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REVIEW

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Regulatory perspectives on post-market evidence generation schemes for high-risk medical devices: a systematic review

Jesús Aranda [a], Agnieszka Dobrzynska [a], Maria Piedad Rosario-Lozano[a], Juan Carlos Rejón-Parrilla [a], David Epstein [b] and Juan Antonio Blasco-Amaro [a]

[a]Health Technology Assessment Area (AETSA), Andalusian Public Foundation Progress and Health (FPS), Seville, Spain; [b]Department of Applied Economics, Faculty of Economy and Business Sciences, University of Granada, Granada, Spain

ABSTRACT

Introduction: The new European Medical Device Regulation has raised the bar for the clinical evaluation of medical devices to gain marketing authorization by Notified Bodies (NBs) regarding certificates of conformity in Europe. Restrictions applied for High-risk medical devices (HRMD) may require further evidence generation. Some other jurisdictions apply similar schemes that may be useful to the European Union. This systematic review focused on extracting lessons from similar schemes worldwide to the European context.
Methods: A systematic review of peer-reviewed and gray literature was performed based on 'Device approval' and 'conditional approval' keywords. Databases such as Medline, Embase, and WoS retrieved documents assessed with the AMSTAR-2 checklist. A descriptive and narrative analysis was conducted detailed in CRD42023431233 – PROSPERO.
Results: We obtained eight documents where conditional approvals for High-risk medical devices in the United States of America, China, and Canada were subject to generate further evidence. In Europe, NBs impose restrictions or limitations to certificates of conformity instead.
Conclusion: Further development of policies, supporting access to HRMD subject to further evidence generation, would help Europe in further defining the appropriate situations for the application of determined regulatory routes, to enhance access to HRMD with promising evidence and further evidence development.
Registration: PROSPERO (CRD42023431233).

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High-risk medical devices; market approval; certificates of conformity; conditional approval; evidence generation; medical device legislation; European union regulation; health technology assessment

1. Introduction

The regulatory landscape for medical devices has historically been less stringent compared to the requirements applied to pharmaceuticals, with regard to their safety and surveillance [1]. A new Medical Device Regulation (MDR [2017/745]) has been introduced in the European Union (EU) to raise the bar for requirements for medical devices, at premarket testing, certification, and post-marketing surveillance [2]. In this context, the European Commission Horizon 2020 Program awarded a research grant to the Coordinating Research and Evidence for Medical Devices (CORE-MD) project (launched in April 2021) to strengthen the methodological and knowledge base supporting the implementation of the new regulation.

According to the World Health Organization (WHO), a medical device is defined as 'an article, instrument, apparatus or machine that is used in the prevention, diagnosis or treatment of illness or disease, or for detecting, measuring, restoring, correcting or modifying the structure or function of the body for some health purpose' [3]. These health products were regulated in the past by three Directives in the EU, as follows: The Active Implantable Medical Devices Directive (AIMDD, 90/385/EC) [4], the Medical Device Directive (MDD,93/42/EEC) [5] and European Directive (98/79/EC) [6]. Although these directives should have been transposed into EU individual members' regulations, the fast advance in new technologies development and their possible effects in individual patients' state of health aimed to standardize, as much as possible, the characteristics and assumptions related to the life-cycle of health technologies. Some of these measures have given place to relevant courses of action: The International Medical Device Regulators Forum, The Global Harmonization Task Force, or the EU MDR [2017/745] of the European Parliament and of the Council of 5 April 2017 on medical devices [2,7–9].

The authorization of a new medical device before entering the market corresponds to 'independent conformity' assessment organizations called NBs which issue Conformité Européenne (CE) marks [10]. The new MDR imposes more rigorous requirements on the evidence on quality, safety, and performance of the device required by NB both before and after market entry [11,12].

Regulatory decisions must sometimes be made in the face of limited or immature evidence. In such situations, some regulators, under very defined circumstances, allow for routes that entail the granting of a marketing authorization subject to the generation of additional evidence to mitigate the uncertainty associated with the evidence base at the point when the initial decision is made.

CONTACT Jesús Aranda jesus.aranda@juntadeandalucia.es Health Technology Assessment Area (AETSA), Andalusian Public Foundation Progress and Health (FPS), Seville, Spain

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Article highlights

- This article highlights the main considerations regarding the regulatory landscape for high-risk medical devices and their conditional requirements in order to be available into the main jurisdictions market from around the world, as well as providing a new approach to explore the diferent HTA bodies, regulations and jurisdictions considering the three international HTA organizations EUnetHTA, HTAi and INAHTA.

A very clear example of this can be found in the European regulation for medicines, where the European Medicines Agency (EMA) can grant a Conditional Approval to a medicine even on less comprehensive clinical data than normally required if: *(1) it addresses an unmet medical need; (2) the benefit-risk balance of the medicine is positive; (3) 'it is likely that the applicant will be able to provide comprehensive data post-authorisation'; (4) the benefit of the medicine's immediate availability to patients is greater than the risk inherent in the fact that additional data are still required.* [13,14]. However, a similar regulatory pathway for medical devices is not as well established in Europe. In situations where an innovative HRMD may offer a therapeutic option for patients with previously high unmet needs, but the available clinical evidence is not sufficient, or gives rise to serious concerns about the benefit/risk ratio (MDR Annex IX), the NB can allow market access for the device with particular restrictions or limitations (MDR, Annex VII) [10]. This allows prompt market access to address patients' unmet needs, while conducting the studies needed to fill evidence gaps. According to article 56 of the new MDR, entitled *Certificates of Conformity*, some restrictions and/or limitations can be imposed on a CE mark when granting it:

3) Notified bodies may impose restrictions to the intended purpose of a device to certain groups of patients or require manufacturers to undertake specific post-market clinical follow-up (PMCF) studies.

4) Where a notified body finds that the requirements of this Regulation are no longer met by the manufacturer, it shall, taking into account the principle of proportionality, suspend or withdraw the certificate issued or impose any restrictions on it unless compliance with such requirements is ensured by the appropriate deadline set by the notified body. The notified body shall give the reasons for its decision.

5) The notified body shall enter in the electronic system referred to in Article 57 any information regarding certificates issued, including amendments and supplements thereto, and regarding suspended, reinstated, withdrawn or refused certificates and restrictions imposed on certificates. Such information shall be accessible to the public.

Furthermore, Health Technology Assessment (HTA) bodies also evaluate safety and efficacy along with non-clinical dimensions of health technologies [15]. Despite our primary focus on regulatory aspects, it is important to acknowledge the significant impact of HTA activities in the broader context of medical device adoption and healthcare system integration. As Tarricone et al. (2014) described [16]: '*Although the objectives of regulators and HTA bodies are, and must, remain distinct, it is also true that HTA is becoming a formal barrier to be overcome in many jurisdictions before a device can be adopted and diffused within the healthcare system. Manufacturers often need to develop clinical evidence for HTA bodies instead of regulators (i.e. in some European countries) or conversely for regulators and not for HTA bodies (i.e. the U.S.A.).*' Hence although the main focus of the paper is on the post-market evidence requirements imposed by regulatory bodies, the review also summarizes the kinds of post-market evidence generation requirements often demanded by HTA bodies in the types of HTA schemes that recommend access subject to further evidence collection [17,18].

