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PERSPECTIVE

Regulatory issues related to the use of sodium hypochlorite solutions in endodontics

Ove A. Peters[1] | **Nidambur V. Ballal**[2] | **Shu Abe**[3,4] | **Gustavo De-Deus**[5] | **Mustafa Gündogar**[6] | **Josette Camilleri**[7] | **Zhi Chen**[8] | **Matthias Zehnder**[9]

[1]School of Dentistry, The University of Queensland, Herston, Queensland, Australia

[2]Department of Conservative Dentistry and Endodontics, Manipal College of Dental Sciences, Manipal, Manipal Academy of Higher Education, Manipal, India

[3]Heiwa Dental Clinic, Kichijoji Minami-cho, Musashino-shi, Japan

[4]Graduate School of Dental Medicine, Department of Restorative Dentistry, Hokkaido University, Sapporo, Japan

[5]Department of Endodontics, Fluminense Federal University, Niterói, Brazil

[6]Department of Endodontics, Faculty of Dentistry, İstanbul Medipol University, İstanbul, Turkey

[7]Division of Endodontology and Operative Dentistry, School of Health Sciences, College of Medicine and Health, University of Birmingham, Birmingham, UK

[8]State Key Laboratory of Oral & Maxillofacial Reconstruction and Regeneration, Key Laboratory of Oral Biomedicine Ministry of Education, Hubei Key Laboratory of Stomatology, Department of Cariology and Endodontics, School & Hospital of Stomatology Wuhan University, Wuhan, China

[9]Clinic for Conservative and Preventive Dentistry, University of Zurich Center for Dental Medicine, Zurich, Switzerland

Correspondence
Matthias Zehnder, Clinic for Conservative and Preventive Dentistry, University of Zürich, Plattenstrasse 11, CH-8032 Zürich, Switzerland.
Email: matthias.zehnder@zzm.uzh.ch

Abstract

Aim: To assess the regulation of sodium hypochlorite (NaOCl) solutions for endodontic usage in some of the world's main dental markets, in view of the European Union's recent move to classify antimicrobial root canal irrigants as high-risk devices under their Medical Device Regulation (MDR).

Methodology: The authors consulted legal texts available online and communicated with local health authorities wherever necessary to assess into which medical device category NaOCl solutions intended for endodontic application were subsumed. Furthermore, it was investigated whether there were sources outside the dental market to obtain NaOCl solutions for root canal treatments.

Results: Upon completion of this text (mid 2024), NaOCl solutions for root canal irrigation had not been classified in the US and Canada, whilst in the European Union, they had just been upgraded to high-risk medical devices, with all the consequences for the dental supply market. This MDR rule was adopted by the EU's close trading partners, the United Kingdom, Switzerland and Turkey. In Japan, the legal hurdles were already high for manufacturers and importers of endodontic NaOCl solutions. Conversely, in China, these solutions were down-graded from a high-risk to a medium-risk status in 2017. A low-medium risk category was applied in the other countries under investigation, that is, Australia, India and Brazil. In some countries

there was a possibility for dentists to procure plain NaOCl solutions from pharmacies. An alternative route to avoid buying NaOCl from dental suppliers was to use (household) bleach solutions for root canal irrigation wherever this practice was not prohibited explicitly.

Conclusions: The legal situation to produce, import and use NaOCl solutions for root canal irrigation differs vastly around the globe. A sensible approach to regulate (yet not over-regulate) endodontic NaOCl solutions appears to be timely and necessary.

KEYWORDS

bleach, EU 2017/745, medical device regulation, pharmacy, root canal

INTRODUCTION

Sodium hypochlorite (NaOCl) solutions administered as root canal irrigants first gained wide popularity with the work of Louis I. Grossman (Anthony & Grossman, 1945). Grossman's concept of mechanical instrumentation and concomitant root canal irrigation (Grossman, 1943) has stood the test of time, and is now the standard root canal treatment world-wide (Dutner et al., 2012; Gopikrishna et al., 2013; Qualtrough et al., 1999; Tsotsis et al., 2021). The concept still relies heavily on the application of a NaOCl solution during and after root canal instrumentation. This is mainly because NaOCl, amongst the known and clinically tolerated aqueous disinfectants, has unique biolytic properties (Grossman & Meiman, 1941; Naenni et al., 2004; Tawakoli et al., 2017). Apart from their clinical effectiveness, NaOCl solutions are also popular amongst dentists/endodontists because of their availability from various commercial sources and their relatively low price (Frais et al., 2001). However, NaOCl solutions are not straight-forward chemicals, that is, they are not simply made from a purified salt dissolved in deionized water. Instead, they are produced electro-chemically on an industrial scale (Goto & Daidoji, 1977). This opens the question on how dentists can obtain NaOCl solutions for endodontic usage that are clean, legal, and safe for their patients.

