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A Review of International Medical Device Regulations: Contact Lenses and Lens Care Solutions

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ABSTRACT

Medical devices are under strict regulatory oversight worldwide and such regulations prioritise patient safety and efficacy over anything else. Contact lenses fall under the medical device category - a result of direct contact with the eye. Equally regulated are the contact lens care product solutions, which include cleaning and maintenance solutions and lubricating and rewetting drops. In the USA, it is the FDA Centre for Devices and Radiological Health (CDRH) overseeing the regulations of medical devices, since 1976. In the European Union, it is the EU Commission responsible for regulating devices in Member States. The categorisation of contact lenses into medical devices is based on their inherent risk to the wearer. Contact lenses are subject to crucial regulatory oversight from concept to clinical evaluation, clinical investigations through to the finished lens product, and finally, strict conditions associated with their marketing approval including post-marketing surveillance. The physiochemical and manufacturing testing, such as biocompatibility testing alongside pre-clinical stability, sterility and microbiological testing are just some of the essential testing lenses must endure. Only through understanding the inherent risks and potential complications that can arise from contact lens wear, can one truly appreciate the need to adhere to strict regulations. The challenge however, lies in the need for more standardised regulations and flexible approaches, ensuring innovative device technologies reach patients in a timely manner without compromising public health and safety. This review highlights some key requirements, differences and similarities between the FDA and EU administrations in the approval of contact lenses.

KEYWORDS

Clinical investigation; market approval; contact lenses; care solutions; Clinical evaluation

1. Introduction

Within the European Union (EU), a medical device can be broadly defined as "any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings"[1]. The commonality between the EU definition with other definitions, such as the United States of America, lies in the purpose of such medical devices: for the diagnosis, treatment, cure or mitigation of onset of certain diseases or conditions and "intended to affect the structure or any function of the body" in man or animals. These can also include active implantable medical devices (or AIMD) or in vitro medical devices. The range of such devices vary significantly, and include: bandages, wheelchairs, endoscopes but also, contact lenses and contact lens care solutions.

For the purpose of this article, emphasis will be on key regulatory agencies including the Food and Drug Administration (USA) and the European Commission (EC) who have regulatory oversight of medical devices in their respected regions. The EC 'harmonizes' both the requirements for and regulations of medical devices inside the European Union. The Medical Devices Directive (MDD) is a central component of legislation. The EC works in close conjunction with each country's ('Member State') respected Health Authorities. The aim, therefore, is to integrate the various national requirements into a single law that could be rolled out and applied across the EU. It is important to note that the new Medical Device Regulation (May, 2017) will replace the existing EU Directive on AIMDS (90/385/EEC) and Medical Device Directive (93/42/EEC), both of which are amended by the Directive from 2007(47/EC) [1-3].

Until the 1990s, each country within the EU adopted its own approach when it came to the evaluation of medical devices. Plans to harmonize this diverse market led to the introduction of EU directives with 'Essential Requirements' that must be met for a device to be marketed across EU member states, post-CE marking [4]. These directives in the 1990s therefore saw the inclusion of contact lenses into the medical device family. In contrast to the US FDA's PMA application process (see later), medical devices in the EU as mentioned are subject to conformity assessment procedures, usually carried out by an independent third party ('notified body'), acting under the control of the national authorities. Once cleared and 'certified', the device receives the CE marking, allowing for harmonization of its use within the EU/EFTA countries [5]. In 2012, the European Commission put forward two Regulations for medical devices (Medical Devices Regulation (MDR)) and in vitro diagnostic devices, which will repeal the existing three medical device Directives (93/42/EEC, 90/385/EEC, 98/79/EC)[1, 2, 6]. The aims of these new regulations are to emphasize the need for safe and effective medical devices whilst adopting a more innovative approach in the sector.

The Food and Drug Administration (FDA) has the legal authority to regulate medical devices in United States (US), as per the Federal Food, Drug & Cosmetic Act (FD & C Act, 1938) in the USA [7]. Through this, the FDA has published and implemented the appropriate regulations, within which exists the CFR, Code of Federal Regulations. More specifically, for the purpose of medical device regulations, medical devices (along with radiation-emitting products) are located in Title 21 CFR, Parts 800-1299. These specific regulations that are codified in the CFR include content on the design, clinical evaluation, manufacturing, packaging, labelling and post marketing surveillance of medical devices

[8]. In 1994, the US regulatory bodies released the Premarket Notification (510K) Guidance Document for Class II Daily Wear Contact Lenses.

Contact lenses in the US have had regulatory oversight from the FDA since the 1960s. However, soft hydrogel lenses were regulated as per 'new drug product' FDA regulations [9]. It was the 1976 Medical Device Amendment to the Federal Food, Drug and Cosmetic Act (FDCA) that paved the way for newfound medical device regulations in the USA and these included contact lenses. This then led to the transition of extended-wear lenses into Class III medical devices, requiring Pre-Market Authorization (PMA) due to their higher risk of adverse events. Daily-wear soft and rigid gas-permeable (RGP) lenses became Class II medical devices in 1994 [9]. Studies of daily wear contact lenses are deemed to be of non-significant risk. Studies investigating extended-wear contact lenses however require an Investigational Device Exemption (IDE) application to the FDA prior to beginning the study [10]. Both however, require Institutional Review Board (ethical) approval. Products of contact lenses were also categorized under Class II medical devices in 1997 and will be discussed further later. FDA Guidance specific to contact lenses, including for example regulations in the region of toxicology, microbiology, manufacturing/chemistry properties, clinical, labelling, equivalence claims and care for solutions is synthesized in the latter part of the article but will be discussed more broadly for medical devices in the following section.

To delve further, it is important to comprehend that the regulation of contact lenses and accompanying contact lens care solution, is crucial for patient safety. The European Commission Classification of Medical Devices discusses the "risk-based system" incurred, based on the "vulnerability of the human body" (MEDDEV 2.4/1 Rev 9, 2010)

[11]. This emphasizes the importance of regulating all medical devices, including those in a lower risk category. In the interest of harmonization, only products that fulfil the EU's 'Essential Requirements' can be put through to market [12]. The acceptance of these standards, directives and regulations can only come from understanding the importance of oversight prior to a medical device making contact with the human body. The FDA, in its Guidance for Contact Lens Care Products Labelling, discuss the importance of emphasizing the risk of eye infections when it comes to the use of contact lens and its relevant care products. Mitigating the potential risks and complications associated with their use is therefore of utmost importance. This arises from ensuring accurate information in the accompanied label and correctly following these instructions for use (IFU). The literature discusses devastating toxic and microbiological complications that can arise from contact lens wear, due to their potential to alter the normal homeostasis of corneal surfaces [13, 14] but also the toxic and allergic effects of preservatives found in soft contact lens solutions, potentially causing ocular delayed hypersensitivity [15-17]. These are just some of the many risks that can occur because of contact lens wear and use of solutions. Therefore, this is justification for why oversight, in the form of regulations, are crucial for patient safety.