A particular challenge for medical device regulation in the EU single market has been to harmonize the system for collecting and publishing evidence. EUDAMED, once it becomes operational, is expected to promote transparency and oversight, while balancing the need for restricted data to remain confidential [9,19–21]. Manufacturers will be required to register the HRMD using a Unique Device Identifier [21] and NBs to publish the certificate and any restrictions. Manufacturers will use the system to publish clinical investigations, and any PMCF studies required by the NB, and report vigilance and post-market surveillance events [22–24], along with any corrective actions. A Market Surveillance module will facilitate coordination between competent authorities in the Member States. It is also hoped that the system will allow wider operational networking, for example, sharing data with the United States of America (U.S.A.), through the Food & Drug Agency from the United States of America (U.S. FDA), or other countries, like Argentina, through HELENA's platform [25]. Nevertheless, some issues regarding the data storing and management standardization processes are still in progress, for example, some individual regulatory bodies from each country input data in their local languages, making difficult this data retrieval procedure [26]. This context covers the kinds of post-marketing evidence-generation activities that are part of the standard regulatory procedures that the regulation of HRMD covers, and will not be the target of this review.

The aim of this review is to summarize how restrictions or limitations to certificates of conformity are applied in Europe and to extract lessons from similar schemes worldwide to the European context. In addition, this work provides a novel approach in the regulatory field by performing a mapping exercise between the regulatory bodies, HTA agencies/institutions, and their respective jurisdictions.

2. Methods

To fulfill this aim, we performed a systematic review of the literature in accordance with the pre-established protocol, which was registered and published on PROSPERO at the beginning of this study (See *CRD42023431233 - PROSPERO* [27]. This review was conducted according to the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [28], and it will be available on the CORE-MD website [27]. In addition, selection criteria were preestablished, as seen in section 2.1, in order to obtain data from different registers and databases, as seen in section 2.2, focusing on our PICO's question described by the following main keywords: 'medical device,' 'high risk,' 'device approval' and 'conditional approval;' These steps were performed by an information specialist through a search strategy, which

provided eight final documents. Data were synthesized and sorted as descriptive results in tables of evidence.

This review focused on how evidence development schemes have been established in order to assess the post-market lifecycle stage of HRMD. According to this, we proposed the following PICO's question:

Population: HRMD (Class IIb and Class III medical devices, according to the MDR-Article 51-Classification of devices [2]).

Intervention: Different types of post-approval/post-market development schemes for HRMD in different regulatory jurisdictions.

Comparator: Given the focus of the study, it was not considered.

Outcome: Report on conditions/requirements for conformity assessments that lead to further evidence generation and post-market surveillance for HRMD in different countries.

2.1. Search strategy & data sources

According to the search strategy and Covidence PRISMA flow diagram (See Figure 1), the scientific literature was retrieved from the following databases: Medline (Ovid), Excerpta Medica DataBase (Embase), Cochrane Library (Cochrane Review Database), International HTA Database (INAHTA), and SCI Science Citation Index (WOS).

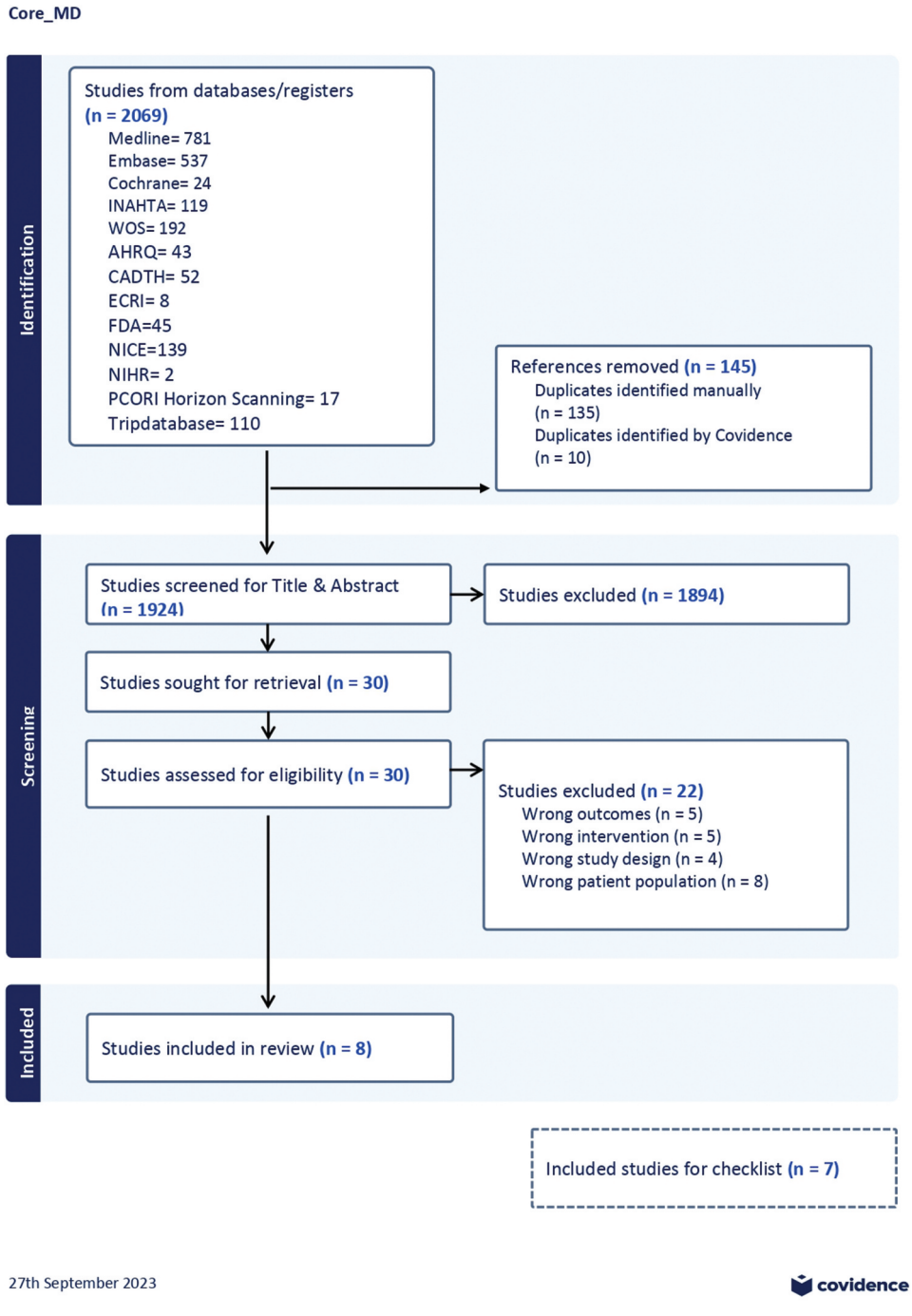

Figure 1. PRISMA flowchart from selected studies and other sources. Source Covidence.