According to the US Food and Drug Administration (FDA), an article that is intended for the diagnosis, cure, mitigation, treatment or prevention of disease can be a medical device (Jin, 2014). A medical device may have a chemical interaction with the body, but should not need be metabolized to achieve its primary intended purpose. This sets it apart from a *medicinal product* (Antich-Isern et al., 2021; Vila Wagner & Schanze, 2019). Medical devices are divided into different risk classes (Vila Wagner & Schanze, 2019), with subclasses depending on the legislature (Table 1). The higher the expected risk, the more regulated a medical device becomes. High-risk devices usually require an application to the regulatory body of the respective country or area that includes data from clinical trials.

Based on some avoidable problems and scandals involving medical devices such as breast and joint implants in Europe (Lübbeke et al., 2018; Martindale & Menache, 2013), and reperfusion catheters in the US (Kadakia et al., 2022), there has been a call for reform of medical device legislation. In the European Union (EU) and countries adopting EU law, this has led to the recent implementation of the so-called medical device regulation (MDR or EU 2017/745), which replaced the formerly implemented medical device directory (MDD) from 1993. The EU MDR has wide-spread consequences in dentistry, many of which appear to not have been fully grasped by the dentists that already are or soon will be affected by it (Mohn & Zehnder, 2023). Amongst other issues, the EU MDR calls for a new and stricter classification of medical devices, which then has implementations on the manufacturers regarding the scrutiny and the requirements in the regulatory process and post-marketing surveillance. Whether these laws will also be exported to other markets or even be fully enforced in the EU is not known at this point, but it is unlikely that they will not have an impact.

To complicate things further, NaOCl solutions for endodontic applications can traditionally also be purchased from pharmacies in some areas (Frais et al., 2001). In that case, they are not medical devices, but medicinal products/chemicals. The pharmacist is then responsible for the content and purity of the product (Christensen et al., 2001). Moreover and perhaps absurdly, depending on the country and legal environment, NaOCl solutions not specifically designated for medical purposes (household bleach solutions) have been used for root canal irrigation (Frais et al., 2001; Iandolo et al., 2019; Jungbluth et al., 2012; van der Waal et al., 2014). However, the dentist/endodontist

TABLE 1 Medical device classes in some main dental markets and the requirements to be met by manufacturers before product can be sold. The risk class dental NaOCl solutions fall into is highlighted in bold letters for each country/region (where applicable).

Country/region	Classes	Regulatory pathway
European Economic Area EFTA (United Kingdom & Turkey)	I (low risk) IIa (medium risk) IIb (medium to high risk) **III (high risk)**	Self-declaration Notified body approval Notified body approval **Notified body approval**
United States[a]	I (low risk) II (intermediate risk) III (high risk)	Self-declaration De Novo or 510(k)[b] Pre-market approval (PMA)
Canada[a]	I (low risk) II (medium risk) III (medium to high risk) IV (high risk)	Health Canada MDEL Health Canada MDL Health Canada MDL Health Canada MDL
Japan	General Class I (very low risk) Controlled Class II (low risk) **Specially controlled Class III (medium risk)** Specially controlled Class IV (high risk)	Self-declaration Certified body approval **PMDA approval** PMDA approval
Australia	I (low risk) **IIa (medium risk)** IIb (medium to high risk) III (high risk)	Self-declaration **TGA approval** TGA approval TGA approval
China	I (low risk) **II (intermediate risk)** III (high risk)	Self-filling **China NMPA approval** China NMPA approval
India	Class A (low risk) **Class B (low moderate risk)** Class C (moderate high risk) Class D (high risk)	CDSCO approval **CDSCO approval** CDSCO approval CDSCO approval
Brazil	Class I (low risk) **Class II (medium risk)** Class III (high risk) Class IV (maximum risk)	Notified body approval **Notified body approval** Full ANVISA registration Full ANVISA registration

Abbreviations: ANVISA, Agência Nacional de Vigilância Sanitária (Brazil); CDSCO, Central Drug Standard Control Organization (India); EFTA, European Free Trade Association; FDA, U.S. Food and Drug Agency; MDEL, Medical Device Establishment Licence; MDL, Medical Device Licence (Canada); NMPA, National Medical Products Administration (China); PMDA, Pharmaceuticals and Medical Devices Agency (Japan); TGA, Therapeutic Goods Administration (Australia).

