3 is that manufacturers monitor protein levels to establish the process limit for leachable protein in the finished latex gloves. The test method to determine this parameter must be either the modified Lowry method, which is described in detail in the standard, or a suitably validated method that has been correlated against it. An acceptable alternative method that is explicitly men-

tioned in the standard is the extraction procedure as prescribed in the ASTM D5712 standard [10]. In an informative annex, a validated method for amino acid analysis using HPLC is described, which is, however, not yet suitable for routine quality control purposes. Furthermore an informative annex is included that presents an overview of immunological methods for the determination of leachable proteins and allergens. At the time of writing of the standard these methods were considered insufficiently developed for inclusion in the normative part of the standard. Because they were seen as the future methods of choice, however, it was judged relevant to include them in the standard. The standard does not specify a maximum allowable limit for leachable proteins in medical gloves because it was not possible to agree on a scientifically based limit.

The second specific requirement is concerned with endotoxins. If a manufacturer wishes to label its gloves with “low endotoxin content,” the endotoxin content must be monitored using the method specified in the standard, or any other method, provided it has been validated and correlated against the described method. In this case a maximum allowable limit of 20 endotoxin units per pair of gloves is specified.

The third specific subject is chemicals. The use of talcum powder is prohibited and a list of chemical ingredients known to cause adverse health effects has to be disclosed by the manufacturer on request. No limits are specified. Although not specifically mentioned in the current version of EN 455-3, it could be argued that this aspect is already covered by the general requirement to comply with the EN ISO 10993 series [9]. Part 17 of this series describes a method to determine the allowable limits for leachable substances. Obviously, this same argument could also be applied to proteins and endotoxins. This question will probably be discussed during the revision process (see below) of the standard, which has been initiated recently.

An important paragraph in EN 455-3 specifies requirements for labeling. Latex gloves must be labeled “(product) contains natural rubber latex which can cause allergic reactions” or an equivalent statement. Powdered gloves must be labeled as such and, in the case of sterile surgical gloves, a caution statement needs to be added requiring the aseptic removal of surface powder prior to undertaking operative procedures. The third labeling requirement has caused a lot of confusion and there are few people who really understand it. If a manufacturer wishes to label the gloves with a protein content, this shall be the process limit measured in accordance with the standard. However, labeling claims below 50 µg/g (50 µg protein/g of glove) are prohibited. This restriction was introduced because of significant uncertainties about the detection and quantitation limits of the modified Lowry method and the dose–response correlation at low levels of exposure.

The majority of the working group that has written the standard deemed it necessary to make a statement in the standard that claims below 50 µg/g are not possible because of these limitations. Undoubtedly this subject will be addressed during the current revision of the standard. Finally, the use of the claim “hypoallergenic” is prohibited because the term is poorly defined and generally misunderstood. It therefore gives rise to a false sense of security.

5. Future developments

As mentioned before, the revision of EN 455-3 has recently started. The rationale for the revision of the standard is that it no longer reflects the current state of the art. New test methods have become available, especially for the determination of allergen content [11,12]. Some countries, e.g., Germany, Finland, and the United States, have developed new national standards and national regulatory recommendations. Furthermore, the Scientific Committee on Medicinal Products and Medical Devices, an advisory committee of the EC, published the Opinion on Natural Rubber Latex Allergy containing an evaluation of test methods [13]. During the revision process the following issues will be evaluated. On the subject of leachable proteins the intention is to include determination of allergenic proteins by an immunological assay in the normative part of the standard. The ASTM has published a method for measuring antigenic protein with polyclonal antibodies from rabbits [11]. In addition a method for the determination of some major allergenic proteins has been developed using monoclonal and polyclonal antibodies [12,14]. The objective of the European standards committee working group is to organize a round-robin study to evaluate at least one and possibly both of these methods. This study should lead to validation of the method(s) and provide insight into its suitability for inclusion in the standard, either as a reference method for validation of a production process or as a test for monitoring purposes, depending on practical and/or economic feasibility. The corresponding ISO and ASTM committees will be invited to participate in the round-robin studies.

An important discussion item will also be the possibility of establishing a clinically relevant limit value—related to the allergenic potential of the product—that could be included in the standard as a requirement. The revision process will take a couple of years. At this moment the international situation is such that in the United States and Asia, a recommended limit for total leachable protein content has been established of 200 µg/dm² glove surface [15], while in Europe there is no limit at all. Therefore, the CEN working group proposed, as an interim measure for the short term, to make an amendment to the standard in which a limit of

200 µg/g³ is specified, accompanied by an important note of explanation to the amendment, pointing out that this cannot be considered a safety limit, because the lowest level of protein capable of inducing sensitization or eliciting an allergic response has not been established. While a case can be made for setting an achievable limit that is likely to be protective against the induction of sensitization, thresholds for allergic effects cannot easily be determined. Thus setting such a limit would be a purely pragmatic measure and one, therefore, for which the comments and views of national standards bodies and regulatory agencies would be crucial. In the event, this proposal was rejected for procedural reasons. Lower levels of protein exposure will obviously reduce the risk of elicitation of symptoms in sensitized individuals; however, it is not possible to define a level of exposure that carries no such risk. Only Germany has expressed a different opinion on this issue. The German delegates to the CEN working group are seeking the introduction of a protein limit of 30 µg/g glove, which they consider to be technically and economically feasible for manufacturers to achieve, and which can be reliably determined by the modified Lowry method in the standard.