In addition, we explored other relevant sources including international and national regulatory institutions and HTA agencies: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Agency for Healthcare Research and Quality (AHRQ), European Credit Research Institute (ECRI), U.S. FDA, National Institute for Health and Care Research (NIHR), the Patient-Centered Outcomes Research Institute (PCORI´s) Horizon Scanning Database, Trip Medical Database.

The following descriptors and keywords were employed adapting the initial strategy to the syntax of each database: medical devices, prostheses, health technology, device approval, evidence generation, condition approval, and conformity certificate (see in detail in *Supplementary Material: Search Strategies*). These searches were restricted by study type to systematic reviews and meta-analyses.

Given the impact of HTA activities on life cycle evidence generation we also considered documentation of organizations belonging to the European network for HTA and to the INAHTA, and the website of the HTA International (See *Supplementary table S1*).

Data extracted from key documents was depicted in Tables 1 and 2 (Detailed information in *Supplementary table S2*).

2.2. Eligibility criteria & quality assessment

A search strategy was developed (See *Supplementary Material: Search strategies*) according to the following selection criteria:

Inclusion criteria: 1) HRMD – class III and implantable; 2) MDR – Article 51 – Classification of devices [2]; 3) Post-market evidence development schemes established by medical device regulatory authorities; 4) Regulation state; 5) Conditional approval/certificate of conformity/Restrictions or limitations; 6) Adverse event reporting schemes.

Exclusion criteria: 1) Non-human studies; 2) Pre-market evidence schemes; 3) HTA reports unless its content included Conditional approval/certificate of conformity/Restrictions or limitations of HRMD, like Coverage with Evidence Development, related issues; 4) Regulatory bodies from countries which do not consider HRMD.

Two researchers (JA & AD) carried out screening by title and abstract, the reviewers compared results and resolved any disagreements through dialogue. In case of discrepancies, a third reviewer intervened to resolve any disagreement. Zotero was employed as a bibliographical reference manager [34]. Publication bias was considered.

An information specialist was responsible for formulating and executing the search strategy. AMSTAR-2 was employed as a quality assessment tool for documents retrieved despite the lack of a comparator, given the focus of the study, and the feasible heterogeneity in the structure of these reviews [35]. The quality assessment considered items as a preestablished and published protocol, the presence of a comprehensive literature search strategy, study selection, and data extraction in duplicate (See further details in *Supplementary Table S3. AMSTAR-2 Checklist* and *5PRISMA-2020-Checklist*).

The extracted results were collected in evidence tables; a descriptive and narrative analysis were conducted, and a qualitative synthesis of the results, based on the main outcome measures, was structured in order to create data tables and figures.

The timeframe for our search was from 1st January to 27 September 2023. Neither language nor date restrictions were established.

3. Results

2069 studies were found (See Figure 1). 30 studies were selected for full-text screening, and 7 [16,18,29–33] of them were selected for further analysis. In addition, one report was included from the FDA [36]. These data were synthesized and structured in tables as depicted in Tables 1 and 2.

Out of seven studies that fulfilled the inclusion criteria, five were systematic reviews and two HTA reports (addressing issues related to conditional approval/certificate of conformity/Restrictions or limitations of HRMD). The included studies were published between 2009 and 2021. The authors provided information regarding the following countries or jurisdictions: EU (The Netherlands, Germany, France, Belgium, Spain, Finland, Denmark, Italy, Latvia, Portugal, and United Kingdom (UK)), U.S.A., Australia, Canada, China, Japan, Brazil, Argentina, Colombia, Brazil, and Mexico (See Table 1).

With regard to post-marketing surveillance and vigilance efforts, several regulatory bodies were identified that implement conditional approval mechanisms for medical devices. Standard regulatory post-marketing regulatory requirements, such as reporting of safety events as part of surveillance monitoring, are outside of the scope of our study. However, to provide a fuller picture of the different kinds of evidence collected after marketing authorization, we extracted information about how different jurisdictions structure surveillance activities regarding adverse event reporting or vigilance reporting that relied on manufacturers, clinicians, and patients to report incidents in the following countries or jurisdictions: EU, U.S.A., Canada, Australia, China, Japan, and Brazil.

In order to summarize the heterogeneous scope of the jurisdictions observed regarding the approval process of HRMD, and their considerations, in the case given, for their respective conditional schemes, we provided a schematic representation of the different relevant pathways in Figure 2-*Approval/Certification/Licensing process and conditional market entry for HRMDs*.

In this picture, we can observe how the process to provide a certificate/license/approval [2,37,38] varies in these six jurisdictions, like the Conformity assessment [2] in the EU, and the Medical Device Registration in China [38]. In addition, we observed how the EU, China, and Australia [2,38,39] considered a determined terminology for those approval names subject to conditions or requirements, while other jurisdictions (U.S.A., Canada, and Japan) had to consider them as a usual approval [40–42]. Furthermore, Figure 2 also provides the different access management tools through the jurisdictions to apply for the market entry of a HRMD, which were mainly focused on contexts of uncertainty and/or high unmet needs [2,42–48].

Table 1. Description of included studies.

