March 2020

To: Competent Authorities for REACH and CLP

EUROMCONTACT represents the European manufacturers of contact lenses and lens care solutions. EUROMCONTACT represents 90% of the soft contact lenses and 50% of the rigid or made-to-order contact lenses distributed in the EU market. MedTech Europe is the European trade association for the medical technology industry including diagnostics, medical devices and digital health. The Association of the European Self-Care Industry (AESGP) is the voice of manufacturers of consumer health products, including non-prescription medicines, food supplements and self-care medical devices in Europe.

Subject: Conflict in EU legislation with respect to use of CMRs in Medical Devices

Dear Competent Authorities for REACH and CLP,

EUROMCONTACT is concerned about the conflicting EU legislation governing the use of substances classified as carcinogenic, mutagenic or toxic to reproduction (CMR) for supply to the general public. The conflict is between the REACH Regulation[1], particularly its Annex XVII, points 28, 29 and 30 (the "REACH CMR Restrictions"), and the Medical Device sectorial legislation, i.e., the Medical Device Directive (MDD)[2] and the Medical Device Regulation (MDR)[3] – the latter which will apply from May 2020.

On the one hand, the potential risks to human health posed by CMRs contained in medical devices are fully addressed by the medical device sectorial legislation, based on requirements including the principles of risk management, material safety testing, clinical evaluation, as well as analysis of alternatives and labelling. On the other hand, the REACH CMR Restrictions ban the placing on the market or use of such CMRs when contained in mixtures (such as medical devices) for supply to the general public. At the same time, the REACH CMR Restrictions include specific derogations for use of CMRs in other categories of products, such as medicinal products for human and veterinary use and cosmetic products.

This conflict has an immediate impact on medical devices for supply to the general public, such as contact lens packaging solutions, lens care solutions and eye drops which may contain borates.

Borates are substances widely used as buffering agents. Boric acid and/or sodium borate, for example, are often used in concentrations up to 1% as a buffering agent in lens care products, eye drops and packaging solutions for contact lenses. The harmonized classification of borates is currently under review. The proposal under discussion foresees to lower the threshold under which mixtures containing borates would qualify as CMRs (Reprotoxic cat. 1B) from a specific concentration limit (SCL), of 5.5% and 4.5% in the case of boric acid and sodium tetraborate, to a general concentration limit (GCL) of 0.3%. Should this proposed GCL limit be adopted, it would trigger the application of REACH CMR Restrictions. This would effectively ban the placing on the market and use in the EU of a wide variety of contact lenses and lens care solutions. Similarly, other

[1] Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH).
[2] Council Directive 93/42/EEC of 14 June 1993 concerning medical devices.
[3] Regulation (EU) 2017/745 of the European Parliament and of the Council on medical devices.

categories of medical devices for supply to the general public, such as rewetting drops and lubricating eye drops, would no longer be available to the public.

Moreover, the REACH restrictions in entries 28, 29 and 30 could result in future bans of medical devices for supply to the general public should they contain CMR substances of category 1A or 1B.

Therefore, we believe there is an urgent need to review the scope of the REACH CMR Restrictions to ensure medical devices are handled in the same manner as medicinal products for human and veterinary use and cosmetic products. Indeed, for these latter categories of products, the authorization to market depends on the evaluation of safety and performance while ensuring benefits outweigh the risks and thus allows such products to contain substances that are CMRs when duly justified.

We have provided in the Annex to this document additional background information. Our requests for the Competent Authorities for REACH and CLP are the following ones:

Asks to the CARACAL

- To address the legislative conflict between the Medical Device legislative framework and the REACH CMR Restrictions as regards the use of CMRs in medical devices for supply to the general public; and

- To delay the application of new harmonised classification on borates (i.e., the generic concentration limit of 0.3%) until the above mentioned conflict of legislation is addressed.