A second important issue will be glove powder. In the revised standard there will be definitions of powdered and powder-free gloves and limits for the maximum allowable powder content. Probably the same values as prescribed by ASTM will be included, i.e., 2 mg/dm² for powder-free gloves and 10 mg/dm² for powdered gloves [15]. Setting limits implies that a test method is available. ISO recently circulated a new work item proposal for the development of a standard describing a method for the determination of powder on medical gloves. According to the scope, described in the working document, this international standard specifies a method for the determination of readily removable residual powder on the surface of gloves. The European working group decided to evaluate this method and possibly adopt it as a European standard. Furthermore, requirements for the use of chemicals will be reconsidered. Details on this subject have not been discussed but, as pointed out above, a possibility is to rely on the application of EN ISO 10993-17.

An aspect that is not covered adequately in the existing three parts of the standards has recently been identified: aging and shelf-life. Although the MDD requires the indication of an expiration date where appropriate, there is no appropriate standard to substantiate a claim for it. A new work item has been initiated that should result in a new part of the EN 455 series describing requirements and testing for shelf-life claims.

³ 200 µg/dm² and 200 µg/g are in practice almost equivalent.

6. Regulatory developments

In 1998 the European Commission's Directorate General (DG) "Enterprise," which is responsible for the European regulations for medical devices, decided that the problem of latex allergy should be evaluated. For this purpose an *ad hoc* working group on medical devices manufactured from natural latex was instituted. This group consisted of representatives from European governments, industry, and other interested parties. The task of this working group was to draw up a list of questions that needed scientific evaluation. The EC could then decide, on the basis of the evaluation, whether or not specific regulations for latex products needed to be developed. In 1999 the working group completed the list of questions, which was subsequently presented to the Scientific Committee on Medicinal Products and Medical Devices (SCMPMD). This committee, which consists of independent scientists, studied the latex allergy problem and specifically paid attention to the questions asked by DG Enterprise. In 2000 the SCMPMD published their scientific opinion on natural rubber latex allergy [13]. See Appendix A for a summary of the major conclusions of the SCMPMD.

Based on the SCMPMD opinion, now under discussion in the Medical Device Experts Group of DG Enterprise is whether any adaptation of the regulations with respect to the presence of allergenic proteins in latex products is warranted. A low protein level reduces sensitization and elicitation; however, the lack of clear scientific evidence on protein thresholds for these effects hampers decisions on regulatory measures. A European Commission guidance document is currently being drafted by experts from Competent Authorities.

Appendix A. Opinion on "natural rubber latex allergy"—Summary of the major conclusions

A.1. Scientific Committee on Medicinal Products and Medical Devices (SCMPMD)

Latex products can induce sensitization of both immediate type hypersensitivity (latex allergy) and/or delayed type hypersensitivity (allergic contact dermatitis), due to proteins and chemicals respectively, that are present in the product. Although sensitization is needed for allergy, there is a clear distinction between sensitization and allergic disease. Not all latex sensitized persons develop latex allergy as a disease. The diagnosis of latex sensitization and/or latex allergic disease is hampered by the lack of standardized materials (allergens). Extracts of latex materials (gloves) can be useful but are far from standardized and can only provide information on proteins/allergens present in that particular extract from that particular product.

The risk for latex sensitization and/or allergic reactions can be reduced by minimizing the amount of leachable proteins. However, the limit of elicitation/sensitization is likely to be close or below the quantification limits of the protein assays (Lowry, amino acid analysis) available, so the protein level cannot be used to define a safe level in latex products. Furthermore, the assays detect the amount of total protein and not just the allergenic proteins. More relevant is the demonstration of the amount of leachable allergens in latex products by immunological assays. Unfortunately standardized reagents (antibodies) for these assays are not (yet) available. The proteins detected are limited to the major allergens of latex, but this may be sufficient to allow identification of latex products with low sensitizing potential.

In terms of prevention one has to realise that the lowest dose (or threshold level) of proteins for inducing sensitization and/or elicitation of an allergic response has not been established. For some rubber products, especially gloves, a dose response relationship has been demonstrated. When using latex products contact with latex allergenic proteins cannot be avoided completely as part of the properties of the latex product are based on the presence of these proteins.

Latex proteins bind to cornstarch powder particles in gloves, however, it has not been demonstrated that powdered gloves are more likely to induce sensitization than powder-free gloves, provided the protein content of the gloves is identical. The role of powder in allergic reactions is limited to its activity as a carrier, thus spreading the allergens in the air.

Allergic responses in sensitized patients can also be induced by some of the chemicals used in the production of latex. These cause allergic contact dermatitis, a type IV delayed type hypersensitivity reaction. Quantification of chemicals present in medical devices such as medical gloves and determination of bioavailability is still a problem. Not only natural rubber latex products but also the currently available synthetic alternatives may pose a risk for allergic contact dermatitis depending on the chemicals used for their production. The risk can theoretically be reduced by substitution of the most potent sensitizers with less sensitizing chemicals, but systematic dose-response studies ranking these sensitizers are not (yet) available in the scientific literature.

To avoid allergic reactions by latex products, products with low residues of residuals of allergenic proteins and sensitizing chemicals should be used. Ingredient information on rubber products would be helpful to prevent allergic responses in subjects who are allergic to latex proteins and/or chemicals. Non-latex medical gloves are available as an alternative for the treatment or handling of allergic patients.

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