Study	Articles retrieved	Databases & Search's Timeline	Aims & main findings	Countries or Jurisdictions -Nr-
Tarricone et al. 2014 [16]	Empirical articles and commentaries describing or discussing the regulatory framework for medical devices and the need for integration between existing regulatory, coverage, and HTA processes. 50 Final studies included: – 30 full-text articles/studies screened. – 20 editorial/Commentary search (n: BMJ = 12 & NEJM = 8).	• Pubmed • Ovid MEDLINE • EMBASE • EconLit • British Medical Journal • NEJM 2000-2014	They focused on Regulatory Authorization & Post-Marketing Surveillance by identifying documents prescribing the processes for Pre-Market Approval and Post-Market Vigilance of medical devices.	USA EU Australia Canada China Japan Brazil –7–
Reckers-Droog et al. 2020 [18]	CED schemes for Medical Devices (MDs). 27 final studies included: 6 reported on challenges with CED schemes in the specific context of MDs. 21 on challenges with CED schemes in the context of different types of health technologies, including MDs.	• WoS • Pubmed (National Library of Medicine) • Embase • Scopus • Google • Google Scholar *in September 2018 & in January 2019	They focused on HTA or Price & Reimbursement schemes to mitigate uncertainty after adoption in national health systems in order to identify and describe the challenges that payers and manufacturers might face when assessing the desirability of, choosing the research design for, implementing, and evaluating CED schemes for MDs.	USA EU (The Netherlands, Germany, France, Belgium, Spain) Australia Canada –4 (8)–
Rey-Ares et al. 2016 [29]	Requirements for medical devices licensing and reimbursement in four Latin-American countries. One specific device was selected to describe its regulatory and coverage trajectory. 74 final studies included: 12 studies from databases. 62 publications from other sources.	• Pubmed • Lilacs • ISPOR Digest • Value in Health Regional Issues Journal • MoHs, HTA, regulatory and Health agencies specific websites (Other sources) • No date restrictions until February 2015	They focused on Regulatory Authorization & Post-Marketing Surveillance by assessing, describing, and comparing the requirements and pathways from licensing to coverage of the decision-making process used for medical devices in comparison to drugs in the Health systems of Argentina, Brazil, Colombia, and Mexico.	Argentina Brazil Colombia Mexico –4–
Pane et al. 2021 [30]	Tools used for medical device safety signal detection. 24 final studies included: 11 review articles 13 studies (12 retrospective studies and 1 prospective study). Twenty-one articles included information on post-market data sources of medical devices, 10 articles included information on signal detection methodologies for medical devices and 4 articles included information on coding dictionaries for medical devices.	• Embase • Medline • Cochrane • Web of Science • Google Scholar Jan-2004 through Jan-2017	They focused on Regulatory Authorization & Post-Marketing Surveillance by describing aspects that influence signal detection of safety issues related to medical devices in order to identify gaps and provide recommendations for optimizing signal detection approaches.	USA Canada Brazil Japan Australia EU –6–
Krüger et al. 2013 [31]	Authorization process and its associated evidence requirements for HRMD in the U.S.A., Europe, Australia, and Canada. (Seven high-risk devices for exemplary presentation). 45 final studies included: 4 observational studies. Randomized -Controlled Trials (RCTs) 20 Case series 1 report 7 Expert opinions 1 Systematic Literature Review	• Pubmed • Official reports from the relevant national regulatory bodies (except NBs): ✓ Centers for Medicare and Medicare Services ✓ Aetna ✓ Blue Cross and Blue Shield ✓ United Healthcare ✓ Kaiser Permanente ✓ AHRQ ✓ College voor zorverzekeringen (CVZ) ✓ MDS, Federal Joint Committee (G-BA), ✓ Institute for Quality and Efficiency in Healthcare (IQWIG) ✓ NICE ✓ Ludwig Boltzmann Institute for HTA ✓ Medical Services Advisory Committee ✓ Canadian Association of Health Care Reimbursement No time period mentioned	They focused on Regulatory Authorization & Post-Marketing Surveillance by performing an insight into four authorization systems evidence at time of approval and reimbursement. Objectives: – Authorization process in the four regions. – Evidence available at the time of approval and reimbursement decision.	USA Europe (England, The Netherlands, Germany, Austria) Canada Australia –4 (8)–

(*Continued*)

Table 1. (Continued).

Study	Articles retrieved	Databases & Search's Timeline	Aims & main findings	Countries or Jurisdictions -Nr-
Carbonneil et al. 2009 [32]	Access with Evidence Generation (AEG) policies, particularly at the coverage decision stage. Data derived from articles description not provided.	• MEDLINE • BIOSIS Previews • Current Contents • EMBASE • INAHTA • DARE • Gray literature (reports on the Web sites of medicines agencies, HTA agencies, and national health insurance bodies) Period: 1990–2008	They focused on HTA or Price & Reimbursement in order to identify the AEG mechanisms implemented in various countries, to use them to draw up a common policy framework applicable at both the marketing approval and coverage decision stages, and to identify the key factors for its successful operation	Australia Canada EU (Belgium, Finland, Denmark, France, Germany, Italy, Latvia, The Netherlands, Portugal, Spain, UK) USA –4 (14)–
Baeyens et al. 2015 [33]	HRMD (class III and implantable devices) after their CE-marking in Belgium Data derived from article descriptions not provided.	• Belgian and European legal databases (BELGIQUELEX, EURLEX) • Communications, Guidelines, and reports of the European Commission • Parliament and Council Parliamentary work of the European and national legislation • Position papers from professional and sectorial associations • Articles published in scientific or legal publications • Legal experts and lawyers from across Europe were consulted • Official websites and documentation from national health products and • Reimbursement authorities in various European countries • Representative from the Belgian health product and reimbursement authorities (Federal Agency for Medicines and Health Products, from manufacturers associations, and from hospitals were consulted)	The aims of this report were as follows: – Getting to know the existing legal opportunities in a selection of European countries, including Belgium, to introduce a high-risk device on the market in a guided manner. – To identify the crucial legislation to apply one or more of the above identifies and new possibilities to have a guided introduction of CE labeled devices (which are not in conflict with European law). – To investigate the possibility of a higher protection of the patients when certain CE-marked HRMD are used (class III and implantable devices).	Data not retrieved.

Abbreviations: The British Medical Journal (BMJ); Health Technology Assessment (HTA); The New England Journal of Medicine (NEJM); The United States of America (U.S.A.); The European Union (EU); The Professional Society for Health Economics and Outcomes Research (ISPOR); The Ministry of Health (MoH); Coverage with Evidence Development (CED); Medical Devices (MD/s); Web of Science (WoS); High-risk Medical Devices (HRMD/s); Notified Bodies (NBs); National Institute for Health and Care Experience (NICE); The United Kingdom (UK); International Health Technology Assessment Database (INAHTA); Excerpta Medica Data Base (EMBASE); Access with Evidence Generation (AEG).

As we observe in Figure 2, despite the established market entry pathways being widely different, all of them have common standards and requirements related to efficacy, effectiveness, and safety in order to perform studies regarding these considerations and the development of post-market evidence generation requirements for novel technologies, orphan devices, and other HRMDs subject to certain initiatives as the strategy of SAKIGAGE, in Japan [49], or the Breakthrough Devices Program from the USA [43].

For example, the FDA acts as the regulatory body for, among other things, medicines and medical devices in the U.S.A. The approval process performed by the FDA is known as Premarket Approval (PMA), and this regulator also considered a scheme for HRMD conditional approval, where the FDA can grant licensing under determined frameworks, like the Breakthrough Device Program (previously Expedited Access Pathway) or the Innovation Pathway [43–45]. As occurs to the rest of licensing (premarket notification (510(k)), or De Novo classification request ('De Novo request')), breakthrough devices (…) <<*must still meet the statutory standard of reasonable assurance of safety and effectiveness at the time of approval*>> [43]. In order to perform this post-market review standard, there were some conditions that medical devices subject to this amendment must meet [44,45]:

<<;(…)

- *Provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating human disease or conditions; and*
- *Meet one of the following conditions:*
  - ✓ *Represent breakthrough technologies;*
  - ✓ *No approved or cleared alternatives exist;*
  - ✓ *Offer significant advantages over existing approved or cleared alternatives, including the potential, compared to existing approved alternatives, to reduce or eliminate the need for hospitalization, improve patient quality of life, facilitate patients' ability to manage their own care (such as through self-directed personal assistance), or establish long-term clinical efficiencies; or*
  - ✓ *the availability of such medical devices is in the best interest of patients.*>>

Table 2. Post-market reporting activities: main outcomes.