ANNEX

1- Conflict of legislation between Annex XVII, entries 28, 29 and 30, and the Medical Devices legislative framework

Based on Annex XVII, entries 28, 29 and 30 (the "**REACH CMR Restrictions**") CMRs of category 1A or 1B, based on their classification in accordance with the CLP Regulation:

> *"**shall not be placed on the market, or used**, as substances, as constituents of other substances, or, **in mixtures, for supply to the general public** when the individual concentration in the substance or mixture is equal to or greater than: either the relevant specific concentration limit specified in Part 3 of Annex VI to Regulation (EC) No 1272/2008, or, the relevant **generic concentration limit** specified in Part 3 of Annex I of Regulation (EC) No 1272/2008"*

The same article provides that "by way of derogation" the above CMR Restrictions "shall not apply" to:

> *(a) medicinal or veterinary products as defined by Directive 2001/82/EC and Directive 2001/83/EC; (b) cosmetic products as defined by Directive 76/768/EEC; (…)*

The conditions of restriction in Annex XVII entry 30 specify that CMRs of category 1A or 1B, based on their classification in accordance with the CLP Regulation:[4]

> *shall not be placed on the market, or used, as substances, as constituents of other substances, or, in mixtures, for supply to the general public when the individual concentration in the substance or mixture is equal to or greater than: either the relevant specific concentration limit specified in Part 3 of Annex VI to Regulation (EC) No 1272/2008, or, the relevant generic concentration limit specified in Part 3 of Annex I of Regulation (EC) No 1272/2008*

The same article provides that "by way of derogation" the above CMR Restrictions "shall not apply" to:

> *(a) medicinal or veterinary products as defined by Directive 2001/82/EC and Directive 2001/83/EC; (b) cosmetic products as defined by Directive 76/768/EEC; (…)*

The CMR Restrictions, including the derogations mentioned above, were adopted through Directive 94/60/EC[5], which resulted in an amendment of Annex I to Directive 76/769/EEC.[6] The latter became part of Annex XVII of REACH in 2006. Directive 94/60/EC was based on a European Commission proposal of 1 June 1992. At that time, human medicinal and veterinary medicinal products, as well as cosmetic products, were regulated by EU directives[7], while medical devices were **not** subject to any EU sector-specific legislation, as the Medical Device Directive (MDD)[8] was only adopted in 1993. Therefore, a similar derogation for medical devices could not be adopted when Directive 94/60/EC was drafted, since medical devices were not regulated at EU level.

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[4] Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures (CLP).

[5] European Parliament and Council Directive 94/60/EC of 20 December 1994 amending for the 14th time Directive 76/769/EEC on the approximation of the laws, regulations and administrative provisions of the Member States relating to restrictions on the marketing and use of certain dangerous substances and preparations.

[6] Council Directive 76/769/EEC of 27 July 1976 on the approximation of the laws, regulations and administrative provisions of the Member States relating to restrictions on the marketing and use of certain dangerous substances and preparations.

[7] Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by Law, Regulation or Administrative Action relating to proprietary medicinal products; Council Directive 81/851/EEC of 28 September 1981 on the approximation of the laws of the Member States relating to veterinary medicinal products; and Council Directive 76/768/EEC of 27 July 1976 on the approximation of the laws of the Member States relating to cosmetic products.

[8] Council Directive 93/42/EEC of 14 June 1993 concerning medical devices.

It seems, based on the history of REACH, the intention of the EU legislator was **not** to ban CMRs in medical devices, since other articles of REACH, which were drafted after the Medical Devices Directive was adopted, include specific derogations for medical devices. By way of example, Articles 60(2) and 62(6) of REACH exempt from the assessment of **Authorization** "the risks to human health arising from the use of a substance in a medical device".

Both the REACH authorization exemption and the CMR Restrictions concern the "use in" medical devices of the substances. The authorization exemption covers the marketing and use of the substances "in medical devices." Similarly, sections 28-30 cover the marketing and use of the substances in the medical devices.

The exemption for medical devices of Article 60(2) and Article 62(6) essentially mirror the initial text of the Commission's legislative REACH proposal. In particular, Article 57(2)(c) of the Commission's REACH proposal stated that when deciding to grant an authorization, the Commission should not consider the risks to human health arising from the use of a substance in a medical device regulated by [the medical devices legislation]. Similarly, Article 59(6)(c) of the proposal stated that an application for authorization should **not include "the risks to human health arising from the use of a substance in a medical device** regulated by [medical devices legislation]."[9]

The Commission's explanatory memorandum of the exemption for medical devices under Article 57(2)(c) of its proposal explained that the authorization application should **not address the risks to human health** arising from the use in medical devices as **these** are "**adequately controlled under other Community instruments** that are applied by the Member States. Therefore, this is necessary not to interfere with such other competences and to avoid differences between the decisions taken under different regulatory regimes as well as the resources in examining an impact twice" (emphasis added).