Firstly, however, one must understand the similarities and differences between the key regulatory authorities. **Table 2.** Overarching the EU regulations when it comes to medical devices is the EU Commission. More specifically, contact lenses require a CE (Conformité Européene - European Conformity) Marking, discussed in the EU 93/68/EEC Directive [18]. CE Marking and its accompanied directives have a set of "Essential Requirements" that need to be met. In the USA, it is the Food and Drug Administration (FDA) overarching the regulation of such medical devices, namely but

not always, through their 510(k) application process for its registration. Both have a core mission: ensuring the safety and effectiveness of drugs and medical devices for patient use. Differences requirements between both regulations mean to have contact lenses or care solutions approved in FDA or EU and not in both at the same time.

A gap in the literature was noted with regards to explaining similarities and differences between the FDA and EU Commission's regulations of contact lens and their care solutions. A consequence of this gap, was therefore the lack of published scientific literature for researchers, clinicians and scientists to fully comprehend the importance of regulatory oversight for patient safety and highlight any differences between nations. The objective of this article therefore, is to review the current literature and international regulatory medical device guidelines, specifically of contact lenses and care solutions, and to compare and contrast the FDA and European Commission administrative regulations in both pre-clinical and clinical studies prior to the registration and approval of contact lenses and contact lens care solutions.

2. Contact lens and care solutions classification

It is important to note that in both the EU and USA, governing bodies classify medical devices according to their low, medium or high risk. This classification in turn allows manufacturers to determine the need for a regulated clinical study (commonly referred to as a 'trial' or 'clinical investigation, specific to medical devices) or a clinical evaluation of prior clinical data and the scientific literature.

Daily-wear contact lenses are deemed to pose a 'moderate risk' to patient safety and in accordance with FDA classifications, are therefore labelled as Class II medical devices

[19], along with contact lens care solutions. Class II devices necessitate additional regulations to ensure adequate safety and effectiveness through for example, their post-marketing surveillance and also labelling of the device. Overnight lenses however (those for extended-wear use) and contact lenses indicated for myopia control, are perceived to have a much higher risk, and so are labelled as Class III devices [20]. Class III medical devices are subject to pre-marketing approval (PMA), in order to achieve FDA acceptance. In the EU, however, the classification is slightly different. As briefly mentioned, in the EU, there is a conformity assessment that manufacturers of devices must demonstrate to comply with Directive 93/42/EEC [1] and their requirements. The classification of these medical devices will therefore play a role on the conformity assessment the manufacturer must adhere to, as a means of achieving CE marking [21]. Short-term corrective contact lenses are Class IIa medical devices, while long-term corrective contact lenses are in Class IIb. Equally labelled as a medical device, contact lens care solutions for the purpose of "disinfecting, cleaning, rinsing" the contact lens, are in Class IIb of the EU Medical Device Guidance on Classification.

3. Pre-clinical studies for contact lens and care solutions approval

Contact lenses and their care solutions must undergo rigorous testing, namely the aforementioned tests in **table 2**, to demonstrate: biocompatibility physical compatibility (between care solutions and contact lenses), stability and sterilization **Figure 1**.

Biocompatibility testing refers to the biological safety evaluation of a product, in this context, medical devices, as a means of mitigating the risk of biological incompatibility with the human body. The FDA has stated that in general, clinical studies are not deemed sufficiently sensitive to determine concerns of biocompatibility - leading to the need for pre-clinical animal testing. Data from in vivo animal studies of the final medical device

may be used instead of certain biocompatibility tests (FDA Guideline, 2016) [22]. Biocompatibility testing for medical devices regulated by the EU Commission also relies heavily on the EN ISO 10993-1 standard [23].

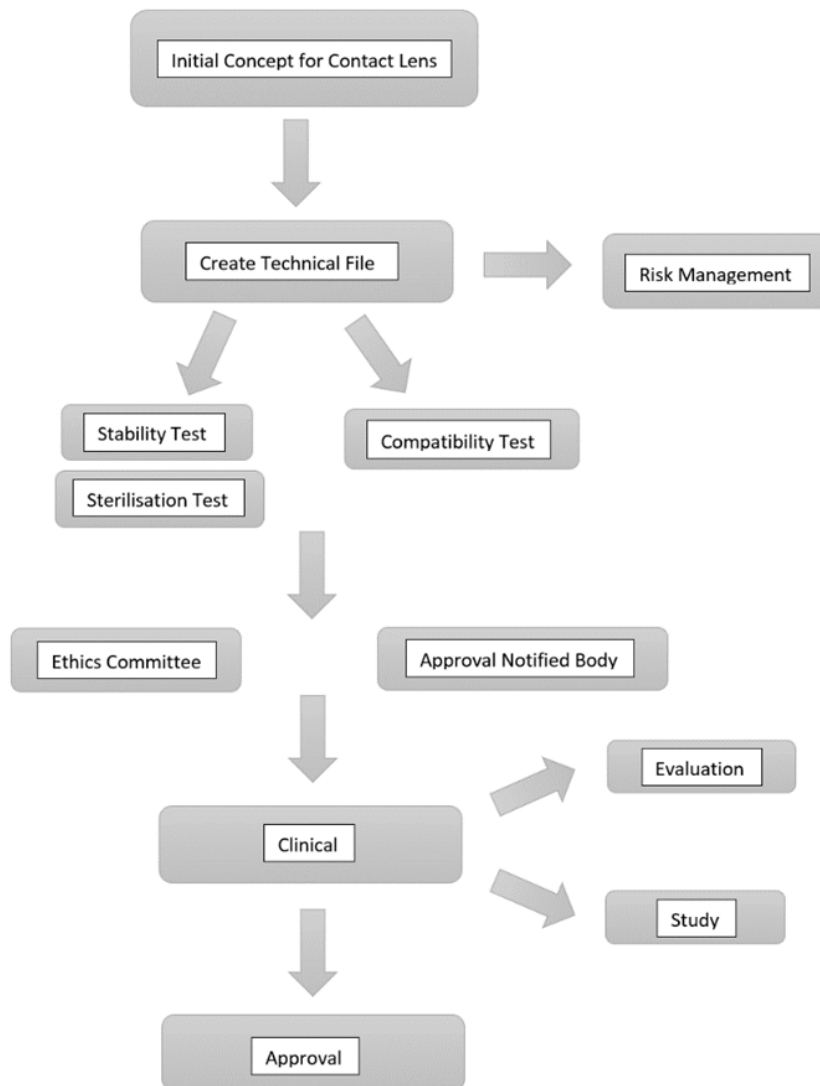


Fig 1. Summary of Approval Steps for Contact Lens and/or care solution

The recent FDA Guideline, issued in 2016 entitled: "Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within

a risk management process" aims to assist those preparing PMAs, 510(k)s and requests for medical devices that are either in direct or indirect contact with the human body. The importance of clear guidance here comes from understanding the possibility of an "unacceptable adverse biological response" that may come from device's materials interacting with the body [23].