Country or Jusrisdiction	Regulatory structures	Key elements of post-marketing surveillance & vigilance activities
EU	Directive 90/385/EC, 93/42/EEC and 98/79/EC) [2,4–6]. The conformity assessment procedure, with the exception of low-risk devices, is carried out by third parties, called NBs, which are designated by the Member States Competent Authorities.	Adverse event reporting or vigilance reporting: MDD (Tarricone, *et al.*) [16]: reporting by medical practitioners or medical institutions is encouraged but optional – Member States may or may not introduce this legal requirement in their national legislation MDR [2]: adverse events and device deficiencies that occur during clinical investigations should be reported to the Member States in which those clinical investigations are being conducted and submit the reports to EUDAMED database. In the case of EU, Notified Bodies act as regulators under the Medical Device Regulation (MDR) [2,16]: – Notified Bodies are the institutions designated by EU members' states to assess the conformity of medical devices before they are placed on the market. – HRMD must undergo a conformity assessment process, including a thorough review of clinical evidence. – In some specific cases, NBs may impose restrictions or limitations on the device's marketing under Article 56.3 of the MDR and Annex IX. These measures are put in place to ensure the device's safety and efficacy. – Manufacturers must provide additional post-market data to confirm benefits and manage any emerging risks.
USA	Title 21 of the Code of Federal Regulations – Food, Drug, and Cosmetic Act (FD&C Act); Medical Device Amendments Act (MDA) and the Bioterrorism Act [36,68]. The 'Premarketing Notification' or 510(k) clearance procedure and the 'Premarket Approval' (PMA) for HRMD, is carried out by the FDA.	Adverse event reporting or vigilance reporting: the manufacturer, distributor, competitor, healthcare providers and patients have the duty to report adverse events (Tarricone *et al.*) [16] (Title 21 of the Code of Federal Regulation, section 803) [68]. The FDA acts as the regulatory body for medicines and medical devices in the U.S.A. The FDA can grant licensing under determined frameworks, like the Breakthrough Device Program (previously Expedited Access Pathway) or the Innovation Pathway [43–45]. Medical devices <<*must still meet the statutory standard of reasonable assurance of safety and effectiveness at the time of approval*>> [43]. Post-market review licensing requires some conditions: <<;(…) • *Provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating human disease or conditions; and* • *Meet one of the following conditions:* • *Represent breakthrough technologies;* • *No approved or cleared alternatives exist;* • *Offer significant advantages over existing approved or cleared alternatives, including the potential, compared to existing approved alternatives, to reduce or eliminate the need for hospitalization, improve patient quality of life, facilitate patients' ability to manage their own care (such as through self-directed personal assistance), or establish long-term clinical efficiencies; or* • *the availability of such medical devices is in the best interest of patients.*>>
Canada	The primary regulatory framework for medical devices in Canada is the Medical Devices Regulations (SOR/98- 282) [69] under the authority of the Food and Drugs Act. The regulatory oversight is provided by Health Canada, specifically the Medical Devices Directorate. Health Canada reviews medical devices to assess their safety, effectiveness, and quality before being authorized for sale in Canada. The license (i.e. notice of compliance) is issued once all requirements are satisfied.	Adverse event reporting or vigilance reporting: According to the Medical Devices Regulations – SOR/98-282 (Section 81), in Canada there is a mechanism established for HRMDs called Conditional Licensing, in which safety and effectiveness are granted but it is necessary to complement with clinical evidence and verify the benefit/risk ratio in a timeframe deadline (See further details in supplementary table S2). Nevertheless, the Government of Canada has provided an amendment where regulations will allow accelerated access to urgent public health needs in which medical devices may be endorsed without relying on temporary regulatory measures [55,69], we can observe some examples: *(f) a risk assessment comprising an analysis and evaluation of the risks, and the risk reduction measures adopted for the purposes of conducting investigational testing of the device, including, as appropriate.* *(iii) information respecting any cautions, warnings, contra-indications and possible adverse effects associated with the use of the device;* *(v) in the event of an incident involving the device and that meets the following conditions, report the incident and the circumstances surrounding it to the Minister and to the manufacturer or importer of the device within 72 hours after the qualified investigator becomes aware of the incident:* *(A)the incident is related to a failure of the device or a deterioration in its effectiveness or any inadequacy in its labeling or in its directions for use, and* *(B)the incident has led to the death or a serious deterioration in the state of health of a patient, user or other person or could do so were the incident to recur.*

(*Continued*)

Table 2. (Continued).

Country or Jusrisdiction	Regulatory structures	Key elements of post-marketing surveillance & vigilance activities
Australia	The specific regulation for medical devices is found in the Therapeutic Goods Act 1989 and the Therapeutic Goods Regulations 1990 [70]. The TGA (Therapeutic Goods Administration) is responsible for evaluating and deciding the incorporation, monitoring, and withdrawal of HRMD. The sponsor needs to demonstrate that the device complies with a set of 'Essential Principles' for the quality, safety, and performance of the medical devices.	Adverse event reporting or vigilance reporting: Manufacturers and sponsors are required to report certain types of adverse events associated with their medical devices to the TGA. Reporting by stakeholders other than manufacturers is only encouraged (Tarricone et al.) [16].
China	Regulations on the Supervision and Administration of Medical Devices (Order No. 739) of 9 February, 2021 [51]. The National Medical Products Administration (NMPA), previously named CFDA (China Food and Drug Administration) is responsible for setting and implementing regulations for the registration, manufacturing, distribution, and monitoring of medical devices and pharmaceuticals in China.	Adverse event reporting or vigilance reporting: Manufacturers and users have the duty (it is compulsory) to report all adverse events that could have potentially led to patient harm within 5 days of their occurrence (Tarricone *et al.*) [16]. In addition, according to NMPA's Guideline on Conditional Approval for Medical Devices, released on December 20, 2019, includes the following [52–54]: • *Premarketing clinical data must be able to show preliminary efficacy or to reasonably predict clinical value;* • *Surrogate endpoints can be allowed;* • *The expiration date on the approval certificate must be identical to the completion date of the post-market study;* • *The risks must be shown on the label and IFU;* • *The standards of safety and efficacy must be unchanged with regular market approval.*
Japan	The Pharmaceutical and Medical Device Act (PMD Act) [71]. The PMD Act is the key regulatory framework overseen by Japan's MoH, Labour, and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA). The PMDA operates under the MoH, Labour and Welfare (MHLW) and is tasked with evaluating and approving pharmaceuticals and medical devices to ensure their safety and efficacy.	Adverse event reporting or vigilance reporting: Reporting of adverse events by outlining the responsibility of both medical device manufacturers and healthcare practitioners to promptly report such events and take corrective measures. (Act 60.10 of Ministerial Ordinance No. 169 Japan)
Brazil	RDC (Resolution of the Collegiate Board) 185/2001 [72]. Brazil's legislation for medical devices is aligned with the GHTF. National Health Surveillance Agency under the MoH (ANVISA) is responsible for the registration of medical devices, it centralizes pre- and post-market surveillance phases. There are two regulatory pathways for market approval of medical devices: notification, a simplified process for devices that are considered lower risk, and registration for high-risk devices listed in the ANVISA normative instruction IN 2/2011 [73].	Adverse event reporting or vigilance reporting: As well as in Australia, reporting by stakeholders other than manufacturers is encouraged, but mandatory for sponsors/manufacturers.