The conflict of legislation will become even more striking from May 2020 when the use of CMR 1A and 1B substances in certain medical devices[10] in a concentration above 0.1% weight by weight of the relevant device, part or material, will be regulated by **Annex I, Section 10.4 of the MDR**, which includes requirements such as mandatory labelling of the CMR substance, an analysis of potential patient or user exposure to the substance, an analysis of alternatives, etc. Only when the benefit-risk ratio for the use of CMRs in medical devices is positive can such substances be used. This assessment is typically reviewed by Notified Bodies as part of the conformity assessment.

2- Evaluation of the use of Cat. 1A and 1B CMRs in Medical Devices

Both the MDD and MDR requires medical devices to meet the general safety and performance requirements that apply to them taking into account their intended purpose. These require that all devices "are safe and effective and do not compromise the clinical condition or the safety of patients or other persons" provided that any "risks which may be associated with their use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety." With respect to the use of any substance, manufacturers must pay attention to "the choice of materials and substances used, particularly as regards toxicity" and must design and manufacture in such a way as "to reduce as far as possible the risks posed by substances."

[9] European Commission, *Proposal for a Regulation of the European Parliament and of the Council concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (Reach)* COM/2003/0644 final (October 29, 2003).

[10] Devices, or those parts thereof or those materials used therein that are invasive and come into direct contact with the human body, that (re)administer medicines, body liquids or other substances, including gases, to/from the body, or that transport or store such medicines, body fluids or substances, including gases, to be (re)administered to the body.

Assessment on any risk related to the construction, functioning, performance and use of a device follows the risk management principles of the EN ISO 14971 standard, which include developing a risk management plan and a risk management report with evaluation of each individual risk as well as well an overall medical device benefit-risk analysis. The risk management program also includes the monitoring of complaints and of (serious) incidents to identify unknown or new hazards as well as to evaluate that residual risk levels and benefit-risk ratio(s) are not adversely affected.

The MDR, applicable as of late May 2020, introduces even more stringent requirement with respect to the use of Cat. 1A and 1B CMRs and endocrine disruptors in concentrations above 0.1% in specific categories of medical devices if manufacturers can justify their use. Such justification of presence must be based on: (i) an analysis and estimation of potential patient or user exposure to the substance; (ii) an analysis of possible alternative substances; (iii) argumentation as to why possible substance and/or material substitutes are inappropriate; and (iv) any available and relevant guidance adopted the Commission's scientific committee[11] which encompass a benefit-risk assessment of the presence of CMR and/or ED substance taking into account the intended purpose and context of the use of the device, as well as any available alternative substances and alternative materials, designs or medical treatments. Then labeling and information supplied with the device informs the user of the substances' presence, the possible risks linked to such presence and the routes of exposure as well as specific information on risks for vulnerable groups and precautionary measures, if applicable.

Before a medical device containing substances or mixtures can be placed on the market, a Notified Body (NB)[12] has to review the data compiled by the manufacturer and to assess the conformity of the product. Such review does not limit to pre-clinical data as the NB will also assess the clinical data pertaining to a device in order to verify the safety and performance, including clinical benefits, when used as intended by the manufacturer. Only devices with a positive ratio i.e. where benefits outweigh the risks, can be certified and be placed on the market.

National authorities, in addition to the NB, also play a role in ensuring that the devices are safe and that the risks posed by a product to not outweigh its benefits. They monitor the NB assessments, perform in-market controls and evaluate any serious incident[13] reported to them by the manufacturer. When, for instance, there is suspicion that a medical device poses an unacceptable risk to health and safety of users or to public health, the national authorities may decide to recall or withdraw a product to ensure that the risks it poses are mitigated.

3- The relevance for Use and Non-Clinical safety of borates in ophthalmic products

The removal of the specific concentration limits of seven borates from the existing CLP entries and the application of a generic concentration limit of 0.3%[14] should be delayed – while the above-mentioned conflict of legislation is addressed – as it will cause medical devices for supply to the general public, such as contact

[11] Scientific Committees on Consumer Safety / Health, Environmental and Emerging Risks

[12] A device containing a substance is likely to be provided sterile to the end user and as such a NB will always be involved at a minimum for the aspects related to sterilization

[13] Any malfunction or deterioration in the characteristics or performance of a device made available on the market, including use-error due to ergonomic features, as well as any inadequacy in the information supplied by the manufacturer and any undesirable side-effect that directly or indirectly led, might have led or might lead to the death of a patient or other person, the temporary or permanent serious deterioration of a patient's or other person's state of health, or a serious public health threat;

[14] Committee for Risk Assessment (RAC) Opinion proposing harmonised classification and labelling at EU level of Boric acid, Diboron trioxide, Tetraboron disodium heptaoxide hydrate, Disodium tetraborate anhydrous, Orthoboric acid sodium salt, Disodium tetraborate decahydrate and Disodium tetraborate pentahydrate - CLH-O-0000001412-86-300/F, Adopted 20 September 2019

lenses, lens care solutions and eye drops – for which presence of borates has been demonstrated to be essential and safe - no longer to be available due to REACH restrictions per of Annex XVII entries 28 to 30.

