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## **GUIDELINES ON MEDICAL DEVICES**

### **IMPLICATIONS OF THE MEDICAL DEVICES DIRECTIVES (93/42/EEC) IN RELATION TO MEDICAL DEVICES CONTAINING NATURAL RUBBER LATEX:**

#### **A GUIDE FOR MANUFACTURERS AND NOTIFIED BODIES**

#### Note

The present Guidelines are part of a set of Guidelines relating to questions of application of EC-Directives on medical devices. They are legally not binding. The Guidelines have been carefully drafted through a process of intensive consultation of the various interest parties (competent authorities, Commission services, industries, other interested parties) during which intermediate drafts were circulated and comments were taken up in the document. Therefore, this document reflects positions taken by representatives of interest parties in the medical devices sector.

## **Background and Scope**

Due to the combination of its superior barrier qualities, strength, flexibility and comfort, natural rubber latex (NRL) has been increasingly used in a variety of medical devices. In particular, the properties of NRL make it a preferred material for medical gloves. The clinical use of latex gloves has increased considerably during the last 20 years, due mainly to escalating risks associated with blood-borne infectious agents. The main function of these gloves is to create a protective barrier between the patient and health care worker and also to facilitate general hand hygiene.

In response to the growing apprehension surrounding medical devices containing NRL, the Directorate General for Enterprise of the European Commission presented questions to the Scientific Committee on Medicinal Products and Medical Devices (SCMPMD). The committee prepared an opinion in June 2000 based on information available from scientific literature and various public reports. The Commission's Medical Devices Experts Group subsequently set up a Working Group on Natural Rubber Latex, composed of representatives from the Member States, to consider and discuss the SCMPMD opinion and explore the possibilities for minimising problems relating to the use of NRL in medical devices. After hearing representations from industry and users, the Working Group was satisfied that the Medical Devices Directive contained adequate provisions to ensure the safety of healthcare workers and patients exposed to NRL medical devices. However, the Working Group was concerned that the interpretation of the Directive in terms of the risk control measures applicable to NRL-containing products appeared to be in some doubt. A guidance document was therefore considered necessary to clarify the implications of the relevant Essential Requirements.

To meet this objective, the Working Group felt it necessary to identify, in this document, the hazards and exposures associated with NRL, and discuss the effects of the limitations in the current state of the art. The document is based on the principle that the appropriate way to manage the risks arising from NRL is to reduce allergenic protein levels to a level as low as reasonably practicable and provide warnings about the residual risks.

This document therefore provides guidance for manufacturers, Notified Bodies and Competent Authorities on the interpretation of the Essential Requirements of the Medical Devices Directive, as they relate to the risk of allergy to natural rubber latex (NRL). The risk control measures recommended in this document do not apply to devices made from other materials. However, similar measures, commensurate with the degree of risk, may be applicable to control risks arising from other materials presenting hazards of a similar nature (for example dry natural rubber (DNR)).

## **The Medical Devices Directive**

As with all products which meet the definition of a medical device (as detailed in Article 1 of the Medical Devices Directive 93/42/EEC) NRL-containing medical devices (i.e. examination and surgeons' gloves, condoms, catheters, etc.) must meet certain conditions as specified by the relevant Essential Requirements under Annex 1 of the Directive. This represents the minimum standard a manufacturer is expected to demonstrate when claiming conformity of a product with the Directive.

Due to the nature of the concerns raised about NRL (i.e. the inherent biological hazards), those Essential Requirements that relate to biological safety are of particular relevance to this guidance document. The Essential Requirements that are most relevant to this situation are 1, 2, 6, 7.1, 7.2, 7.5 and 13. Toxicological risks need to be assessed through an expert scientific assessment that takes into account the extent, relevance and quality of the available data (such as that provided by the SCMPMD in relation to allergenic risks). The conclusions from the scientific assessment, and the level of confidence in it, are used to determine appropriate control measures to ensure the safety of those exposed to the toxic hazards identified. EN/ISO10993-17 provides a method of determination of acceptable levels of exposure relevant to toxic substances that can leach out of medical devices.