Emphasis here is on discussion of 'risk-based approaches' required to determine whether biocompatibility testing is necessary. This comes from the responsibility of sponsors to state whether their device "does not have any direct or indirect tissue contact" and therefore additional biocompatibility information would not be required. If, however, a 'change' exists that could alter tissue-containing components of the device, either directly or indirectly, a biocompatibility evaluation is required to evaluate this impact.

In brief, cytotoxicity testing involves cultured cells being exposed to the lens solution while sterility tests investigate the microbiological aspects of the lens (UNE EN ISO 10993-5) [24]. Other similar tests, such as those to test for ocular irritation are performed on rabbits and labelled under the necessary 'pre-clinical studies' that regulators request prior to registration and approval (UNE EN ISO 10993-10) [25].

It is crucial to make reference to the ISO 11981: 2017 standard when discussing the procedures and performance criteria to assess the physical compatibility of contact lenses and their associated care products. By definition, ISO standards are international and therefore recognized by both FDA and EU regulatory oversight. The procedures aim to detect changes in the characteristics of contact lenses and investigate methods to differentiate irreversible changes from reversible changes in lens characteristics [26]. A

completed list of the key ISO standards relevant to contact lenses was created through handsearching the ISO website and can be found in Table 1.

Although almost a quarter of a century old, an FDA guidance (1994) provides further information on the compatibility of lenses with its proposed care regimen, as per the labelling (Amendment 1 to May 12, 1994, Premarket Notification (510(k)) Guidance Document for Daily Wear Contact Lenses) [19]. The guideline briefly discusses a 30-day cycle lens/solution compatibility test. Justification for not submitting a compatibility test with a 510(k) application is if such cleaning, rinsing or disinfecting products have prior approval with a lens of the same hydrophilic or hydrophobic lens group, respectively. The FDA also requests the content of documents submitted by manufacturers, to include aspects of chemical composition of lenses and purity of monomer components. Manufacturing methods, polymerization and annealing conditions, sterilization methods and packaging methods and materials are just some of the manufacturing information also requested by the FDA. This is alongside criteria of investigating: leachability, physical and optical parameters of finished lens and their tolerances, preservative uptakes and release (for new/modified lens materials), physiochemical properties and information on lens blanks.

Table 1: Key ISO Standards specific to Contact Lenses

| ISO Name | Brief Details/Title |
|----------------------------|--|
| EN ISO 11980:2012 | Ophthalmic optics - Contact lenses and contact lens care products - Guidance for clinical investigations |
| EN ISO 14534:2011 | Ophthalmic optics - Contact lenses and contact lens care products - Fundamental requirements |
| EN ISO 18369-1:2017 | Ophthalmic optics - Contact lenses - Part 1: Vocabulary, classification system and recommendations for labelling specifications |
| EN ISO 18369-2:2017 | Ophthalmic optics - Contact lenses - Part 2: Tolerances |
| EN ISO 18369-3:2017 | Ophthalmic optics - Contact lenses - Part 3: Measurement methods |
| EN ISO 18369-4:2006 | Ophthalmic optics - Contact lenses - Part 4: Physicochemical properties of contact lens materials |
| EN ISO 11978:2017 | Ophthalmic optics - Contact lenses and contact lens care products - Labelling |
| EN ISO 11986:2017 | Ophthalmic optics - Contact lenses and contact lens care products - Determination of preservative uptake and release |
| EN ISO 14729:2017 | Ophthalmic optics - Contact lenses and contact lens care products - Microbiological requirements and test methods for products and regimens for hygienic management of contact lenses |
| EN ISO 13212:2014 | Ophthalmic optics - Contact lenses care products - Guidelines for determination of shelf-life |
| EN ISO 11981:2017 | Ophthalmic optics - Contact lenses and contact lens care products - Determination of physical compatibility of contact lens care products with contact lenses |
| EN ISO 9394:2017 | Ophthalmic optics - Contact lenses and contact lens care products - Determination of biocompatibility by ocular study with rabbit eyes |
| EN ISO 18189:2016 | Ophthalmic optics - Contact lenses and contact lens care products - Cytotoxicity testing of contact lenses in combination with lens care solution to evaluate lens/solution interactions |

Table 2: Comparison FDA and EU Commission in Regulations of Medical Devices, specially contact lenses and their care solutions.

| | FDA | EU Commission |
|---|--|---|
| Market Approval via | 510(k) or PMA | CE Mark assessment. |
| Key Requirement | Safety and Efficacy | Safety and performance |
| Regulatory Acceptance by | CDRH/FDA Central Governmental Agency (Central Regulatory Authority) | Notified Bodies, (non-governmental) |
| Categorisation of Contact Lenses | <ul style="list-style-type: none"> • Daily-wear soft and rigid gas-permeable lenses – Class II (Moderate Risk) • Contact lens care products – Class II (Moderate Risk) • Extended-wear lenses – Class III (High Risk) | <ul style="list-style-type: none"> • Short-term corrective lenses – Class IIa (Medium Risk) • Long-term corrective lenses – Class IIb (Higher Risk) • Contact lens care products – Class IIb (Higher Risk) |
| Guidance | FDA 21 Code of Federal Regulations 800-1299 21 CFR 886.5916 21 CFR 886.5918 21 CFR 886.5925 21 CFR 886.5928 | EU Directives – Conformity to Essential Requirements MDD 93/42/EEC as amended (now, MDR and IVDR) EU Regulation 2017/745 |
| Checks | PMA: preapproval inspection and postapproval inspections. Post 510(k) clearance - FDA inspection. Design control Manufacturing control | CE marking requires at least 2 preapproval audits: product technical file audit and quality management system audit |
| Contact outside Country | Outside of USA, FDA requires 'US Agent' if importing medical devices into US | Outside EU, contract 'Authorised representative' |
| Quality | 21 CFR 820 | QMS compliant with ISO13485 |
| Documentation | Summary of safety and effectiveness Device identification and class Indications and Contraindications Warnings and precaution Alternative practices and procedures Technological characteristics | Technical file Device description Design and manufacturing information General safety and performance requirements Benefit risk analysis and risk management Product verification and validation |

| | | |
|---------------------------|--|---|
| | Non clinical test Clinical tests | |
| Biocompatibility | FDA Guideline, 2016: Device master file for biocompatibility evaluations | ISO 10993-1, "Biological evaluation of medical devices Biological safety report |
| Pre-Clinical Tests | Cytotoxicity Ocular irritation Acute systemic toxicity Sensitization Leachables Physical/optical Stability Compatibility with lens care tests Preservative interaction Bioburden Shelf life Sterilization | |
| Clinical Studies | Clinical Investigation and/or Clinical Evaluation | |
| Standards | EN ISO, ANSI | EN ISO |

*FDA (Food and Drug Administration), federal agency of United States of America Department of Health and Human Services

*EU (European Union) Commission - politically independent commission involved in European legislation

*PMA (pre-market approval) in FDA to show safety and effectiveness of class III medical devices.