[a]Root canal irrigants are not classified.

[b]510(k) premarket submission can be made if a device is equivalent to a legally marketed counterpart.

can avoid personal liability using medical products that are specifically designed and legally approved for the *intended purpose*, which, in this case, is the cleaning and disinfection of root canals.

The aim of this article was to review current (mid 2024) legislation regarding the use of NaOCl solutions in endodontics in some key geographic regions/dental markets. Specifically, it was investigated whether NaOCl solutions were considered to be medical devices, which could be procured from dental suppliers, and if yes, which class they fell into. Secondly, alternative sources for dentists to obtain NaOCl solutions for root canal treatments legally were investigated.

METHODS

The authors consulted legal texts available online and communicated with local health authorities wherever necessary to figure out which medical device regulatory classes existed in each country or region, and into which legal category NaOCl solutions were subsumed. Furthermore, it was investigated which consequences relevant to the endodontist derived from the local legislation, and whether there were other sources dentist could obtain their NaOCl solutions from.

The findings are summarized in present tense, and reflect the situation at the time of the composition of this text.

RESULTS

Europe and related regulatory areas

European economic area

The European Economic Area (EEA) was founded in 1994. It currently consists of all member states of the EU plus the European Free Trade Area (EFTA) countries Norway, Iceland and Liechtenstein. The EEA goes beyond traditional free trade agreements (FTAs) by extending the full rights and obligations of the EU's internal market to the EEA EFTA countries (with the exception of Switzerland).

In the ongoing debate regarding the implementation of the EU MDR, root canal irrigants have taken a centre stage in debate on new (and more stringent) classification of medical devices. Traditionally, root canal irrigants were classified as Class IIa (low to medium risk), as they do not enter the body beyond the confines of the root canal unless inadvertently extruded, and are used for cleansing rather than exerting any biological effects. The Classification Working Group, a subgroup of the Medical Device Coordination Group (MDCG), has produced a manual on their recent discussions on 'borderline cases' (European Union Commission, 2023). Root canal irrigants were considered borderline between medical devices and medicinal products (Antich-Isern et al., 2021). With regards to a classification as a medical device, the working group came to the conclusion that root canal irrigating solutions containing NaOCl or chlorhexidine (CHX) should be classified as class III per rule 14 of Annex VIII to the EU MDR. In principle, the main mode of action of endodontic CHX and NaOCl solutions is still rinsing and irrigation to remove debris and necrotic tissues (mechanical action), which therefore falls into the definition of a medical device rather than a medicinal product (MDR, Art. 2 (1)). The rationale behind subsuming CHX and NaOCl solutions under a higher medical device risk class (from IIa to III) was that they do not only clean (as for example EDTA does), but also disinfect. These MDCG guidelines shall advise manufacturers of medical devices. It can be assumed that notified bodies, who issue the CE marking of a medical device (Table 1), will work according to these recommendations. The problem for manufacturers is that a Class III medical device has to undergo a much more stringent assessment before and after marketing than a Class IIa counterpart (Mohn & Zehnder, 2023). It is therefore unclear at this point whether dental companies will be able to continue to market NaOCl or CHX solutions in the EU under its MDR. Currently, there is not one medical device listed in the European Database on Medical Devices (EUDAMED) under the code Q01010301: dental medication compounds with disinfectants, antibiotics and anti-inflammatories (last checked: August 21, 2024).

Another option to legally supply and market NaOCl is via the regulatory route of being a medicinal product. As indicated, NaOCl can also be considered as a medicinal product due to its primary mode of action being pharmaceutical (here antibacterial). A certified manufacturer can thus follow national legislation and market endodontic NaOCl solutions as pharmaceuticals. This can also be an 'escape route' for dentists, who can obtain plain and clean NaOCl solutions through pharmacies. Interestingly, already under MDD, some manufacturers of dental NaOCl solutions in Europe marketed their more concentrated endodontic NaOCl solutions as pharmaceuticals, whilst the diluted counterparts (1% NaOCl and 3% NaOCl) were sold on the dental market as Class IIa medical devices (SPEIKO, Bielefeld, Germany, personal communication). This practice will most likely continue under MDR, with the difference that the Class IIa devices will be upregulated to Class III.