In determining whether a product meets these Essential Requirements, it is necessary to balance the risks arising from the biological hazards known to be associated with NRL against the benefits attributed to the use of NRL, particularly in respect of effectiveness as a barrier to infection. EN/ISO 14971 specifies an appropriate process for judging of the acceptability of risk.

Essential Requirement 2 indicates that the first priority is the elimination of risk. It is recognised, however, that no medical procedure is without risk and it is inevitable that some risk must be accepted in the interests of improving the health or prognosis of the patient. In practice, the elimination, or minimisation of risk is taken to mean that the risk can be considered to be so low that there is "no need to bother about it". Such risks are termed "broadly acceptable" (see Annex E of EN/ISO 14971)

If it is impossible to implement controls that ensure that a risk is broadly acceptable, the Medical Devices Directive requires that the risk must be reduced as far as possible. In such cases it is necessary to implement risk control measures to ensure that the risk is reduced to a level "as low as reasonably practicable" (ALARP). That is to say the risk is placed in the "ALARP" region of the chart in Annex E of EN/ISO 14971. The ALARP concept recognises that exposure to an appreciable degree of risk is inherent in the use of many medical devices. The expectation is that the risk should be reduced to the lowest practical level, bearing in mind the practicality of any further risk reduction, the benefits arising from the use of the product and the state of the art. Because the "state of the art" is a moving target and the Essential Requirements' preferred option of "broadly acceptable risk" is not yet achieved, risk control measures need to be reviewed regularly. Changes in the state of the art could lower the ALARP levels.

For risks in the ALARP region, assessments of risks, benefits and the feasibility of risk control are indispensable components of the conformity assessment process. A manufacturer has to determine what risk control measures can reasonably be adopted to achieve the optimum balance of risks and benefits. Any risk remaining after all applicable risk control measures have been taken is termed the “residual risk”. The residual risk must be outweighed by benefits.

The manufacturer has a responsibility to communicate effectively with users to inform them about residual risks to allow them to manage these risks effectively. Therefore it is necessary to include appropriate warnings in the documents accompanying the product. This may include the provision of specific advice to users and healthcare managers on any measures that should be taken to mitigate the risk. Users may take risk control measures in addition to those advised by the manufacturer, such as the establishment of local policies on the purchase and use of NRL-containing products, however this aspect of risk management lies outside the scope of the Medical Devices Directive.

## **Hazard identification**

### **Allergy to natural rubber latex**

Various studies have verified that immediate (Type I) hypersensitivity to NRL appears to be caused by certain naturally occurring soluble allergenic proteins found in latex. Reported symptoms encountered range from mild wheal and flare reactions to gloves, to fatal anaphylaxis from latex balloons used with barium enema examinations. The identity of most of the clinically relevant allergenic proteins in NRL (both major and minor allergens) now appears to have been established, and there has been a progressive decline of glove allergen content. Although the manufacturing process includes washing phases for the removal of excess proteins and chemicals, residues of proteins and chemicals remain in the material. More complete removal of latex proteins from NRL-containing products manufactured using current technology may adversely affect their properties, such as elasticity, tensile strength and barrier function.

The prevalence of NRL sensitisation varies between the different populations that have been studied. Principal risk groups for NRL allergy include atopic individuals, patients with hand dermatitis and atopic children, especially those with food allergy. Among health care workers the reported prevalence rates range from 2.7% to 15% in most studies, depending on the methods used for diagnosis and on the allergenicity of the latex gloves used, although studies do not always distinguish between those who are positive in skin prick testing and those with clinical allergy. NRL allergy has been described in several other occupations in which protective gloves are used (e.g. housekeeping personnel, hairdressers, greenhouse workers and workers in textile factories). The frequency of Type I NRL allergy in the general population, based on skin prick testing and stringent diagnostic criteria, is relatively low, clearly under 1%. There is evidence suggesting that latex devices with low levels of leachable allergenic protein do not induce sensitisation.