Abbreviations: Notified Bodies (NBs); Medical Devices Directive (MDD); Medical Devices Regulation (MDR); European Database of Medical Devices (EUDAMED); High-risk medical devices (HRMDs); Food & Drug Administration (FDA); The National Medical Products Administration (NMDA); China Food and Drug Administration (CFDA); The Pharmaceutical and Medical Device Act (PMD Act); The Ministry of Health (MoH); Ministry of Health Labour and Welfare (MLHW); Resolução Da Diretoria Colegiada (RDC); Global Harmonization Task Force (GHTF); Agência Nacional de Vigilância Sanitária (ANVISA); Instructions for use (IFU).

The approval process for HRMD in the U.S.A. is based on preliminary evidence showing a reasonable assurance of safety and effectiveness. With regard to this issue, manufacturers must continue with post-market studies to confirm long-term efficacy and safety. In addition, the FDA may also require post-approval studies and ongoing market surveillance of the device [16,43–45,50].

In the case of China, the National Medical Products Administration (NMPA), which is the regulatory body responsible for setting and implementing regulations for the registration, manufacturing, distribution, and monitoring of medical devices and pharmaceuticals [51], has a scheme for HRMD conditional approval through its Registration Certificate for Medical Device (See Figure 2) [38]. However, the competent authority that provides the application is the Drug Regulatory Department. This form of approval can be granted under the Guidelines for Conditional Approval for Marketing of Medical Devices [52–54]:<<; (. . .)

- *Premarketing clinical data must be able to show preliminary efficacy or to reasonably predict clinical value;*
- *Surrogate endpoints can be allowed;*
- *The expiration date on the approval certificate must be identical to the completion date of the post-market study;*
- *The risks must be shown on the label and IFU (Instructions for use);*
- *The standards of safety and efficacy must be unchanged with regular market approval.*>>

The Drug Regulatory Department can grant conditional approval based on preliminary data if the device offers significant public health benefits. The NMPA requires post-market studies to collect additional safety and efficacy data, and these health technologies are conditionally approved only in case they are subject to rigorous monitoring and continuous clinical data collection (See Figure 2) [38]. The Drug Regulatory Department requires manufacturers and users to report any adverse events/safety/incidents derived from the use of the medical device in the first five days from the event [16], in order to be submitted to the List of Medical Devices (MDD – Medical Devices

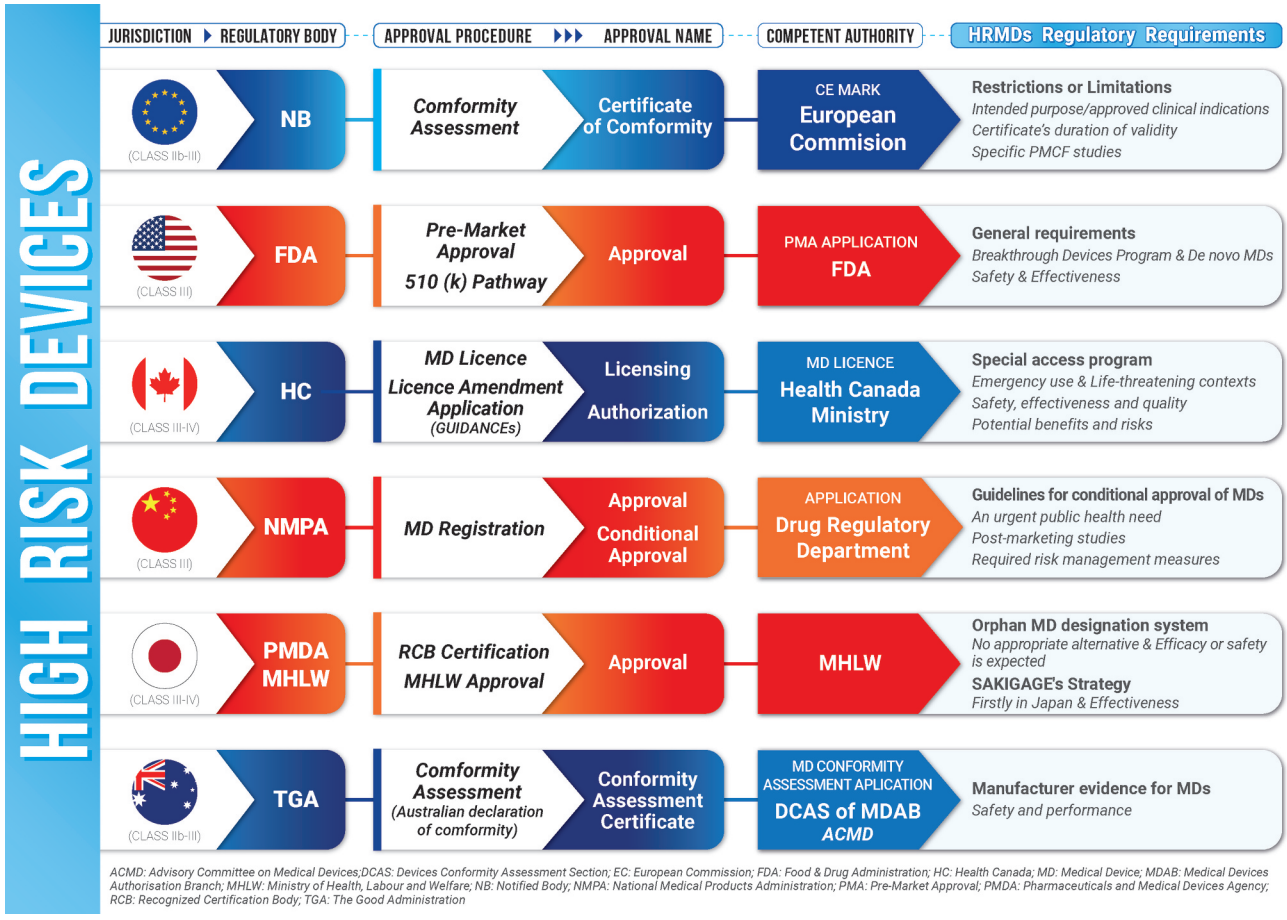

Figure 2. Approval/Certification/Licensing process and conditional market entry for HRMDs.

