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POSITION STATEMENT

# Position statement: The need for EU legislation to require disclosure and labelling of the composition of medical devices

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## Abstract

**Background** In recent years, skin reactions secondary to the use of medical devices (MD), such as allergic contact dermatitis have increasingly been observed (e.g. to continuous blood sugar monitoring systems, insulin pumps, wound dressings, medical gloves, etc.): this is regarded as a developing epidemic. Lack of labelling of the composition of MD, as well as frequent lack of cooperation of manufacturers to disclose this relevant information, even when contacted by the clinician for the individual case of an established adverse reaction, significantly impede patient care.

**Objectives** To advocate for full ingredient labelling in the implementation of EU regulation for MD.

**Methods** This position paper reviews the scientific literature, the current regulatory framework adopted for MD to date, and the likely impact, including some costs data in case of the absence of such labelling.

**Results** Efforts made by several scientific teams, who are trying to identify the culprit of such adverse effects, either via asking for cooperation from companies, or using costly chemical analyses of MD, can only partly, and with considerable delay, compensate for the absence of meaningful information on the composition of MD; hence, patient management is compromised. Indeed, without knowing the chemical substances present, physicians are unable to inform patients about which substances they should avoid, and which alternative MD may be suitable/tolerated.

**Conclusion** There is an urgent need for full and accurate labelling of the chemical composition of MD in contact with the human body.

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## Conflict of interest

The views expressed in this position paper are the personal views of the author as experts in the field of allergy and may not be understood or quoted as being made on behalf of, or reflecting the position of the respective national competent authority, the European Medicines Agency, or one of its committees or working parties.

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## Introduction

A medical device (MD) is defined as any instrument, equipment, material or product intended to be used in humans for medical purposes, the main action of which is not of pharmacological or immunological nature.

A great number of MDs exist, ranging from simple contact lenses and adhesive plasters to sophisticated pacemakers. As defined in Annex VIII (Classification rules, Regulation EU 2017/745), they are classified into 4 categories (I, IIa, IIb and III) according to their risk level, which is based on several criteria, including indications, invasiveness, duration of use (<1 h, ≤30 days, >30 days) and implantability, but also the risk for the patient.

On 5 April, 2017, two new regulations for medical devices (MD) were adopted in the European Union, in order to provide better protection of public health and patient safety; these concerned medical devices (Regulation EU 2017/745)[1] and *in vitro* diagnostic medical devices (Regulation EU 2017/746).[2]

These two regulations entered into force on 25 May, 2017, progressively replacing the existing directives, and were supposed to become fully applicable in May 2020 for medical devices, and in May 2022 for *in vitro* diagnostic medical devices.[3] However, due to urgent priorities related to the coronavirus crisis, the Council and the Parliament adopted Regulation 2020/561[4] amending Regulation (EU) 2017/745 on medical devices regarding application dates of certain of its provisions on 23 April, 2020. It postpones the date of application of the Medical Devices Regulation until May 2021, whereas for the *In Vitro* Diagnostic Medical Devices Regulation (IVDR, Regulation (EU) 2017/746), the corresponding date of application remains the same (May 2022).

These regulations contain important changes to the previous system to enable the sector to produce safer and more innovative devices and help address future challenges.

Regarding patient benefits, the new regulations are intended to introduce:

- 'Better protection of public health and patient safety', that is stricter pre-marketing control, particularly for high-risk devices (e.g. coloured contact lenses or equipment for liposuction), strengthening of clinical evaluation and investigation and stricter requirements on the use of hazardous substances.
- A comprehensive EU database on medical devices, a large part of it available for the public, such as a newly introduced summary of safety and performance for all Class III and implantable devices.
- A new device identification system that will allow easier traceability of medical devices.
- An 'implant' card for patients containing information about implanted medical devices.
- A robust financial mechanism to ensure patients are compensated in case they receive defective products.

However, despite the claim for better protection of public health and patient safety, the two new regulations do not offer a decisive benefit for the prevention and management of adverse events, such as irritant and allergic contact dermatitis caused by ingredients present in medical devices; they do not mention their qualitative composition nor explicitly require ingredient labelling on the packaging of MDs.

Although there is no doubt that MDs contribute to improve the quality of clinical care, adverse reactions following their use in patients are to be expected, including skin reactions, which should be considered in the implementation process of the Medical Device Regulation.