*CE Mark (Conformité Européenne): European Conformity mark indicating conformity with health and other key standards in the European Economic Area

*CDRH (Center for Devices and Radiological Health) promote and protect health in the FDA

*ANSI (American National Standards Institute) is the member body to ISO based in the USA.

*CFR (Code of Federal Regulations) – codification of permanent rules by Federal Government of USA

*MDD (Medical Device Directive) for the safety and performance of medical devices in the EU

*ISO (International Organization for Standardization) – create and publish international standards

4. Clinical studies (trials and investigations) for contact lenses and care solutions

It is important to differentiate between a clinical trial and a clinical investigation. A randomized controlled clinical trial (RCT) can be defined as a prospective study on humans to test the safety and/or effectiveness of an interventional treatment. Methodologically sound trials assess patient safety and efficacy of: medicinal

compounds, surgical interventions, nutritional supplements, behavioural and exercise interventions. However, clinical studies involving medical devices are referred to as 'clinical investigations' (CI). While clinical trials and clinical investigations do share some similar characteristics (**table 3**), **table 4** shows some differences.

One aspect, as per table 4, crucial to an RCT to minimize subjectivity bias but not always possible in medical device clinical investigations, is that of blinding. Clinical investigations may see blinding when it comes to the assessment of outcomes [27]. This involves data managers, independent data monitoring committee members and statisticians being blinded to the patient data and not knowing whether it belongs to treatment or control group - similar to a clinical trial, with a key difference of the difficulty blinding the healthcare professional (e.g. clinician implanting the device) and the patient being aware of the intervention. Another key characteristic of RCTs not present in clinical investigations includes that of randomization and control groups, as briefly noted in table 3. It would be considered highly unethical to 'randomize' or leave up to chance the assigning of a sham device (in lieu of a placebo in drug trials) to a patient. This would involve exposing patients to unnecessary invasive procedures to insert the medical device. This point is covered in more detail elsewhere by other authors (Neugebauer et al., 2017).

Contact lens clinical investigations are often designed as 'clinical outcome studies'. In terms of a comparator, control lenses are provided to be tested against the test lens. Certain observations and outcomes that are assessed in these investigations include: best-corrected visual acuity, slit lamp analysis and, keratometry/topographic analysis, corneal thickness evaluation (pachymetry), wearing time and subjective symptoms [28].

In the clinical investigation, defined as a study conducted on human subjects to assess the safety and/or efficacy of a medical device, the aim is not only to establish the safety and performance of the device being investigated, but also to assess whether it is suitable for its intended use and targeted population. The EC MEDDEV 2.7/4 (Guidelines on Clinical Investigation: A Guide for Manufacturers and Notified Bodies, 2010) emphasizes the importance of properly conducted clinical investigations, their compliance to their clinical investigation plan (CIP) and adherence to national laws and regulations, to protect subjects and ensure the integrity of the data [29]. In line with EU regulations, the data that is obtained is required to be acceptable to demonstrate conformity to the Essential Requirements. Clinical investigations, must be conducted in adherence with Good Clinical Practice (GCP), where EN ISO 14155 is the standard for the GCP of medical device clinical investigations (see ISO 11980:2012 below for more detailed guidance on CI of contact lenses) [30]. It also goes without saying that as with any clinical study, a trial or an investigation, "the rights, safety, and well-being of clinical investigation subjects shall be protected, consistent with the ethical principles laid down in the Declaration of Helsinki" [31].

In its aim for 'global harmonization', ISO released standard 11980:2012 - a guidance for clinical investigations of the safety and performance of contact lenses and lens care products [30]. Despite its international recognition, uniformity proves challenging, where national regulations and legal requirements takes precedence over international guidance, such as the ISO standards. Elements central for the rigor of reporting CI includes: study design, duration and size, variables, statistical considerations for extended wear evaluations, adverse events/effects, evaluation of visual, refractive and lens performance and subject acceptance, lens fitting characteristics and lens surface characteristics. ISO

11980:2012 also discusses special indications for CI of contact lenses in paediatrics, inclusion/exclusion criteria of patients recruited to the CI, the need for a statistical analysis plan, monitoring procedures for the collecting and recording of data, details of controls (e.g. historical)/comparator, information in the case of an uncontrolled study and the contents of the clinical research plan [30].

Table 3: Characteristics of Clinical Trials and Clinical Investigations

| | Clinical Trial | Clinical Investigation |
|--|-----------------------|-------------------------------|
| Requiring 'favourable opinion' from a relevant ethics committee | ✓ | ✓ |
| Conducted under Declaration of Helsinki ethical guidance | ✓ | ✓ |
| Appropriate insurance and clinical indemnity schemes required at each study site | ✓ | ✓ |
| Request for investigators to have relevant training, qualifications and experience to conduct study (ICH GCP E6 /ISO 14155/ISO 11980) | ✓ | ✓ |
| Protocol/Investigation Plan | ✓ | ✓ |
| Informed Participant Consent | ✓ | ✓ |
| Randomisation | ✓ | x* |
| Blinding | ✓ | x |
| Comparator Group | ✓ | ✓** |
| Sample Size Calculation | ✓ | ✓ |
| Risk Analysis | ✓*** | ✓ |
| Inclusion/Exclusion Criteria | ✓ | ✓ |
| Follow up schedule | ✓ | ✓ |
| Clinical endpoints | ✓ | ✓ |
| Reporting of Adverse Events (Vigilance) | ✓ | ✓ |
| Adherence to Data Protection Acts and GDPR | ✓ | ✓ |
| Register on Trial Registries | ✓ | ✓ |
| Post-marketing Surveillance | ✓ | ✓ |

*randomisation in medical device clinical investigations have proven to be a challenge but approaches to randomising in these studies do exist

**while clinical trials often see a placebo as a control, it would be unethical for medical device studies to use a 'sham' device and so often the comparator can be other approved devices

***interventional clinical trials are required, under the revised ICH GCP E6 guidelines to take a more 'risk-based approach' to monitoring. Monitoring for contact lens clinical investigations on the other hand, are part of the safety analysis and looks out for adverse events such as corneal ulcers, inflammation of the iris, central and peripheral infiltrates, conjunctivitis and abrasions, amongst many others (Lippman, 2012).