United Kingdom and Switzerland

In the United Kingdom (UK) that left the EU in 2020 and Switzerland as a non-EU EFTA member, EU law is not adopted automatically, but still has local impact.

After Brexit, the UK has adopted the EU MDR almost verbatim (Mohn & Zehnder, 2023). Because the bilateral contracts were not renewed between Switzerland and the EU, the mutual recognition and related trade facilitating effects for medical devices between the EU and Switzerland ceased to apply on 26 May 2021 (European Union Commission, 2021). Therefore, in terms of the EU MDR, both the UK and Switzerland, are currently regarded as third countries from an EU perspective and vice versa.

In the UK, the Medicines and Healthcare products Regulatory Agency (MHRA) is the regulatory body that oversees the registration and compliance of materials and medicinals. The British Standard Institution (BSI) also has a committee of experts for standards that regulate all dentistry materials and equipment and forms part of the International Standards Organization committee ISO TC/106 (Jacobsen, 2008). The MEDDEV 2.1/3 rev.3 states that irrigation solutions for mechanical rinsing are considered to be medical devices unless the principle intended purpose is to provide a local antimicrobial effect. The majority of wound irrigation solutions with antimicrobial action are intended primarily to mechanically rinse the wound whilst also reducing the bacterial load. The antimicrobial effect may be then considered as an ancillary action. Since in dentistry, the use of NaOCl is not

only as an anti-debris but also intended for antimicrobial effect, it is classified as a Class III device (European Union Commission, 2023). In the UK, similarly to the EU, the Directive 2001/83/EC is adhered to.

The Swiss Agency for Therapeutic Products (swissmedic) is following the European regulations on medical devices and is already implementing enforcement for medical devices according to the requirements of the EU MDR until the Swiss Medical Devices Ordinance (MedDO) is revised. This means that it is highly unlikely that the Swiss regulations regarding NaOCl will differ from those in the EU.

Turkey

At the time of the composition of this text, Turkey is neither a member of the EU nor the EFTA. It does, however, have a bilateral trade agreement with the EFTA countries dating from 1991, which was renewed in 2018. In that context, the EU MDR has also been implemented in Turkey. Turkish dental manufacturers hitherto have produced or acquired NaOCl solutions for the dental market as Class IIa devices. This, however, may change in the future if Annex VIII to the EU MDR gets implemented and enforced, as dental companies may not be able to comply with Class III device regulations. Therefore, Turkey faces the same regulatory environment issues that the EU does, and the availability of endodontic NaOCl solutions may become more restricted.

NaOCl solutions are not available from pharmacies in Turkey.

North America

USA

Irrigation with NaOCl solutions of varying concentrations is standard in dental and endodontist practices in the US (Tsotsis et al., 2021). Clinicians typically purchase bleach solutions intended for home use in bulk. Commercialized NaOCl concentrations vary in concentration of chlorine ions and pH (Jungbluth et al., 2012). Of note, the use of NaOCl in dental practice is not regulated by the FDA (checked on 26. March 2024 from https://www.accessdata.fda.gov/). However, some endodontic NaOCl solutions such as Chlorcid (Ultradent), and ChlorXtra (Inter-Med) 26. March 2024 are listed under the 510(k) premarket notification (product code KJJ), as are some other endodontic irrigants such as BioPure or QMix 2in1 (Dentsply Sirona, PA). These products are subject to a 510(k) pathway but are unclassified, that is, not subsumed in a risk class according to the FDA. However, the fact that they are listed under the product code KJJ would suggest that they are technically considered a Class II (intermediate risk) device.

As a side note, in Europe, neither BioPure nor QMix 2in1 are marketed, because as 'combined products' containing more than one chemical/active element, these endodontic irrigating solutions would have been Class III already under EU MDD. This highlights the problem under scrutiny: the higher a product is classified, the more regulatory hurdles need to be overcome to get it to market, with the effect that, depending on the expected sales, the product may not be made available in a specific dental market at all.