## **The use of powder in latex gloves**

The use of modified cornstarch powder as a glove donning / manufacturing aid has also been the subject of particular anxiety in recent years. Latex proteins bind to cornstarch powder particles in gloves and the powder can thus act as a carrier of the allergen. The dust aerosol that can be created when donning and removing powdered gloves may increase the risk of allergic reactions because uptake, via the lungs, by people in the vicinity represents an additional route of exposure. Case reports had been published to indicate that this sort of exposure may provoke allergic symptoms (asthma, rhinoconjunctivitis, urticaria, anaphylaxis) in latex sensitised individuals. However, the SCMPMD<sup>1</sup> reported that there has been no conclusive scientific study to indicate that the use of powdered latex gloves increases the frequency or rate of sensitisation when compared to powder-free gloves, so long as the powdered glove has an equivalent total extractable allergenic protein concentration. Thus, the extent to which powder can play a role in allergic reactions is limited to its activity as an airborne carrier of allergens.

Concerns have been expressed regarding the use of powdered gloves in surgical operations and the formation of adhesions or starch granuloma, however a causative relationship has not been firmly established.

## **NRL additives**

A wide range of hazardous processing chemicals is used during the manufacture of NRL products. These include accelerators such as thiurams, carbamates and mercaptobenzothiazoles, which are known contact sensitisers posing a risk for the development of Type IV allergic contact dermatitis. Currently only one study is available ranking the relative hazard potential of these chemicals.

Quantification of chemicals present in latex medical devices and determination of their bioavailability are problematic. The composition of the final product is highly dependent on the initial ingredients, which fluctuates more than with synthetic polymers, and the chemical reactions and leaching that occurs during processing. The uptake of chemical residues by the skin or tissues is dependent on the physicochemical properties of the substances and the conditions of use of the devices. For example, chemical uptake via mucosal membrane exposure such as for condoms, is likely to exceed that of exposure of an equal concentration to intact skin. However, regardless of these variables, a reduction in the amount of chemical residues in rubber products has been shown to also result in a reduction in the bioavailable amounts of chemicals and in the Type IV sensitising capacity of the material.

The risk of Type IV allergic contact dermatitis is not confined to NRL products; the currently available synthetic alternatives may pose a similar risk, depending on the chemicals used for their production.

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<sup>1</sup>European Commission Scientific Committee on Medicinal Products and Medical Devices (SCMPMD); Opinion on Natural Rubber Latex Allergy; Adopted 27 June, 2000. Doc.SANCO/SCMPMD/2000/0009 Final

## **Exposure Assessment**

Exposure to NRL may come from dermal (cutaneous) or mucous membrane contact. The latter includes inhalation, and genito-urinary tract exposure (e.g. from condoms, wound drains, tracheostomy tubes, balloons used in barium enema examinations and urinary catheters). Direct tissue or intra-vascular exposure also occurs via an open surgical wound through the use of surgeons' gloves and containers of injectable materials.

### **Exposure to allergenic proteins**

The risk of sensitisation or allergic reaction to NRL can be reduced by minimising the amount of leachable allergenic protein to which a subject is exposed. A distinction should be made, however, between the prevention of sensitisation and the prevention of allergic reactions in those individuals already sensitised to latex allergenic proteins. Once a person is sensitised to NRL, any subsequent exposure to latex may trigger an allergic reaction. It is not currently possible to establish a threshold level of exposure for sensitisation, but it is generally understood that greater exposure is required to sensitise an individual than to elicit a response in a sensitised individual. Studies have shown that latex gloves with a low leachable protein content elicit a lower percentage of positive responses in latex sensitised individuals than gloves with higher protein residues. However, the correlation between protein content and allergen content is not strong enough to justify selection of low allergen gloves on the basis of leachable protein content. Nevertheless, it can be expected that lower levels of leachable protein will also result in a lower prevalence of induction of sensitisation.

A precise indication of an individual's susceptibility to latex allergy is difficult to achieve. One standardised extract for skin prick testing is available in Europe and Canada, but not in the U.S. Extracts of latex materials (e.g. gloves) can be useful but are far from standardised and can only provide information on allergenic proteins or allergens present in a particular extract from a particular product.