Table 4: Differences between Clinical Trials and Clinical Investigations

| | Clinical Trial | Clinical Investigation |
|-------------------------------|--|--|
| Participants | Early phase trials often see healthy volunteers being randomised. Late phase trials are more likely to test the intervention on patients | Due to the invasive nature of some clinical investigations, they are only carried out on patients of the condition in question, where it will be of some benefit investigating it in the targeted population |
| Prior Approval | A study can be known as a trial if it is investigating a new drug compound or an existing drug compound for a new use/new dosage, different than that already with marketing authorisation | Devices that already have CE marking should not undergo clinical investigation, unless the investigation is for a different purpose than that intended |
| Sponsors | Sponsors of a trial can vary, from academic institutions to private pharmaceutical companies | Manufacturers (or an authorised representative if not in the same country) of the device generally act as the sponsor of the investigation |
| Number of Participants | Some phase 3 drug trials can see up to thousands of patients from different sites | Total number of participants to demonstrate safety and effectiveness may only be a few hundred |

5. Clinical evaluations of contact lenses and care solutions

Another way to achieve the CE mark (EU) for contact lenses and their care solutions, without a complete clinical investigation, is to perform a clinical evaluation. It can be defined as a "methodologically sound, ongoing procedure to collect, appraise and analyse clinical data" of a given medical device, as a means of evaluating whether there is

adequate clinical evidence to demonstrate compliance of that device with the Essential Requirements (EC MEDDEV 2.7/1, Clinical Evaluation: A Guide for Manufacturers and Notified Bodies) [32]. **Figure 2.** In the MEDDEV 2.7/1 Revision 4, clinical investigations or completed studies of similar devices (demonstrating equivalence to the device in question) published in the scientific literature are described under the “clinical data” category and therefore imply they can be used as a source to retrieve data on a device in question. This has its origin from Article 1.2.k MDD and Article 1.2.k AIMDD.

Clinical evaluations therefore may include clinical data such as those retrieved from a literature search, previous clinical investigations, clinical experience or relevant clinical data from equivalent devices (EC MEDDEV 2.7.1) [32]. Clinical evaluations also serve the purpose of seeing which clinical data remains to be delivered, i.e. a gap only to be filled by a full clinical investigation. Some clinical evaluations however may see scientific reviews of the literature as sufficient to demonstrate both safety and efficacy of a medical device, equivalent to one registered on the market. The goal however, of all clinical evaluations is to create a benefit/risk profile for the product under investigation. These profiles request the nature of the risks, their probability, extent, duration and frequency to be included [32]. Manufacturers are responsible for ensuring that the profiles and reports produced by clinical evaluations are based on current knowledge in the field. It is important to note that manufacturers of medical devices have a post-marketing surveillance (PMS) system in place to monitor the clinical performance and safety of their device (discussed further below). This involves retrieving new clinical data as a means of keeping up-to-date on novel and incoming data, that can be sourced from the published scientific literature, safety reports or registries [29]. The authors here therefore emphasise the importance of collating new clinical evidence for an objective and holistic

understanding of both performance and safety of medical devices, under a quality management perspective. Aspects that should be taken into consideration when searching the clinical literature, such as search strategies in relevant scientific literature databases, literature search protocols and forming literature search reports, are provided in MEDDEV 2.7/1 Revision 4 with further recommendations for the evaluation of clinical and scientific literature in the context of clinical evaluations.

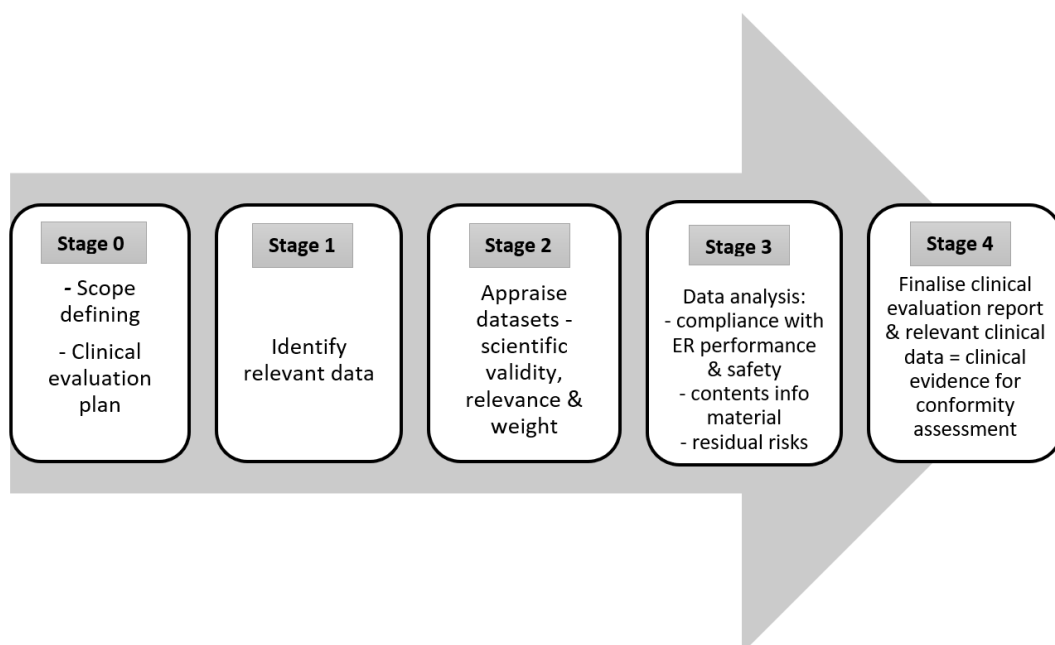


Fig. 2: Stages of Clinical Evaluation under EU Commission (adapted from MEDDEV 2.7/1. V4)

6. Post-marketing surveillance (PMS)

Regulators could request certain information on medical devices, including: effects on human and animal tissue, potential for toxicity, microbiological and sterility aspects - but this may be considered a 'provisional review' alongside chemistry and manufacturing information of the contact lens before the approval [33]. A more in-depth review however,

of these aspects is postponed until the marketing authorization submission has been filed [9, 33]. This therefore stresses the importance of continuation evaluations, studies and retrieving of information related to the device in question. Manufacturers are granted approval on the basis of conducting such post-approval studies (or 'post-marketing surveillance') as a means of collecting further data with regards to the safety and performance of the device. These studies monitor "patient experiences" [33, 34] to allow for a more holistic representation of the risks of a device. These data are then collated and synthesized to ensure only the relevant and important information can be added to the product's label.