Canada

Canadian clinicians appear to follow the same pattern as their US-American colleagues; the regulator, Health Canada, provide a list of devices but irrigation solutions *are not on that list*. Recently the use of NaOCl was subject to periodic review (PRCV2022-21) to determine that products labelled as pesticides continue to meet health and environmental safety standards and continue to have value. In Canada, NaOCl and calcium hypochlorite are listed in Schedule 2 of the Pest Control Products Regulations. The currently non-regulated uses of NaOCl solutions include but are not limited to health care facilities.

After the assessment process Health Canada has concluded that the continued registration of NaOCl products meets current standards for the protection of human health and the environment. Moreover, updated product labels must now include risk mitigation measures to protect human health. Of note, none of the products listed in the directive are specific for dental application and all have concentrations above 5.25% (Government of Canada, 2022). Again, these regulations relate to pesticides/biocides, that is, the use of NaOCl solutions as surface cleansers, and not their use in the human body.

Australia

The use of NaOCl for root canal irrigation is regulated by the Therapeutic Goods Administration (TGA, https://www.tga.gov.au/). Dentists must only use products with TGA approval that was, until recently, limited to a 4% concentration of active (available) chlorine (Cl_2), which equals a NaOCl concentration of 4.2%. The TGA is classifying medical devices and materials according to their risk profiles (Table 1). This has been first codified in the

Therapeutic Goods Act registered in 1989. However, as late as 1998, Milton's solution (available as 1 or 2% chlorine in 16.5% sodium chloride, Procter & Gamble Australian Pty. Ltd., Parramatta, NSW, Australia) and diluted domestic bleach were frequently used in Australian dental practices. Milton's, due to its salt content in conjunction with the hypochlorite, is highly corrosive to endodontic instruments (O'Hoy et al., 2003).

Currently, NaOCl solutions for root canal irrigation are accordingly classified as Class IIa medical devices, and considered as root canal cleansing solutions. These solutions are only obtained from dental supply companies, not pharmacies. Of note, recently NaOCl solutions with higher concentrations (e.g. CanalPro 6%, Coltène, Henry Schein Halas, Mascot, Australia) have been commercially available in Australia. Such imported solutions must comply with the regulations set forth by the Australian government. For a Class IIa product, a respective documentation is requested from the country/region of origin, namely EU MDR, Japanese per-market certificate, Health Canada Class II licence, or US FDA de novo decision summary or 510(k) summary.

Household bleach, for example, for swimming pool disinfection, is labelled under Schedule 5-Caution. It cannot be excluded that some practitioners still use Milton's or other bleach solutions for root canal irrigation. However, medical regulations are generally followed strictly in Australia.

India

NaOCl solutions for endodontic application in India are also considered to be dental cleansing solutions by the governing body, the Central Drug Standard Control Organization (CDSCO). These solutions are regulated and governed by the Indian Medical Device Rules 2017, which were developed by the CDSCO and amended in 2020 and 2022. Because endodontic NaOCl solutions are produced in India, they are available to clinicians at an affordable price through dental suppliers and pharmacies.

Any company who intends to import NaOCl for sale or distribution in India, shall obtain medical devise import licence (MD-15) from the CDSCO. The Central Licensing Authority of India classified medical devices into four classes depending on their purpose, invasiveness, usage duration, and potential for harm (Table 1). NaOCl is categorized as a low to moderate risk device. For manufacturing and marketing NaOCl in India, a so-called MD-5 license is required (https://medicaldevicelicense.com/get-md-5-license-india/). After filing an application to get an MD-5 licence, the application will be forwarded to an independent notified body. The notified body conducts an audit at the manufacturing facility to check the compliance with Quality Management System and Medical Device Rules, 2017.

The device master file must contain the post-marketing surveillance and vigilance reporting procedures and data collected by the manufacturer encompassing the details of the complaints received and corrective and preventive actions taken for the same. Post-marketing surveillance includes the collection of data from various sources like feedback from users and patients, analysing the retain samples, social media, scientific literature, medical device registries, incidents reported to the organization, post-market clinical follow-up (PMCF) studies, market surveillance activities by regulatory authorities, and their related publications and recommendations.