Considerable progress has been made in the identification and characterisation of latex allergens, indicated by the fact that 15 allergens had received WHO/IUIS Allergen Nomenclature designation by August 2002<sup>2</sup>. Exposure assessment is, however, hampered by the lack of validated methods for their direct detection. While direct allergen measurement would be the preferred option, specific assays currently available are waiting for international validation. Since a relationship between leachable protein levels and the risk of allergic reaction or sensitisation has been demonstrated in several studies, leachable protein levels are currently used as a surrogate for allergen exposure. Two methods, the modified Lowry and an amino acid analysis, both measuring total extractable protein, have been described and standardized for some types of products, making the comparison between alternative brands of products possible. However, neither of these methods distinguishes between sensitising and non-sensitising proteins.

Although some European laboratories may produce rather consistent results in their modified Lowry tests, experience from many round-robin tests performed in high-

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<sup>2</sup> [www.allergen.org](http://www.allergen.org)

standard laboratories both in the US and in Europe has revealed serious problems in the reproducibility of the results.

Immunoassays based on the use of human IgE antibodies recognising specific NRL allergens have been developed and used in a limited scale to measure total allergen contents of latex gloves and other NRL devices. The major drawback in such assays is the limited availability of proper human sera and problems in standardisation.

Specific tests for measuring individual latex allergens in medical devices have recently been developed and are currently under international evaluation. Interim recommendations now are thus not well grounded.

### **Exposure to powder**

A standardised technique for the determination of the powder content of medical gloves is available. Relevant standards require that surgeons' gloves carry labelling advising users that powder must be removed by washing prior to use. Some studies have questioned the effectiveness of such washing.

### **Exposure to chemical residues**

Several techniques are available for the detection of the chemicals present in latex products such as medical gloves. Although these methods allow the identification of the chemicals present in NRL products, this does not mean that these chemicals are also bioavailable for the induction of allergy or the elicitation of a response. Cross reactivity can occur between various chemicals and mixtures of chemicals may also be present. There seems to be no agreement on the best applicable method of analysis.

In vitro tests that measure clinically relevant, bioavailable residues of rubber chemicals in the products are not yet available.

## **Risk Estimation and Evaluation**

### **Extractable Protein**

Studies that suggest a correlation between the presence of leachable protein in NRL gloves and the risk of allergic reaction or sensitisation lead to the conclusion that reducing the amount of available leachable protein can reduce the risk. Determination of a leachable protein level that represents an acceptable risk is problematic, however, because of the significant uncertainties that limit the extent to which this risk can be analysed.

While the SCMPMD was able to reach clear conclusions on a number of important issues relevant to the management of risks arising from medical devices manufactured from NRL, the number of good quality scientific studies relevant to the current situation across the EU is limited. Moreover, exposure assessments are inaccurate because analytical methods available today do not differentiate between allergenic

and non-allergenic proteins, but detect the amount of total protein instead. As a result, the risk of sensitisation or elicitation arising from contact with NRL-containing products cannot be estimated with any confidence.

Even if a more meaningful risk estimate were possible, limits for elicitation and sensitisation are likely to be close to or below the quantification limits of the protein assays currently available, so the protein level cannot be used to define a level of exposure that could be deemed “safe” with a realistic margin of safety.

In addition to the lack of a sufficiently sensitive analysis method, it is recognised that there is currently no toxicological method available to identify a threshold for either of these endpoints. One implication of this is that terms implying minimal allergenic risk (e.g. hypoallergenic) are inappropriate.

Because the probability of harm occurring at low levels of exposure cannot be estimated on the basis of scientific data, the risk to patients or users cannot be estimated. For a significant hazard, such as sensitisation, no level of exposure can therefore be determined that corresponds to a broadly acceptable risk. Elimination of the risk (in line with the primary expectation of the first bullet point of Essential Requirement 2) is thus not possible.

For the above reasons, the rationale behind various proposed limits is subject to strong criticism: biologically significant amounts of relevant allergens may be overlooked and, on the other hand, the amounts of irrelevant non-allergenic proteins may exceed any selected upper limits. Under these circumstances it is inappropriate to set an allowable limit for leachable protein content in medical devices containing NRL.

Failing the implementation of controls that ensure a broadly acceptable risk, it is necessary to reduce the allergic risk arising from NRL to a level as low as is reasonably practicable (ALARP) and consider the presence of protein residues to be a residual risk.