Post-marketing surveillances are mandated by the FDA, for reasons mentioned above - one of which is the assessment of the risk of microbial keratitis in lenses such as the 30-night continuous wear silicone hydrogel [35]. The FDA may also request what is known as a 522 Post market surveillance study once a product has received approval. This is usually a result of emerging safety questions from the "clinical community" [35]. Chalmers and Gleason [35] discuss the importance of eye care practitioners to report adverse events associated with contact lenses and their associated care products. These "surveillance systems" are crucial to protect future contact lens wearers and such adverse events systems are further discussed by the other authors [35]. Oftentimes, the elements of risk discovered in post approval studies are not similar to those gathered in the preapproval studies [35]. One advantage here however, is the ability to compare the performance of the various products that are not investigated in future trials. Post approval studies allow for pragmatically investigating 'real-world' data – where assessments are made based on larger populations for whom contact lenses were intended. The independence of PMS studies is noted [35], where the funding originates with the

manufacturers of the lenses and lens products, but independent scientists conduct the study, presumably for a fair and unbiased assessment.

In the push for transparency, the European Databank on Medical Devices ('EUDAMED') and the relevant Council contain extensive requirements for uploading clinical data on marketed devices into EUDAMED. A Communication from the Commission to the European Parliament regarding Council adoption of the medical device regulation briefly discusses the requirements for a PMS system from the manufacturer and a PMS plan. The guidance document discusses a PMS report for low-risk devices, where conclusions are made based on the post-approval data analysis and a periodic safety update report for higher-risk devices [5]. Equally important to these PMS studies, are the post-marketing clinical follow-up (PMCF) studies, a requirement under the medical device directives. Similar to the EUDAMED, the FDA also maintains a database with general information regarding PMS studies, which include the status of plans and reports.

In terms of timing, the EU Commission guidance states clinical evaluations should be updated when the manufacturer is in receipt of new information from PMS studies that could change the existing evaluation. If, however this information is not received, the manufacturers are advised by the regulators to conduct an annual evaluation to identify any risks, or if the full extent of its risks are not yet known, or, between every 2 to 5 years if no significant risks are anticipated [32]. Guidance from the EU also mentions "surveillance audits".

7. Risk management

The risks associated with the use of contact lenses and their respected solutions are widely emphasized in both published journal articles and international standards. Methodologically rigorous investigations and evaluations to determine their safety and efficacy is therefore crucial. It is important to understand that the objective of both the FDA and EU Commission is to ensure a reasonable safety and efficacy profile of drugs and devices even after they have received marketing approval. Regulatory oversight necessitates, in most cases, drugs and medical devices to undergo pre/non-clinical testing prior to being exposed to human subjects in clinical trials/investigations. The aim of this is to, as mentioned, assess the efficacy and safety of the product through understanding its manufacturing, physical and chemical characteristics but also its toxicological and microbiological profiles. Regulatory oversight of contact lenses, and their solutions request they be sold in a sterile condition, until opened by the person using it. The aim of sterility testing is therefore the elimination of microorganism populations. Alongside this, is the requirement for stability testing and shelf-life dating. Manufacturers also have a responsibility to ensure the shelf-life date presents the extent at which such sterility and the chemical integrity are maintained, until it is opened immediately prior to use. Materials and solutions used for contact lenses and their products undergo testing of their chemical composition, in terms of irritation or being sensitive to ocular tissues [36]. Lens polymers, additives and solutions are therefore evaluated in a laboratory setting prior to exposure in a clinical setting. Regulations, including ISO standards discussed above, in the field of pre-clinical testing include the Draize test, investigating ocular irritation in rabbits through slit lamp biomicroscopy and histology, Agar Diffusion or MTT assay to test for cytotoxicity and a systemic toxicity test. Table 5 [28, 37]. Ensuring these regulations are met leaves the manufacturers, healthcare professionals, patients and the consumers of these products with reassurance that the products are safe and efficacious.

Abiding by regulations, national laws and international guidance, substantially reduces the risk of sight-threatening complications.

In terms of physical biocompatibility and combining both FDA and EU Commissions perspectives, aspects such as lens diameter, base curve, power and other similar physical measurements are looked out for to ensure such parameters are not changed by solutions for use with all kind of contact lenses (hydrophilic, silicone hydrogel and gas permeable contact lenses). This ensures the efficacy is not compromised.

Table 5: Pre-Clinical Trials for medical devices approval. Descriptions, goals and expected outcomes

| Test | Description | Goal | Expected outcomes |
|------------------------|---|---|---|
| Citotoxicity | <ul style="list-style-type: none"> - In vitro experiment. MTT (3-(4,5-Dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide) test is used to assess cellular viability - Fresh MTT solution (0.5 mg/ml) is added to cells culture with sample to assay and incubated for 2 h at 37°C. The cells are then lysed, and purple formazan dissolved using dimethyl sulfoxide. Absorbance was measured | To evaluate the cells viability though their metabolic activity after the sample contact. | Cells viability must be more than 70%, compared with control for considering the device non-citotoxic. |
| Ocular irritation | <ul style="list-style-type: none"> - Draize test. Adult white rabbits are used (n=3). - To instil sample to assay in one eye; contralateral as control. - To evaluate cornea, conjunctiva and iris 24, 48 and 72 hours after instillation. | To evaluate the potential ocular irritation provoked by the contact lens or the care solution | <p>No differences between both eyes (assay and control).</p> <p>Severe reaction in only one animal is considered as ocular irritant material.</p> |
| Systemic Sensitization | <ul style="list-style-type: none"> - Animal model experiment. Guinea pigs (n=15). Ten animals for study group and five for control. - Intradermic injections or patch with sample extract is | To grade or rank chemical constituents on a scale of I through V as to their potential for inducing | The grades of rankings are based on the number of animals sensitized, and from grade I grade V. |

| | | | |
|--|---|---|---|
| | applied in the animal skin for 15 days. - Erythema is assessed | sensitivity response in the guinea pig model. | It is expected no differences between both animal groups (assay and control). |
|--|---|---|---|

8. Challenges in the Regulatory Field

There is a tight balancing act between the regulation of safe and effective medical devices and timely innovations in the field. The hurdles to achieve regulatory approval of a medical device, namely contact lenses in this context, include ones of an administrative and financial nature. The long timelines and added costs associated with achieving contact lens or their care solutions approval means companies are slow to invest. A recent report by Stanford University discusses the average time for companies speaking with the FDA regarding conducting a low-to-moderate risk medical device clinical study was 31 months, for the premarket process' initial communication to clearance for marketing the device [38]. Respondents of this survey reported an average of 7 months in Europe, from initial communication to market, of the same or equivalent device – a significant difference between the two administrations [38].