Division; Hong Kong) or the NMPA Database (See *Supplementary table S1)*.

With regard to Medical Devices, from 23 countries revised just seven (Australia, Canada, Latvia, Spain, Switzerland, United States, and UK) identified Access with Evidence Generation (AEG) tools for marketing approval. For example, in Canada, there was a mechanism established for HRMDs called Licensing, in which safety, effectiveness, and quality data were granted, but it was necessary to complement with clinical evidence and verify the benefit/risk ratio in a timeframe deadline (See further details in *Supplementary table S2* & *figure S2*) [37]. Nevertheless, the Government of Canada has provided an amendment where regulations will allow accelerated access to urgent public health needs in which medical devices may be endorsed without relying on temporary regulatory measures [46,55]. Despite these lessons can be useful for our scope, there were no details as well defined as in the case of the U.S.A. and China in the literature retrieved.

In the case of EU, NBs act as regulators under the MDR [2,16]:

- NBs are the institutions designated by EU members' states to assess the conformity of medical devices before they are placed on the market.
- HRMD must undergo a conformity assessment process, including a thorough review of clinical evidence.
- In some specific cases, NBs may impose restrictions or limitations on the device's marketing under Article 56.3 of the MDR and Annex IX. These measures are put in place to ensure the device's safety and efficacy.
- Manufacturers must provide additional post-market data to confirm benefits and manage any emerging risks.

Although this review also retrieved information from other countries/jurisdictions, these three authorities already were considered the most relevant for this study's scope (see Tables 1 and 2).

Information about additional post-market schemes that are outside of the scope of this paper is included in *Supplementary table S2* in order to complement the present findings from the following jurisdictions: U.S.A., EU, Australia, Canada, China, Japan, Brazil, Argentina, Colombia, and Mexico, all members of the *International Medical Devices Regulators Forum*. With regard to Table 1, four studies focused on Regulatory authorization and post-marketing surveillance [16,30–32] offering insights specific to each country or jurisdiction. For example, in the case of Pane et al. 2021 [30], highlighted signal detection issues, related to medical devices that reduced evidence identification gaps, while Tarricone et al. 2014 [16] focused on pre-market approval and post-market vigilance on medical devices.

After a regulatory decision is made to grant access to a HRMD while generating additional evidence to mitigate identified uncertainties, these devices continue their lifecycles and additional decision-makers will also handle the evidence

base that is available when they face decisions about these devices. Two of the selected studies described HTA or Price and Reimbursement [30,33] schemes for handling or reducing uncertainty. In order to describe challenges to be considered by different stakeholders (for example, on the study design to perform) [30], these studies retrieved information regarding the policy frameworks that treated marketing approval and coverage decision stages [33]. The countries or jurisdictions that considered conditional approval of HRMD at the HTA stage were the U.S.A., Australia, Canada, and the following countries from the EU: The Netherlands, Germany, France, Belgium, Spain, Austria, and England.

Standard regulatory post-marketing requirements, such as reporting of safety events as part of surveillance monitoring, were outside of the scope of our study. However, to provide a fuller picture of the different kinds of evidence collected at after marketing authorization, we extracted information about how different jurisdictions structure surveillance activities were in *Supplementary table S2*, because of '*the licensing or registration process also imposes obligations on the manufacturer for post-market surveillance*' [16], which varied across countries despite efforts by the Global Harmonization Task Force [8,20]. In China, not only for manufacturers but users (i.e. practitioners), it is compulsory to report adverse events related to injury or death. In the U.S.A., it is a duty for manufacturers, distributors, competitors, healthcare providers, and patients. Furthermore, the deadline to report these adverse events is crucial: <<*In the U.S.A. (…) the adverse event within 30 days following the date of awareness and within 10 days if the event caused death or serious deterioration in the state of health, and in Australia within 48 h if the event represents a serious threat to public health*>> [16]. This information is publicly available in real-time. In the case of the EU, manufacturers notify these events in real-time, while improvements and corrections are published as Field Safety notices, with neither a limit or specific timeframe for this process nor a mention about the surveillance and vigilance points considered adverse events notifications and the period of time to submit this information.

The use of the AMSTAR-2 online checklist (https://amstar.ca/) [35] to assess the quality of the studies showed that all of them displayed either low or critically low quality (See *Supplementary table S3. Amstar 2 Checklist*).

4. Discussion

In Europe, NBs apply restrictions or limitations to certificates of conformity to allow medical devices access subject to further evidence collection in defined situations, such as unmet need and promising technology but sparse evidence among other scenarios. The objective of this review was to analyze this policy and similar ones from other jurisdictions and extract learnings applicable to the European regulation for medical devices, from how similar schemes are organized in jurisdictions beyond the EU.

Some regulatory bodies grant conditional marketing authorizations for certain types of health products, provided that some prerequisites, like post-market evidence generation, among other variables, will be performed, in order to guarantee the safety and effectiveness of these products. A given example was the case of HRMD and the FDA-associated evidence requirements [16,31,36].

Our findings indicate that the United States and China implement evidence development schemes for the conditional approval of HRMD, which can offer valuable insights for the European Union. In China, the Drug Regulatory Department, from NMPA, grants conditional approval based on preliminary efficacy data and requires manufacturers to conduct post-market studies to confirm the safety and effectiveness of the device (See Figure 2) [38,52–54]. Similarly, the FDA in the U.S.A. has pathways such as the Breakthrough Devices Program [43], which allows for accelerated approval of devices that provide more effective treatment for life-threatening conditions, contingent upon post-market evidence generation. Parallel to this, other jurisdictions have mechanisms with similar purposes, such as the Canadian institution, Health Canada, which performs AEG tools called Licensing, and impose the necessity to generate clinical evidence and verify the benefit/risk ratio in HRMDs already granted with safety and effectiveness standards, subject to a timeframe deadline [46] (See in detail Figure 2).

In EU MDR permits NBs to impose restrictions or limitations on HRMD. These restrictions may include limiting the device's intended use to certain patient groups or mandating specific PMCF studies. This approach is aligned with the practices observed in other jurisdictions, emphasizing the need for continuous evidence generation to manage the risks associated with HRMDs.

Our findings revealed heterogeneity regarding key elements that are relevant to be standardized in order to obtain lessons or data of interest about the evidence generated in post-market stages, for example, the classification of medical devices. These health technologies were categorized into different groups based on the level of risk involved in their management in different countries. This discrepancy is particularly evident for the HRMDs, which may belong to class III and/or IV depending on the country [16,29,31,36] (See in detail *Supplementary table S1* and *Figure S2*). Nevertheless, this example about how the type of data, regarding HRMDs, were differently classified may be a clear representation about how some international measures are difficult to be implemented in some jurisdictions. Overall, because of their intended purpose is to standardize performance and management processes, as well as to provide safety and surveillance information, for example, with regard to storing data from HRMD (20). This scenario must be considered due to the relevance of different routes that regulatory bodies impose regarding the classification III and/or IV in their respective scope areas, and the awareness to get to know that the evidence generated may vary according to the classified technology, whose classification granting may vary based on the country or jurisdiction system.