China

NaOCl solutions have been used as endodontic irrigants in China for over 20 years. In the beginning, there were no NaOCl products specially marketed as root canal irrigants in China. Endodontists used chemical or disinfection products (bleach), preparing 1%–2% NaOCl working solutions by diluting a 10% NaOCl stock solution. In the year 2000, however, the Chinese government enacted laws to strictly regulate medical and dental devices, leading to the commercialization of NaOCl irrigants. The National Medical Products Administration (NMPA, http://www.nmpa.gov.cn) oversees the regulation of medical and dental devices, similar to how drugs are regulated. The Regulations on the Supervision and Administration of Medical Devices were first enacted in 2000, fully revised in 2014, partially revised in 2017, with the latest revision coming into force in June 2021. According to these regulations, medical devices including dental devices, are classified based on their risk levels. The state has formulated and issued the Rules for Classification of Medical Devices and Classification Catalogue of Medical Devices, dividing them into three categories, from low to high risk (Table 1). Class III products are high risk and requires strict management measures. The catalogue is periodically revised. Of note, in the latest edition in 2017, root canal irrigants were reclassified from Class III to Class II, making NaOCl the most widely used root canal irrigant in Chinese dental clinics.

Currently, NaOCl irrigants with concentration of 1%, 3% and 5% are easily accessible through various commercial channels, including unified government procurement for public dental institutions, local dealer distribution and online procurement for private dental clinics.

Japan

The Law on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices currently regulates and seeks to optimize the manufacture, sale and safety control of pharmaceuticals and medical devices in Japan. Pharmaceuticals are classified into prescription pharmaceuticals and commercial products (behind-the-counter drugs, non-prescription drugs), and in-vitro diagnostics, whereas medical devices are classified into four classes based on their impact and level of risk to the human (or animal) body: general medical devices (Class I), controlled medical devices (Class II) and specially controlled medical devices (Classes III and IV; Table 1). Like elsewhere, the licensing and approval process becomes stricter as the impact and risk to the body from the pharmaceutical or medical device increase.

NaOCl solutions in Japan have historically been approved as 'pharmaceuticals' and are clinically used as 'prescription pharmaceuticals' that have met the strictest standards under the current legislation. However, some new products have been approved as adjuncts to ethylenediaminetetraacetic acid (EDTA) in the sense that they function primarily as cleansers rather than disinfectants. This was made possible by amendments of legislation (Ministry of Health, Labour and Welfare of Japan, 2014a, 2014b). EDTA is classified as either a pharmaceutical or a medical device depending on its method of use, but as a dental root canal cleaning agent, it is approved as a medical device in all cases. NaOCl solution approved as a component of EDTA is therefore classified as a Class III medical device (specially controlled medical device) in the form of a 'pharmaceutical-containing material for aiding dental root canal cutting'.

There are currently five types of NaOCl solution available for endodontic treatment in Japan: three are approved as prescription pharmaceuticals (two at 10% and one at 3–6%), and two are approved as medical devices (2.5% and 3%). These solutions are only obtained from dental suppliers.

At present, Japan's university schools of dentistry and dental clinics basically provide dental care in accordance with the National Health Insurance System. Under this system, all pharmaceuticals and medical devices used for treatment must be approved. In this context, it is inconvenient for endodontists and general practitioners that Japan has approved only five types of NaOCl at relatively high concentrations, since these concentrations must be diluted for clinical use, and there are few price options.

Some dental clinics provide treatment outside of the insurance system, and it is possible, with the consent of the patient, to use off-label NaOCl solutions that are not yet approved in Japan. However, off-label use is not recommended due to the lack of government approval and because it entails safety risks.

In recent years, the requirements for the development of pharmaceuticals and medical devices have become increasingly strict (Ministry of Health, Labour and Welfare of Japan, 2021). In principle, to market an NaOCl solution that differs from a previously approved concentration, the manufacturer must provide data proving the safety of the difference. Therefore, the hurdles for dental manufacturers to market new NaOCl solutions are very high. Nevertheless, pathways for product development remain open, either by obtaining approval as a medical device through combination with a component such as EDTA or by approving a generic version of a previously approved product. It is hoped that such strategies will lead to supply of new NaOCl solutions for root canal cleaning and more options for endodontic treatment.

Brazil

Brazil's medical device market regulator is the National Health Surveillance Agency (ANVISA). It is responsible for registering medical devices and maintaining a registered products database in Brazil. RDC 751/2022, applicable since 1 March, 2023, is the regulation that applies to all medical devices (ANVISA, 2024).