For medical gloves containing NRL, both their effectiveness as a barrier to infection and the cost of their production have public health implications that are relevant to the risk:benefit assessment. Efforts to reduce the leachable protein content of NRL gloves must therefore be balanced against any reduction in properties of the product that are critical to their function and any financial implications that have an impact upon the preservation, promotion or improvement of human health.

## **Starch Powder**

While powder-free products exist for which acceptable performance is claimed, it does not necessarily follow that these are appropriate for all uses. It is important to recognise that both risks and benefits can vary appreciably with the intended use of a product. This is particularly so in the case of powdered medical gloves, where risks and benefits need to be considered in relation their use in surgical intervention and non-invasive procedures.

The use of powder does not increase the allergenicity of the gloves, but allows airborne exposure to the allergen. Thus, there is an additional risk of reactions to



respiratory exposure in sensitised individuals. However the population at risk is the same as that at risk of allergic reaction to NRL alone. If the content of latex allergens in the gloves is low, the use of powdered gloves has not increased sensitisation rates, implying that controlling the powder content of gloves provides no additional protection to non-sensitised individuals.

The risk of adhesions or granuloma formation is relevant only to patients undergoing surgical procedures. The SCMPMD was not asked to advise on this risk and, in the absence of clear evidence that powder causes these complications, it is not appropriate to introduce regulatory measures to prevent the use of powdered surgeons' gloves. However, in view of the scientific uncertainty, the presence of powder remains a residual risk.

The presence of glove powder does not significantly affect the barrier properties of gloves so a lack of glove powder does not itself introduce a risk to patients or users. The benefits of glove powder lie in ease and comfort of use, which have an indirect effect on effectiveness. User preference is therefore a significant factor in determining the acceptability of powdered gloves. Cost and the additional environmental impact of processes involved in producing powder-free gloves can also be important considerations for the purchaser, which will vary with the circumstances of use. Users need to be in a position to weigh these factors and take effective action to manage the residual risks relating to the use of powdered gloves.

## **Chemical residues**

Exposure to residues of chemicals added to NRL formulations or resulting from reactions during processing should be kept below a level that could result in harm to users or patients. For most chemicals, a level of exposure can be determined which is considered to be without risk of appreciable harm to health. This level, termed the "tolerable intake", is determined on the basis of available toxicological and clinical data. It incorporates a safety margin that accounts for the uncertainties inherent in estimating potential effects in humans from the scientific data available (see EN/ISO 10993-17). The risk arising from exposure to chemicals at levels up to the tolerable intake can be classified as broadly acceptable.

Exposure below the tolerable intake cannot be guaranteed where it is not feasible to manufacture products with sufficiently low residue levels. Moreover, for some chemicals (particularly sensitisers), it may not be possible to determine a tolerable intake. In these circumstances, exposure must be reduced to a level as low as reasonably practicable, the risk must be outweighed by benefits arising from the use or presence of the chemical and the presence of the residue must be treated as a residual risk.

Substituting the most potent sensitisers with less sensitising chemicals can theoretically reduce the risk but, so far, only one dose-response study capable of ranking sensitisers is available. The acceptability of any such risk control measure must be judged as part of the overall risk evaluation.

## **Clinical aspects**

Persons who know or suspect that they may have Type I latex allergy must avoid contact with latex products. If they are treated in healthcare they should inform the personnel about their allergy. Alternatives to NRL gloves are available, but these alternatives may pose risks depending on the chemicals used during the production process. Data on the risk associated with substitute non-latex materials is very limited.

## **Risk Control**

### **Extractable Protein**

Any risk control measures adopted must reflect the nature of the hazard, and should therefore be directed towards both the risk of induction of sensitisation and the risk of elicitation of an allergic reaction. Because of the variabilities and uncertainties inherent in the risk estimate, it is inappropriate to stipulate risk control measures specific to particular exposure groups. Furthermore, the nature of the risk means that no single risk control measure can protect all of them.

As long as NRL-containing products are used, the possibility of exposure to allergenic proteins cannot be eliminated, since the presence of these proteins is currently essential to some of the critical properties of latex products. Nor is it possible to determine a level of exposure that would not be expected to lead to sensitisation in either atopic or non-atopic individuals. It is therefore not possible to reduce residues of leachable protein in NRL products to a level that can be guaranteed either to induce sensitisation or to elicit a reaction in sensitised individuals. Controlling leachable protein levels is thus not a quantifiable option for the control of risks to these groups and the only viable risk minimisation measure is avoidance of exposure wherever possible.