Indeed, case series of allergic contact dermatitis (ACD) caused by MDs have recently been published, particularly from medical devices in diabetic patients, such as glucose sensors and insulin pumps. The first case caused by an insulin pump was described in 1985[5] and by a glucose sensor in 2016,[6] followed by a considerable number of similar cases. As a result of investigative chromatographic analyses and the performance of patch tests in patients to confirm sensitization, various known allergens were identified in several types of MDs, that is ethyl cyanoacrylate,[6,7] isobornyl acrylate (IBOA),[8–11] *N*,*N*-dimethylacrylamide[12] and colophonium.[13]

As briefly illustrated above, the problem regarding the presence of allergens in MDs is not limited to devices for diabetic patients. Many other cases of ACD from various devices have been reported in the literature in recent years. For example, medical dressings and adhesives containing acrylic compounds,[14] or foam wound dressings containing alkyl glucosides, well-known allergens in cosmetic products,[15] for which no cooperation from the respective manufacturers could be obtained during the clinical investigation of patients. Surgical glues containing cyanoacrylate,[16] described as causes of ACD in diabetic patients as well,[7,17] MDs used in cardiology, such as silicone in pacemakers,[18] and even colophonium and herbal extracts in self-adhesive electrocardiography electrodes[19] are involved. Dental prostheses, endoprosthesis, etc. are also concerned. Medical gloves, labelled as medical devices and personal protective equipment, used by healthcare workers containing latex and rubber chemical accelerators are also responsible for ACD.[20,21]

Publications have reported mislabelling in several products labelled 'accelerator-free' gloves.[22]

The list of MDs causing ACD is extremely long, affects all medical specialties, is extremely varied and ever-changing, making it impossible to establish an exhaustive and current date list on this subject.

## Discussion

It is noteworthy to point out that labelling the list of ingredients is an integral component of European legislation concerning packaged foodstuffs (Regulation (EU) No. 1169/2011), medicinal products (Directive 2001/83/EC) and also cosmetics (Regulation (EC) No. 1223/2009), which informs consumers exposed to them, and protects them from re-exposure in case of known allergy. Paradoxically, no equivalent provision on labelling of components present in MDs has been laid down in the Medical Device Regulation. From a medical point of view, it remains elusive why such devices are currently not subject to a similar legislation as there is no plausible substantial difference regarding consumer or patient safety.

For consumers and patients, but also prescribers, that is medical professionals, it is important and urgent to obtain more transparency regarding the composition of MDs. Therefore, as medical experts and members of scientific societies specialized in allergy and adverse skin reactions (European Society of Contact Dermatitis, European Environmental and Contact Dermatitis Research Group, European Academy of Dermatology and Venerology, and European Academy of Allergy and Clinical Immunology), we strongly recommend that the European Commission review the current regulations for MDs with regard to labelling of all ingredients.

Although requirements for labelling are addressed in several sections of Regulation EU2017/745, Annex I, 10.4.5. (on labelling) does not mention allergenic or sensitizing components. Yet, Annex I 23.4 (Information in the instructions for use) states: '[. . .] The information shall cover, where appropriate: -precautions related to materials incorporated into the device [. . .] that could result in sensitization or an allergic reaction by the patient or user'.

To comply with this claim, a specification regarding labelling of ingredients should be included in the Question & Answer (Q & A) list for implementation. Preferably, this should include full labelling, but at least the following minimum requirement 'Labelling needs to include skin (and airway) sensitizers as identified in CLP (H317) used at any stage in the production of the medical device with body contact, with or without drugs included'.

Although there are probably several steps at different production sites in the manufacturing of MDs and because many relevant allergens in the MDs are not yet CLP (H317) classified, we believe that it is important to require full labelling for any device, as is the case for pharmaceutical products and cosmetics. Standardization in nomenclature of pharmaceutical ingredients and certainly of cosmetic ingredients is well established.[23] The current absence of such requirements for MDs might explain why there is an increasing tendency to market topical preparations, for example wound gels and skincare products as medical devices, possibly in order to avoid the more restrictive regulatory framework of the community code related to medicinal products for human use and the cosmetic regulation.

Furthermore, with regard to information regarding materials incorporated into the device that could result in sensitization or an allergic reaction by the patient or user, we strongly encourage implementation of an obligation of MD manufacturers to cooperate and disclose all information necessary for the management of patients who have suffered an adverse event. This particularly concerns full disclosure of the components (to the treating physician) of the device that has induced the reaction in order to carry out patch testing in case of ACD.

Instead of, or in addition to the respective specification in the Question & Answer list for implementation as outline above, an overarching guideline or multifaceted legislation amending the existing Regulation EU 2017/745 in order to make ingredients in MDs transparent (e.g. by full qualitative labelling on the package, similar to cosmetics) could endorse better protection of public health and patient safety. Beyond the complete and precise information that could be provided, following a standardized terminology such as INCI and INN, complete labelling of MDs would contribute to reduce direct and indirect cost of illness associated with the management of allergic complications.

Moreover, based on full labelling requirements within the EU regulation implementation, physicians prescribing MDs would be able to identify the presence of allergens in a sensitized subject. In these cases, a safer and more suitable alternative can then be proposed.