Medical devices are classified in Brazil following a risk-based approach comparable with the European Union and the FDA classification systems, which means that the classification is according to the level of risk they present to the patient and the regulatory process will change as the risk level increases. ANVISA's classification system is based on the classification rules in Annex VIII of the Medical Device Regulation (MDR) No. 2017/745 which embraces 22 rules and split the devices into Risk I–low risk, Risk II–medium risk, Risk III–high risk and Risk IV–maximum risk. As such, classifications are frequently consistent between Europe and Brazil. For example, a Class IIa/IIb device in Europe is usually a Class II/III device in Brazil. Medical devices classified in risk classes I and II are subject to notification, per Article 6 of the RDC 751/2022 ANVISA resolution. Class III and Class IV devices are subject to listing and full registration, per Article 7 of the resolution. Class III and IV registrations are valid for 10 years whilst Class I and II registrations no longer have an expiration date.

The commercialized NaOCl solutions for root canal treatment are classified as Class II (medium risk) in Brazil. They are used amongst GPs and specialist in concentrations ranging from 0.5% to 5.0% NaOCl. Alternatively, NaOCl solutions for endodontic application can also be acquired from authorized pharmacies

(pharmaceutical-grade NaOCl solutions, very common amongst the specialists in Brazil) and dental suppliers, which are also in charge for any NaOCl solution imported to be distributed and sold in Brazil. For that situation, the dealer needs to apply to ANVISA for the import licence for a Class II device. Of note, there is a significant undetermined, but for sure non-negligible number of dentists that purchase the NaOCl solution primarily intended for home use (household bleach) for clinical practice.

DISCUSSION

This review demonstrates a high variability in NaOCl regulation around the globe. NaOCl solutions used for root canal treatments can be anything from non-classified to high-risk products (Table 1).

The topic under scrutiny is highly controversial. On the one hand, and from a patient's perspective, regulation can be a good thing as long as it ensures the safety of a medical procedure involving the material in question. A tighter regulation may also prevent manufacturers of endodontic NaOCl solutions from making non-substantiated claims regarding their product, such as the notion that their (non-declared, proprietary) additive should improve soft tissue dissolution (De-Deus et al., 2013). Independent research has shown over and over again that the NaOCl concentration is the driving force behind the efficacy of NaOCl solutions, and not any proprietary additives (Kottathil et al., 2024). Moreover, as has been shown in peroxide-based preparations for tooth bleaching, unknown or non-declared additives may influence product toxicity (Llena et al., 2019). On the other hand, whether dental companies in highly regulated environments such as the EAA will be able to comply with the ever more stringent regulations that they are confronted with remains to be seen. A prominent recent example was the idea by the EU to classify dental fillings in the highest risk class, because they contain nanomaterials. Enactment of this proposal was prevented by the Federation of the European Dental Industry (Mohn & Zehnder, 2023). However, in the context of NaOCl production and use in dentistry, it is questionable whether any lobby groups exist who could exert similar political pressure. It is beyond question that NaOCl solutions, given their high cytotoxicity in standard laboratory tests (Ballal et al., 2019), would be hard to impossible to introduce to the dental market today, had they not a long history of safe clinical usage.

The fear that the MDR could lead to a shortage in medical devices (including NaOCl solutions) has become a reality in Europe. EU-independent European countries such as Switzerland now consider to allow FDA-approved devices, as they have done for medicinal products through a mutual agreement (Swissmedic, 2023). However, in the case of NaOCl, that is of little help as long as the production of endodontic NaOCl solutions is not regulated in the US (Table 1). Moreover, it is now the standard procedure for internationally active European companies producing medical devices of a higher risk class to launch these products in the US first, and to only do so in Europe once they gathered clinical data (Fink & Akra, 2024).

NaOCl solutions are produced by an electrochemical process that involves the conversion of lye and chlorine gas into sodium hypochlorite and sodium chloride (NaCl). This can result in contamination with metals (iron) from the electrodes. Household bleaches contain non-declared amounts of heavy metal from their electrolytic manufacturing process, which may explain why they can contain polyacrylate to bind these components. What sets the pharmaceutical-grade solutions apart from the household bleaches is their controlled production process from purified water, the filtering process, and their controlled content of iron and heavy metals (Hedinger GmbH, Stuttgart, Germany, personal communication).