Non-latex alternatives are available for some products such as medical gloves and condoms. However, where exposure avoidance is not possible, lowering leachable protein levels to as low as reasonably practicable (ALARP) is indicated because the lower the bio-available allergenic protein level, the lower the risk for inducing sensitisation and eliciting reactions. To decide what protein level is acceptable in any particular case, it is necessary to take account of the generally accepted state of the art and balance protein content against technological and financial factors relevant to the supply of products that meet users' needs. The state of the art in this respect has shifted considerably in recent years, resulting in a gradual reduction in leachable protein levels. Future technological developments may allow further reductions in protein levels without adversely affecting product quality or increasing production costs, in which case further reductions would be prudent. Until then, pressure for further reduction in residue levels can only come from evidence indicating that levels of protein currently found in medical products present a problem. Such evidence is limited at present.

A number of risk control measures are considered necessary, including measures to ensure that exposure to allergenic protein is maintained below an acceptable level.

For any medical device containing NRL, the technical documentation needs to contain:

- a technical justification, including reference to supporting data, for the use of NRL;
- an indication of the allergen content, determined and reported in line with the state of the art<sup>3</sup>. (Such information to be made available to users on request).
- a technical justification for the measured level of allergen, indicating how this conforms to the ALARP (“as low as reasonably practicable”) principle.

Since the risk to non-sensitised, sensitised or atopic individuals cannot be eliminated from the product, this must be treated as a “residual risk”. Product labelling should thus include a warning about the presence of NRL.

For any medical device containing NRL, the product labelling needs to include:

- a prominent indication, on the product’s primary packaging, that the device contains natural rubber latex;
- a warning that the product may elicit allergic responses in individuals who are sensitised to latex;

Warnings on product labelling need to convey an accurate estimate of the risk. For the vast majority of NRL products, it is not possible to establish relative allergenicity, so any labelling claims suggesting a lower than usual level of risk cannot be justified. Similarly, it is important that only those devices with an appreciable NRL content are labelled as such. Labelling a device with a statement such as “may contain natural rubber latex” simply because the possibility of contamination with small amounts of NRL cannot be excluded, would lead to devices being withheld unnecessarily from sensitised patients or users. Such warnings should not be applied unless they are justified.

For any medical device, the product labelling may not include:

- any term suggesting relative safety, such as low allergenicity, hypoallergenic or low protein;
- any unjustified indication of the presence of allergens

Unfortunately, there is no standardised definition by which NRL-free products can be distinguished from those containing NRL. The European Standards Committee is

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<sup>3</sup> The state of the art for the measurement of allergens will be reflected in the appropriate harmonised European Standard when it becomes available. Meanwhile the current harmonised standard specifies a method for measuring a broad approximation for the allergen content, i.e. total leachable protein. There is no direct correlation between total leachable protein and allergen content. A commercially available quantitative method to measure allergenic NRL proteins is in the process of validation. Until the validation results are available, allergen levels should be estimated by currently available state of the art methods.

therefore requested to clarify the distinction between products containing NRL and those that can be designated NRL-free, and to define symbols for NRL-containing and NRL-free devices.

## **Glove Powder**

A control limit has been established by ISO for the designation of powder-free gloves (2 µg/glove). The implementation of labelling requirements in conjunction with this definition is an appropriate risk control measure. There is no case for introducing further controls on the powder content of gloves, since users can mitigate the residual risk effectively, providing they have access to appropriate information on the risks and benefits of powdered gloves.

For any medical glove, the technical documentation needs to contain:

- data verifying that any glove labelled powder-free conforms to an appropriate standard.

For any medical glove, the product labelling needs to include:

- a prominent indication of whether the glove is powdered or powder-free.

For sterile powdered gloves, the product labelling needs to include:

- a warning about the need to minimise tissue exposure to powder residues.

## **Chemical residues**

Control measures are needed to verify that, as far as possible, exposure of users and patients to chemicals is maintained below levels that could result in harm to health. Where this cannot be guaranteed, the ALARP principle applies.