In terms of costing, it appears that approximately 77% of the total cost to bring a low-to-moderate risk product under the 510(k) processes from concept through to clearance, goes towards regulatory activities, under the FDA [38]. The Stanford University report shows some staggering figures, emphasizing the initial financial burden to bring a product through the development pipeline, which leads to a separate point about the rising costs of innovative and methodologically rigorous research and development. This is unfortunate news for medical technology start-up companies, with the report stating less

than 25% of those in a "venture-backed industry" succeed [38]. The authors of the report discuss the "device lag" that patients must face and the waiting game for devices to get marketing approval, a result of untimely and inefficient regulatory oversight [38]. This creates a clear divide in terms of gaining approvals in separate countries, where the report's respondents found EU approval to be timelier than the US. It is not evident however, whether these time lags from the regulators contribute to the assurance of patient and public safety and may in fact be perceived as a burden to companies and not to mention the unnecessary delay to patients receiving their treatment/product.

9. Differences between FDA and EU regulations

While regulatory oversight in the USA is through the one administration, the European Commission sees more of a challenge, having 28 Member States (see glossary). The EC aimed to merge regulations to "harmonize inter-state commercial interests while preserving national 'autonomy'" [10, 36]. It is worth mentioning that alongside the FDA, is the Federal Trade Commission participating in the regulation of contact lenses in the USA. Their primary objective is to enforce the US' 'Contact Lens Rule' which sees contact lenses only being sold accompanied with a valid prescription. In the interest of patient safety, illegal sales of non-verified contact lenses are to be reported to the Federal Trade Commission.

It is also important to note that the medical device field is preparing for the application of the new In Vitro Diagnostic Regulation (IVDR) in 2022 and Medical Device Regulation (MDR) in 2020, where regulatory oversight of contact lenses will fall under the latter. Officially published in 2017, the new regulations aim to modernize the existing regulatory system in areas such as clarity on data requirements, firmer pre-marketing surveillance

requirements for devices in a higher-risk classification and more prescriptive requirements in the processes undertaken by Member States' Notified Bodies. The new MDR also sees an improved system in place for the co-ordination and consistent performance of Member States when it comes to vigilance and reporting for patient safety [39]. The call for more transparent and stricter reporting has also been advocated for in the new MDR as well as hopes for a more innovative approach in the sector [40].

Furthermore, a key similarity between both the FDA and EU Commissions is the categorization of contact lenses into classes according to risk, with the higher risk classes undergoing firmer conformity assessment procedures (EU) for marketing approval. Marketing approval of devices in the USA are conducted entirely by a governmental administration (i.e. FDA) while the EU sees the use of companies (i.e. Notified Bodies) under the supervision of the government. One could perceive this as an issue in terms of conflicts of interest, but it is important to remember that they are both independent and have no financial stake in terms of the success of the device and patient safety is priority.

While the creation of a harmonized international regulation for both USA and Europe would be challenging, there are potential solutions to ensure uniformity in certain aspects of the safety and efficacy of devices. Examples of where uniformity of device approval may be made easier is where, the CE marking for European devices acts as a legal stamp for authorization, whereas no such approval stamp exists within the FDA for medical devices (not including Federal Communications Commission (FCC) marks for FDA approved electrical appliances). Furthermore, significant differences in time lags between EU and FDA approvals means manufacturers may prefer going through the EU route to get their devices on the market faster. However, if there was a centralized system for

approvals, patients in both continents could have access to their device in similar time periods.

The MEDDEV guidelines aims to harmonize the interpretations of medical device legislations within the EU Commission and its requirements. One important aspect to note however is that MEDDEV guidance is not legally binding. Therefore, one other challenge in the discussion of standardizing FDA and EU regulations is that of the difficulty merging national and international legal requirements, since they vary greatly per country.

Under the new MDR, Notified Bodies will be required to apply for new designations and plan for demonstration of compliance to meet the expectation of the European Commission Medical Device Coordination Group (MDCG). There is estimated to be little over 83 Notified Bodies under the current system. The new regulations will see Notified Bodies undergoing more audits, by their local Competent Authorities and by a Competent Authority from another Member State, adding to existing pressures. It is predicted that the new MDR brings with it the need for additional employee training in Notified Bodies to meet these stricter requirements and so has an increased burden in terms of investment of resource [38]. There is now a greater emphasis on Notified Bodies, in their reviews, to ensure manufacturers of devices are fully compliant in all aspects of the regulations, including, their support by sufficient data and technical documentation. One drawback however to having multiple Notified Bodies within the European Commission is that each interprets the regulation differently, given the context and nature of their local governing laws. This presents a challenge in terms of uniformity, but the new MDR is hoped to shed

light on this to somewhat standardize the approach Notified Bodies take in their communication with manufacturers.

The new MDR brings with it firmer guidance with regards to reporting, in the current era of transparency. As it stands, the FDA may request further information from device manufacturers if it is felt needed for the protection of public health. Manufacturers worldwide therefore have a responsibility to report to the regulators whether a marketed device has caused or contributed to injury of any kind and/or death. For this reason, therefore exists the PMS studies, often a condition when a device is approved in the US. In the European Medical Device Directive, manufacturers are called to be up-to-date with reviews on their devices and to have the necessary procedures in place when it comes to “corrective actions”, including for example: device recalls, modification to devices in use or their labelling. PMS studies in the EU rely on information from devices retrieved in the form of complaints, published literature, surveys to customers/patients and of course through the clinical evaluations discussed above. Manufacturers are required to be responsible for notifying authorities and being aware of the vigilance systems in place. In the EU, there is no legal requirement for users of products to report incidents to manufacturers or Competent Authorities. However, in the interest of promoting public health and safety, health care professionals have a moral obligation to report. Referring to the international ISO standards, number 13485, requirements are in place for manufacturers to have a quality management system [41].

10. Contact Lenses and care solution in China (CFDA regulation)

It is important to make a reference to a new emerging market as China, who has an own medical device regulation, regulated by China Food and Drug Administration (CFDA).

In 2014, it was revised and updated the medical devices regulation in China, introducing important changes. The regulation was simplified for low risk medical devices (class I) and harder for class II and III medical devices, where contact lenses and their care solutions are included. Currently, manufacturers need to provide more clinical and technical information to obtain the CFDA approval [42].