HTA agencies also play a crucial role in the adoption of medical devices. Although the goals of regulators and HTA agencies differ, HTA activities significantly impact post-market evidence generation and the integration of these devices into healthcare systems. Manufacturers often need to develop

clinical evidence for both regulators and HTA agencies, depending on the jurisdiction. This dual requirement can complicate the commercialization process but also ensures a more comprehensive evaluation of the devices. However, in many cases, such evidence was weak at the time of HTA evaluation [9,15,17]. In order to complement the evidence derived from our review, *Supplementary Table S1* provides a detailed mapping of the regulatory bodies, HTA institutions, and Ministries of Health with a role in the access pathway for medical devices in their respective jurisdictions (See *Supplementary table S1*). This allowed us to obtain, for example, an overview about the different risk classification systems for medical devices, in accordance with current regulations and laws in each country. Additionally, it includes information about the approach employed in HTA for the classification of medical devices (extracted from the three main HTA's networks in the world [56]). This mapping is important for comparing post-market evidence-generation schemes for HRMD at regulatory and HTA levels globally.

Similar to pharmaceuticals, it is a regulatory requirement, for some medical devices, to submit a report which must be assessed by their corresponding regulatory authority, depending on the country or international jurisdiction, as the FDA in the case of the U.S.A. (Premarket approval -*PMA*; and *510(k) pathway*, as part of the Breakthrough Device Program), or a NB in the case of the EU [24,57,58]. With regard to the required data, and in spite of being premarket procedures (for example, in the case of the U.S.A.), these measures considered the post-market evidence generation as a conditional requirement for MDs' entry market, in the premarket stage. This scenario is particularly pronounced when the variability given among different countries regarding requirement submission data for HRMD is considered. Or, as another example, when reporting has a crucial point for manufacturers, in order to introduce a health product into a particular market country [33].

The use of different schemes for post-launch evidence generation and its relationship with regulatory approval procedures depends on the geographical and jurisdictional context and their regulatory requirement. Nevertheless, emerging technologies may be highly convenient in contexts where some populations present vulnerabilities regarding their inequities in health [59]. In fact, the healthcare network established in different healthcare systems makes difficult the task to perform correct approaches in terms of diagnosis and treatment in patients with certain diseases, like cancer or mental disorders, overall in critical scenarios where these systems have been critically affected, for example, in pandemic contexts as COVID-19 [59–62]. With this regard, some theragnostic technologies could benefit from the availability of parallel pathways by reducing time and standardizing procedures, consequently, preventing complications in health, in vulnerable populations [63,64]. The new MDR should be adapted in order to assess innovative and emerging technologies for therapeutic and/or diagnostic purposes such as genetic testing, advanced therapies, and theragnostic technologies. Providing a specific conditional approval for innovative technologies focused on the prevention of clinical unmet needs could lead to a holistic caring plan by reducing the uncertainty in high prevalence known diseases, as well as providing an improvement of the lifestyles in vulnerable populations, as it has been shown in cases for drugs and determined contexts associated to vulnerable populations [62].

We included some of the intended activities considered to report or collect safety and/or efficacy data regarding HRMDs after CE mark concession (or the corresponding market authorization, if we described cases outside of Europe).

Post-market evidence generation for HRMD is crucial for ensuring long-term safety and efficacy. Different jurisdictions have established varied approaches to reporting and surveillance. In China, the NMPA requires manufacturers to report serious incidents and conduct post-market studies, ensuring that safety and efficacy standards remain consistent with regular market approval [16,52,53]. In the U.S.A., reporting obligations extend to manufacturers, distributors, health providers, and patients, while in other jurisdictions, like Brazil and Australia, they primarily place this responsibility on manufacturers [16]. The EU mandates users and patients to report serious incidents to manufacturers and authorities, with data being entered into the EUDAMED database to enhance transparency and availability of information [2,65]. Globally, similar adverse event reporting systems exist, such as Helena's system in Argentina [25], the NMPA Database in China [65], INVIMA in Colombia [66], and South Korea's medical device information portal [67] (See further details at Supplementary table S1). These examples illustrate some global efforts to standardize post-market surveillance and ensure the safety of HRMDs. Databases like EUDAMED provide a comprehensive view of the lifecycle of medical devices, promoting transparency and facilitating real-world evidence generation. These databases may serve as examples to standardize safety information and promote innovative study designs, supporting the monitoring required under conditional approvals, and enabling better post-market surveillance and evidence-based decision-making.

Limitations found were mainly based on the heterogeneity of terms used in the corresponding jurisdiction, as well as the difficult task to find the corresponding information from the web and regulatory documents, that in some cases, like China, the language employed did not belong to the preestablished criteria. In addition, our findings were presented in a descriptive way according to the evidence available and retrieved, but we assumed as a limitation the lack of assessment of our findings. Nevertheless, due to the lack of a quality assessment tool for methodological reviews, we performed the quality assessment of the studies selected with the AMSTAR-2 checklist (See *Supplementary Table S3*).

5. Conclusion

Our systematic review summarizes the limited evidence available of the application of restrictions or limitations to certificates of conformity in Europe, imposing the requirement to collect further evidence post-CE mark. Despite it being a provision described in European regulation, its application is very sparse, which might be indicative of a need for further development. Additionally, this review identified examples from other competent authorities, like the FDA, the NMPA, and the Health Canada, that apply similar schemes to restrictions to certificates of conformity, which could potentially

orientate future reforms in Europe. Further research on legislation and regulation is required in order to reduce injuries or deaths derived from the use (or lack of access to, and subsequent use) of HRMD. Further development of policies supporting the application of limitations to certificates of conformity, and the explicit definition of circumstances, such as fragility of certain patients or healthcare users, that would be appropriate for the application of such regulatory instrument, could enhance access to promising HRMD while enabling the development of further evidence. Despite the lack of a robust developed regulatory procedure for conditional approval in Europe for HRMD, several HTA authorities have established Coverage with Evidence Development schemes for HRMD. This disparity between the regulatory and the HTA levels might create an evidentiary gap in Europe, which might become a leap too large to bridge for sponsors.

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Declaration of interest

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Author contributions

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Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

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ORCID

Jesús Aranda http://orcid.org/0000-0002-5626-5214
Agnieszka Dobrzynska http://orcid.org/0000-0001-6455-6452
Juan Carlos Rejón-Parrilla http://orcid.org/0000-0002-0680-7353
David Epstein http://orcid.org/0000-0002-2275-0916
Juan Antonio Blasco-Amaro http://orcid.org/0000-0002-5500-8187

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