Wherever possible, for each hazardous chemical used or generated during NRL processing, the technical documentation needs to include:

- identification of a tolerable intake, determined on the basis of a toxicological risk analysis;
- an estimate of anticipated exposure to patients and users, to the extent necessary to verify that the tolerable intake will not be exceeded.
- identification of process control limits or quality control measures, sufficient to verify that exposure will not exceed the tolerable intake.

Where the above is not possible, the technical documentation needs to include:

- a technical justification for not being able to apply the risk control measures described above;
- data providing confirmation that the total residues level is as low as reasonably practicable;

- an evidence-based assessment indicating the level of risk from the residues is broadly acceptable (for example via finished product testing);
- a technical justification for the method chosen to demonstrate acceptable risk;
- identification of process control limits, determined on the basis of the risk assessment, and corresponding quality control measures;

### **Clinical aspects**

In order to manage the residual risks associated with NRL products effectively, users need to be adequately informed about the nature of the risks and applicable risk control options. To facilitate effective control of residual risks by healthcare providers, it is desirable that healthcare establishments implement appropriate management policies relevant to purchasing and the provision of treatment to sensitised patients or by sensitised users. Member states are therefore invited to consider measures for the provision of information on the risks and benefits of NRL-containing medical devices (including those related to allergenic protein, residual chemicals and glove powder) to healthcare providers to assist their management of residual risks.

## Annex 1 : Necessary Risk Control Measures

For any medical device containing NRL, the technical documentation needs to contain:

- a technical justification, including reference to supporting data, for the use of NRL;
- an indication of the allergen content, determined and reported in line with the state of the art<sup>4</sup>. (Such information to be made available to users on request).
- a technical justification for the measured level of allergen, indicating how this conforms to the ALARP (“as low as reasonably practicable”) principle.

For any medical device containing NRL, the product labelling needs to include:

- a prominent indication, on the product’s primary packaging, that the device contains natural rubber latex;
- a warning that the product may elicit anaphylactic responses in individuals who are allergic to latex;

For any medical device, the product labelling may not include:

- any term suggesting relative safety, such as low allergenicity, hypoallergenic or low protein;
- any unjustified indication of the presence of allergens

For any medical glove, the technical documentation needs to contain:

- data verifying that any glove labelled powder-free conforms to an appropriate standard;

For any medical glove, the product labelling needs to include:

- a prominent indication of whether the glove is powdered or powder-free.

For sterile powdered gloves, the product labelling needs to include:

- a warning about the need to minimise tissue exposure to powder residues.

Wherever possible, for each hazardous chemical used or generated during NRL processing, the technical documentation needs to include:

- identification of a tolerable intake, determined on the basis of a toxicological risk analysis;

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<sup>4</sup> The state of the art for the measurement of allergens will be reflected in the appropriate harmonised European Standard when it becomes available. Meanwhile the current harmonised standard specifies a method for measuring a broad approximation for the allergen content, i.e. total leachable protein. There is no direct correlation between total leachable protein and allergen content. A commercially available quantitative method to measure allergenic NRL proteins is in the process of validation. Until the validation results are available, allergen levels should be estimated by currently available state of the art methods.

- an estimate of anticipated exposure to patients and users, to the extent necessary to verify that the tolerable intake will not be exceeded.
- identification of process control limits or quality control measures, sufficient to verify that exposure will not exceed the tolerable intake.

Where the above is not possible, the technical documentation needs to include:

- a technical justification for not being able to apply the risk control measures described above;
- data providing confirmation that the total residue level is as low as reasonably practicable;
- an evidence-based assessment indicating that the level of risk from the residues is broadly acceptable (for example via finished product testing);
- a technical justification for the method chosen to demonstrate the acceptable risk;
- identification of process control limits, determined on the basis of the risk assessment, and corresponding quality control measures;

The European Standards Committee is requested to clarify the distinction between products containing NRL and those that can be designated NRL-free and to define symbols for NRL-containing and NRL-free devices.

Member states are invited to consider measures for the provision of information on the risks and benefits of NRL-containing medical devices (including those related to allergenic protein, residual chemicals and glove powder) to healthcare providers to assist their management of residual risks.