Such a refinement of implementation of MD-legislation is urgently required in view of the many publications highlighting allergic complications, including ACD, and challenges of management of adverse events following the use of MDs:

### Frequent occurrence of severe chronic skin reactions

Following several isolated cases of ACD caused by MDs during the last 5 years, the number of cases has increased considerably, making ACD from glucose sensors a 'hot topic'. This increasing epidemic could easily have been limited if manufacturers had collaborated and replaced the actual culprit ingredients. But in practice, replacing known sensitizers with less allergy-prone subassemblies is probably considered a delicate task and a real challenge for manufacturers. However, due to this lack of collaboration, an increased prevalence of ACD among users of FreeStyle™ Libre™ (Abbott Diabetes Care, Witney, Oxfordshire, UK) has been observed by many dermatologists. In May 2018, the ANSM (Agence Nationale de Sécurité du Médicament et des Produits de Santé) reported that about 0.2% of FreeStyle Libre

users reported a skin reaction.[24] In 2019, a Belgian study reported that ACD occurred in 5.5% of FreeStyle Libre users.[25]

### Lack of cooperation provided by MD manufacturers in the diagnostic process

Several papers and communications between colleagues from all over Europe have revealed the lack of communication with, and cooperation from, the manufacturers regarding the qualitative composition of the MDs.[26] Surprisingly, despite numerous requests from the medical profession, reported in the literature over the last 3 years, manufacturers continue to refuse collaboration and communication. Due to lack of cooperation, some medical centres have carried out physico-chemical analyses, such as gas chromatography–mass spectrometry (GC-MS) themselves in order to identify the sensitizing culprits in medical devices.[7,8,10–12] However, such complicated chromatographic analyses are not available in all centres. The correct diagnosis (ACD vs. irritant contact dermatitis) may be delayed or, even worse, missed if patients are not tested with all relevant allergens. As a result, most patients remain poorly advised with delays in diagnosis and management. In the case of glucose sensors, 35% of the patients reduced the wear time of their medical devices or stopped using them because of dermatological complications,[27] with significant deterioration of their quality of life. Due to lack of labelling and lack of information provided by the manufacturers in case of adverse events, physicians are limited in their information about safe alternatives.

Analytical techniques such as the one described above do not provide a guarantee to identify every possible allergen. This means that in addition to those having been identified, other sensitizers might also be present, which renders identification of all possible culprits impossible. Adequate management thus remains at stake.

### Cost of illness to the patients and the society

Skin problems that occur after using MDs also increase the treatment costs. Not only the purchase of new treatments (adhesives, emollients, protection creams or even topical corticosteroids), prescribed for prevention or treatment, but also additional follow-up consultations by physicians or dermatologists who perform patch testing. For example, a Danish study revealed that the cost for paediatric patients with skin complications due to glucose sensor is 154.3 USD higher than patients without skin problems.[28] It should be noted that this price does not take into account the real costs related to appointments for diabetes check-ups, visits to the dermatologist, the loss of income for the patient due to work stoppages and medical consequences of a poorer control of diabetes. The price for the patient is thus well underestimated. Moreover, the analytical analyses described above are very time-consuming and create a considerable cost for the society as well.

### Impact on the quality of life of the patients

Skin reactions due to MDs have been repeatedly reported to decrease patient quality of life.[28] For example, itching due to the skin complications associated with MDs leads to impaired concentration, distraction, but also drowsiness owing to impaired sleep[29] and experience additional stress. The patient is already suffering from a pathology beforehand, for which a MD has been used; hence, it is often difficult for the patient to see himself suffering from another problem related to his medical device. When the problems are dermatological, they are visible and may affect the patient even more due to stigmatization. According to some authors, patients perceived their skin as disfigured.[29] The lack of clear information (also on alternatives) noted above greatly increases the distress of patients affected by dermatological complications, particularly ACD.

### Severe cases of type I hypersensitivity

While the majority of skin complications secondary to the use of medical devices are either irritant contact dermatitis or ACD, there exist rare cases of Type I hypersensitivity as well, such as in the case of anaphylaxis following the contact with an alginate dressing.[30] Information about the presence of a known allergen is already important in delayed-type hypersensitivity, but is even more crucial in the case of potentially life-threatening anaphylaxis.

## Conclusion

The two new regulations concerning medical devices (Regulation EU 2017/745) and *in vitro* diagnostic medical devices (Regulation EU 2017/746) intend to provide better protection of public health and patient safety. However, they do not provide a benefit for the prevention and management of adverse events, such as contact dermatitis. Due to the increasing number of cases of allergic contact dermatitis from medical devices leading to deleterious effects on quality of life of the patients and increasing cost of illness, this gap should be closed by appropriate specifications in the Q & A documents produced for implementation of the new Medical Device Regulation or respectively in an overarching guideline or an amendment to the Medical Device Regulation. As a minimum requirement, the following should be specified and implemented: 'Labelling needs to include skin (and airway) sensitizers as identified in CLP (H317) used at any stage in the production process of the medical device with body contact, with or without drugs included'. It would be preferable to have full labelling as is the case for cosmetics and pharmaceutical products, because some ingredients are not yet recognized as contact sensitizers. Moreover, full cooperation of manufacturers with the medical community is essential in case – sometimes even severe – adverse (skin) reactions occur.

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