RELEVANCE FOR USE. Chemists and formulators have used borates for many decades as a safe and useful buffering system in aqueous formulations. Borate buffers have been used primarily due to their unique characteristics of holding a formulation near physiological pH (~ 7) with a secondary impact of imparting bacteriostatic characteristics to formulations. They are not preservatives, but do tend to be bacteriostatic and help keep bacterial colonies from growing and spreading in an aqueous formulation[15]. Borates have also been documented to enhance preservative efficacy in some formulations[16].

Formulations in the ophthalmic and ocular health fields have safely and successfully used borate buffers over the years. Eye wash and rinses, borate buffered saline, borate buffered artificial tears solutions, contact lens packaging solutions, contact lens storage and disinfection solutions, prescription eye drops, OTC eye drops, rewetting drops and contact lens cleaning solutions are examples of such products. The addition of borate compounds to these formulations has shown to be safe and beneficial to the patient over this prolonged time. In fact, replacing borates in these formulations could be a potential patient risk due to possibly allowing bacterial growth to occur that otherwise would not occur due these compounds being present. Alternatively, the risk to the patient may be jeopardized by a need to increase the concentrations of disinfecting agents to ensure equivalent disinfection efficacy of the product.

In addition to the more commonly known mechanisms of boric acid described above, borates (boric acid) have also been demonstrated to create a unique and beneficial cross-linked network with hydroxypropyl-guar (HP-guar) through a pH-dependent process. This cross-linked network creates a low-viscosity gel on the eye to improve the ability and duration of the product to relieve dry eye symptoms in these HP-guar-based products.

NON-CLINICAL SAFETY. According to MDR, manufacturing companies using GHS category 1B which includes Borates, will have to justify the use on compound and label it. However, when evaluating the potential impact of borate-containing substances on patient safety, it is important to consider exposure to determine actual risk to patient. Consequently, the product's intended use and route of administration significantly impact overall exposure. For example, borate-containing compounds present in dry eye products, contact lens packaging saline or contact lens disinfection products are not ingested. They are dosed into the ocular environment and subject to a much lower absorption by the patient when compared to oral administration.

In fact, as a non-clinical safety model, the rat is the most sensitive species and developmental toxicity is the most sensitive endpoint. The oral dose that did not cause any adverse effect (NOAEL, no observed adverse effect level) in rats was 9.6 mg boron equivalents/kg body weight/day (Price et al. , 1996) [17].

As an example, for a typical dry eye product containing 1% borates (boric acid) actual exposure to boron is approximately 0.045 mg boron equivalents/kg body weight/day, assuming a total of 32 drops per day, based on 2 drops/eye, 8-times/day) and absorption of the entire dose. This exposure, when adjusted for a 50kg patient, is approximately 200 times lower than the rat NOAEL of 9.6 mg boron equivalents/kg body weight/day. Given that systemic absorption of these products from the ocular environment is less than 100% (topical versus oral application), the actual human exposure decreases further and the safety margin increases.To provide a more comprehensive evaluation of patient safety, similar exposure estimates were calculated for other common ophthalmic products that can contain borates (e.g. eye rewetting drops, contact lens disinfection systems and contact lens package saline). In addition to the exposure calculations for adults,

[15] Adriztina, I.; Adenin, L. I.; Lubis, Y. M. (January 2018). "Efficacy of Boric Acid as a Treatment of Choice for Chronic Suppurative Otitis Media and Its Ototoxicity". Korean J Fam Med. 39 (1): 2–9.

[16] EP 0 180 309 B2, Ogunbiyi L. et al, "Improved disinfecting and preserving solutions for contact lenses and methods of use," 7-May-1986.