Regulation also drives the price. Regulated NaOCl solutions, be it as medical devices in the dental market or pharmaceuticals, are inherently more expensive than their common household bleach counterparts (Frais et al., 2001; Jungbluth et al., 2012). This may be a reason why dentists around the world appear to not necessarily adhere to local regulation and use some household bleach product procured from the supermarket. Endodontists appear to be more or less ignorant of any regulations, and even if such regulations exist, they may not be enforced at this point in time.

Household bleach solutions are naturally sterile and not necessarily impure. However, they are sold in concentrated form, with an available chlorine concentration between 5% and 10%. A prominent example is Clorox Germicidal Bleach (The Clorox Company), which is sold as a concentrated surface disinfectant and bleaching agent for inanimate objects, yet is commonly used as a root canal irrigant where available. Such chlorine-based household bleach solutions are intended for dilution to fit their intended purpose, which can be anything from bleaching laundry to surface decontamination. Their chlorine content is not controlled or specified properly. Moreover, 'full strength' stock solutions are non-stable; their content in available chlorine decreases quicker, and even more so in warm climates, than that in diluted counterparts for direct clinical application (Piskin & Türkün, 1995). It is therefore an inherent problem when using such solutions that dentists do not know what concentration of active chlorine they are applying (van der Waal et al., 2014). In addition, such industrially produced

solutions may contain non-disclosed contaminants such as iron and other heavy metals from their production process (Jawami et al., 2022), and other additives that may not be suitable for use in humans. Even though NaOCl accidents are quite rare (Kleier et al., 2008), from a legal and an ethical standpoint, the authors would strongly advise against the use of household bleaches in endodontics. In the day and age of patient safety and the ever-evolving regulatory environment that dentists and dental companies face, the use of such solutions for endodontic irrigation is anachronistic.

In essence, plain and pure NaOCl solutions without any additives are all that endodontists and dentists performing root canal treatments need to enable chemo-mechanical root canal cleansing and ensure patient safety. This should be realized by governments, and the regulatory rules should be adjusted accordingly. As discussed in this article, not doing so can lead to multiple avoidable problems. When NaOCl solutions are not classified and regulated, most dentists use household bleach solutions, as is the case in the US and Canada. Manufacturers of dental solutions then may feel the urge to make unsubstantiated claims regarding their NaOCl solutions containing some extra additives. Conversely, when NaOCl solutions are over-regulated, as is the case in Japan and is about to happen in Europe, fewer products will be on the market, and their price will be high. If there are no clear guidelines and controls by health authorities regarding the actual use of products in dental offices, dentists may then still use household bleach for root canal irrigation, and the patient benefit will be nil. It may therefore be up to endodontic societies to contact their respective departments of health, discuss this issue, and find reasonable solutions wherever necessary.

Finally, the long-term validity of articles like the current paper is always hampered by the fact that regulations change, and what was found and described here may not apply in the future. It would therefore appear relevant that endodontic researchers and clinicians remain involved in the topic under scrutiny.

CONCLUSIONS

The legal situation to produce, import and use NaOCl solutions for root canal irrigation differs vastly around the globe. A sensible approach to regulate (yet not over-regulate) endodontic NaOCl solutions appears to be timely and necessary.

AUTHOR CONTRIBUTIONS

MZ involved in conception and design. All authors, OAP, NVB, SA, GD, MG, JC, ZC and MZ involved in acquisition of information and interpretation, drafted manuscript. All authors critically revised the manuscript and gave the final approval.

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CONFLICT OF INTEREST STATEMENT

None to declare.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

DISCLAIMER

This text was composed based on the information that was available to the authors in early 2024. The content of this article is not legally binding, and legislation may change over time. Furthermore, this article is not supposed to be Eurocentric, it is merely hinged on a new interpretation of EU 2017/745 (EU MDR).

ETHICS STATEMENT

This article was not based on any human or animal experimentation, and therefore did not require an ethics approval.

ORCID

Ove A. Peters https://orcid.org/0000-0001-5222-8718
Nidambur V. Ballal https://orcid.org/0000-0002-2208-9443
Shu Abe https://orcid.org/0000-0002-9165-4194
Gustavo De-Deus https://orcid.org/0000-0001-7778-047X
Mustafa Gündogar https://orcid.org/0000-0001-8656-7101
Josette Camilleri https://orcid.org/0000-0003-3556-6365
Zhi Chen https://orcid.org/0000-0003-2095-1324
Matthias Zehnder https://orcid.org/0000-0001-9545-7828

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