For contact lens or care solutions distribution or manufacturing in China, manufacturers should register their medical devices, following the instructions of CFDA. As class II or III (depending of the level of risk), contact lenses and care solution require to be approved by their country of origin administration. For US devices approved by FDA and European devices with CE mark. Moreover, it is mandatory to appoint a native representative in China for communication with CFDA. This point is critical due to the language difficult and cultural differences between China and US and European countries. In most of cases, the successful registration depends of the correct representative selection.

An important difference between CFDA and FDA or CE is the pre-clinical test performing. CFDA requires to perform the trials by authorized test laboratories in China. At this moment, there are 22 authorized medical device evaluation centers in China to carry out the tests required by CFDA. Together in-country medical devices test, CFDA will require a clinical evaluation report (CER), that must contain data from either scientific literature and/or clinical trial. The CER should be unique and contains a comprehensive comparison to an equivalent device already in the China market. In addition, clinical data used for the medical device approval in the manufacturer's country could be used, but if the clinical trials have been conducted outside China, it must be

demonstrated that ethnic differences do not affect the safety and efficacy of the device during its used by Chinese population [42].

In some cases, when equivalence with other device currently approved in China has not been demonstrated or the medical device data from scientific literature or clinical trial performed in the country of origin is not considered enough by the expert panel meeting of CFDA, a clinical trial in China will be required [43]. In 2018, CFDA have published a recent clinical guideline on RGP lenses, mainly orthokeratology lenses, and another on soft contact lenses and facilitate their respected clinical trials [44].

For orthokeratology lenses, the CFDA clinical guidelines takes in account the FDA guidance for premarket submissions of orthokeratology rigid gas permeable contact lens. Curiously, the aim of the clinical trial does not include the myopia control efficacy.

The clinical trial for orthokeratology lenses should enrol more than 200 patients during at least 1 year of follow up in two different clinical sites, performing a comparison with a device approved in China. Nevertheless, for soft contact lenses, the recruitment could be less, 120 patients, and the follow up time no less than 3 months.

In conclusion, to register medical devices as contact lenses or care solutions in China is an important regulatory challenge. Foreign manufacturers should be aware that the process could be long and complicated, mainly due to the language and cultural differences.

11. Regulatory Challenges for Novel Therapeutic Uses of Contact Lenses

The rate of myopia incidence in young people is growing faster than ever and presents an unmet clinical need along with heightened costs [45, 46]. Myopia brings with it the potential for added complications of an ocular nature. Spectacles with a bifocal or progressive lens have been suggested to reduce the progression of myopia [8, 47]. A recent review [47] discusses the research advancements being made to slow the progression of myopia in children and the ineffectiveness of methods such as alignment fit gas-permeable lenses and bifocal or multifocal spectacles. Walline sheds light on the positive effects of orthokeratology and soft bifocal contact lenses but also of antimuscarinic agents, such as pirenzepine and atropine, whose clinical trial findings appear to reduce the progression of myopia but are not without their side effects [43]. Now, however, there is increasing interest in the use of contact lenses for the control of myopia but brings with it added challenges in the regulatory field [48-52]. These include orthokeratology lenses, soft multifocal lenses and soft daily lens, as per the Cooper Vision website, who to the authors' understanding, have the only EU CE approval marked contact lens for a myopia control indication (MiSight®). It is mandatory to regulate the approval of this kind of lenses since their indications of myopia control require to measure specific parameters as axial length and during long-term wear (at least two years) [53].

An emerging field in the last decade or so, contact lenses have been investigated as a delivery system of pharmaceutical compounds into the eye [54, 55]. The use of medical devices, such as contact lenses, as ophthalmic drug delivery systems however raise a regulatory concern as to whether it should be regulated as a medical device, a drug or a combination of both [56]. If the product in question poses merely to deliver the product, then it should be regulated as a drug. If, however, the system is a device with an indication

(for instance, non-erodible implants such as Vitrasert, approved as a drug for cytomegalovirus retinitis and others [56]) it could be considered a combination product [56]. The research in this field is more advanced than regulation, provoking a strong gap in the regulations with regards to clarifying this emerging technology.

Despite there being primitive evidence, the argument for the use of contact lenses as a drug delivery is debatable, [56]. Discussion however also extends to the use of contact lenses not just as a drug delivery mechanism but also as a diagnostic tool. Contact lens sensors have the ability to analyse the glucose composition of tears and also to measure intraocular pressure in the diagnosis of glaucoma [57, 58]. The use of polymer synthesis, electronics and micro/nanofabrication in contact lens sensors to quantify biomolecule concentrations in ocular fluids is discussed elsewhere [57] but is an important point to be raised as an emerging field. Much like the other aspects of medical devices discussed, contact lens sensors too require compliance with the relevant governing regulations to obtain marketing approval. Classification of these contact lens sensors also depends on the performance of the sensors and their materials, where diagnostic lens sensors formed from PMMA (poly methyl methacrylate) fall under Class II of FDA criteria [57]. Furthermore, such contact lenses possess a strong capacity to detect biomarkers in ocular fluids thereby monitoring physiological parameters. As per all medical devices, it is crucial that such emerging technology adhere to requirements of pre-clinical testing prior to human exposure. Therefore, in-vivo and in-vitro tests with live rabbits and bovine eyeballs with these lens sensors are discussed elsewhere [59].

This review was an attempt to fill the gap in the literature of comparing FDA and EU contact lens regulations. No such research, to the authors' knowledge, has been

conducted. Bowden et al. do however raise awareness to the differing legal regulations in terms of the prescribing and sales of contact lenses between the UK and Germany. Furthermore, while scientific literature exists on the regulations of contact lenses, the authors believe these to be primarily focused on those from an FDA perspective [60]. There is a lack of published peer-reviewed articles or research on regulations in the European context, as per EU Commission regulations, particularly the new MDR and IVDR. This review therefore integrates the existing body of literature, whilst providing the authors' own views on the comparison of both administrations.

12. Conclusion

The key regulatory considerations regarding contact lens and care solutions development, approval and registration in the FDA and EU Commission are discussed. The new EU Medical Device Regulation due to replace the existing Directives sheds light on the importance of prioritizing safety and efficacy prior to achieving marketing approval, and on transparency of device information. Contact lens regulations are discussed in the context of key pre-clinical and clinical tests required for either CE mark (EU) or FDA approval (USA) with their associated lens care products. Registration and approval of contact lenses could be through a clinical evaluation (EU) of either pre-existing data of an equivalent product, or scientific literature, but mainly through a clinical investigation (both FDA and EU), with the key features of a clinical trial. It is important to pay attention in emerging therapies in the field of contact lens use, as a diagnostic tool and ocular drug delivery system, given their context and its benefits, is yet a regulatory challenge under the medical device regulations.

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