[17] Price CJ, Strong PL, Marr MC, Myers CB and Murray FJ, 1996. Developmental toxicity NOAEL and postnatal recovery in rats fed boric acid during gestation. Fundam Appl Toxicol, 32, 179-193.

similar calculations were performed for children where lower body mass will increase overall exposure. Child patient exposure would be greater assuming adult posology and is directly proportional to body weight. The daily exposure range for the same daily dose (32 drops) at the same borate concentration from the example here above is estimated to be between 0.025 and 0.113 mg boron equivalents/kg/day for a 20kg child (approximately 6-7 years old)[18]. While overall exposure to boric acid will be higher due to lower body mass, the safety margin in children is still expected to be at least 85-fold from the rat NOAEL even when assuming 100% absorption, which again is not expected due to topical administration of these ophthalmic products.

The bar graph in Figure 1 provides a comparison of boron equivalent exposure for several ophthalmic products relative to the reported rat NOAEL, including safety factors[19]. The bar graph highlights the misrepresentation when patient risk is tied only to borate concentration in the product as opposed to also taking into account the amount of product the patient is exposed to. The upper and lower exposure estimates are based on ranges of concentrations of borate in typical ophthalmic products – the assumed dosing and absorption are held constant. The lower magnitude of exposures for contact lens disinfection solutions and package salines is due to the assumption that lenses (either directly from new packaging or after disinfection) are applied once per day, as directed. These low exposures are consistent with the use of borates as excipients in medicinal products per the EMA[20].

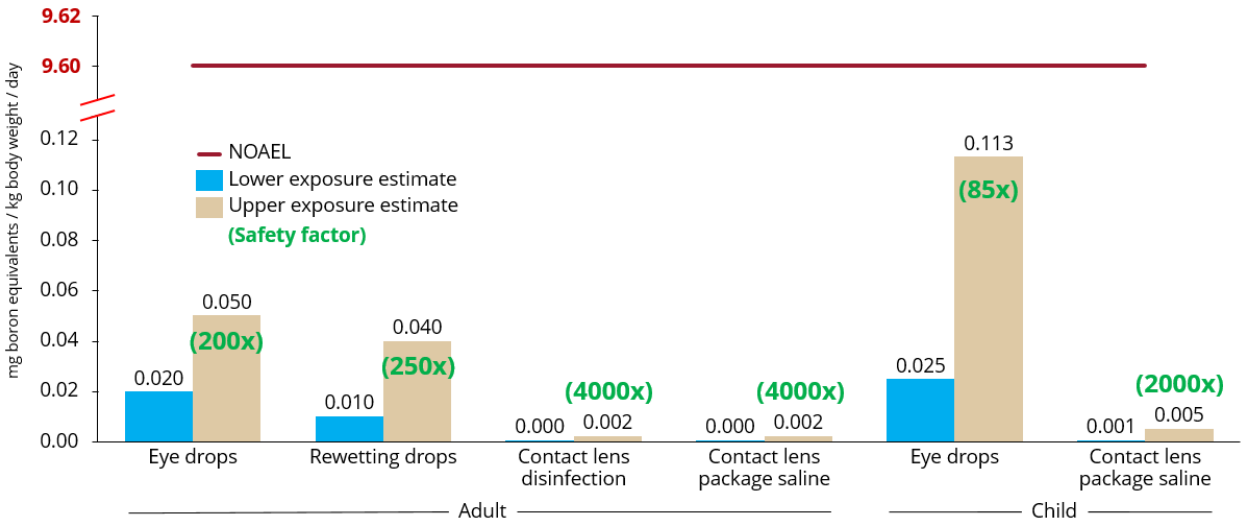

Figure 1. Estimated boron equivalent exposure for example ophthalmic products and safety factors (value in parenthesis) relative to the no observed adverse effect level in rats (NOAEL, red line) assuming 100% systemic absorption.

Compared to the non-clinical NOAEL that supported the classification of boron as a GHS Category 1B substance, the actual daily exposure following use of typical ophthalmic products is at least 200-times lower (e.g. a 200x safety factor).

[18] U.S. EPA. Exposure Factors Handbook 2011 Edition (Final Report). U.S. Environmental Protection Agency, Washington, DC, EPA/600/R-09/052F, 2011.
[19] TDOC-0056055. EU Medical Device Regulation (EU 2017/745) Safety Assessment of Dry Eye Products. Alcon data on file.
[20] European Medicines Agency. Background review for the excipient boric acid. EMA/CHMP/765436/2012. 23 July 2015.