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PERSPECTIVE

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Orphan and paediatric medical devices in Europe: recommendations to support their availability for on-label and off-label clinical indications

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ABSTRACT

Introduction: The Medical Device Regulation (EU)745/2017, increased the regulatory requirements and thus the time and the cost associated with marketing medical devices. For a majority of medical device manufacturers, this has lead to reconsiderations of their product portfolio. The risk of important or essential devices being withdrawn is particularly relevant for pediatric patients and other rare disease patients where limited numbers of devices can be sold and hence the investment needed may not be recovered. This generates critical challenges and opportunities from a regulatory and public health perspective.

Areas covered: This paper is based upon the experience of the authors who contributed to working groups, guidance development and research related to orphan and pediatric devices. We examine the use of medical devices in orphan and pediatric conditions, the relevant aspects of regulations and associated guidance, and we suggest possible policy and practice interventions to ensure the continued availability of essential devices for children and people with rare diseases.

Expert opinion: We recommend a more proactive approach to identifying devices at risk and essential devices, increasing the use of exceptional market approvals, expanding the role of expert panels, engaging with the rare disease communities and supporting registries and standards.

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KEYWORDS
Rare diseases; paediatrics; medical device; orphan products; off-label use

1. Introduction

Medicines legislation in the European Union defines rare diseases as those with a prevalence of < 1 per 2,000 people [1]. There are between 6,000 and 8,000 known rare diseases, which affect 30 million people in the EU [2], and so their cumulative impact on public health is far greater than the term 'rare disease' implies. Particular device technologies can be 'high impact' for individuals.

Devices or medicinal products that are needed in low numbers for specific rare diseases or for certain pediatric indications, where alternative options are limited, can be considered 'orphan' products. Orphan status for medicines is provided for, in EU legislation, with a number of actions to facilitate *and* incentivize the development and marketing of medicines for rare diseases. European medical device *legislation* does not have a definition of an orphan medical device but recent regulatory *guidance* from the Medical Device Coordination Group has provided the first EU-based definition of an orphan medical device – as one that is 'specifically intended to benefit patients in the treatment, diagnosis, or prevention of a disease or condition that presents in not more than 12,000 individuals in the European Union per year' [3].

The United States Institute of Medicine (now the National Academy of Medicine) noted in a 2010 review of rare diseases and orphan products that when devices for rare conditions are discussed, it is generally in connection with pediatric populations, due to the nature of rare diseases which often have their onset during childhood [4]. In this paper, medical devices used in the context of rare diseases and orphan devices used for pediatric patients are referred to jointly as orphan and pediatric devices or 'OPDs.'

Medical devices represent a great diversity of technologies, with estimates suggesting that 500,000 different medical device products are available in the European Union [5] and that 2 million are available worldwide [6]. In the future, the European Database on Medical Devices (EUDAMED) will provide further public information on devices available in the EU [7]. The numbers of medical devices used for the treatment of rare diseases or for pediatric conditions are unknown. The number of OPDs that have been withdrawn from the market in the EU is also unknown. Some national

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Article highlights

- The Medical Device Regulation (EU) 745/2017 has increased regulatory requirements, and thus the time and cost, associated with bringing medical devices to market and maintaining them on the market.
- For medical devices used rarely this change in market dynamics may lead to the withdrawal of products.
- This is particularly relevant for the pediatric population and people living with rare diseases.
- Changes to the market are a particular threat to devices used 'off-label,' which is often unavoidable for the pediatric population and people living with rare diseases.
- We recommend a more proactive approach to identifying devices that are at risk of withdrawal from the market, increasing the use of exceptional market approvals, expanding the role of expert panels, engaging with the rare disease communities and supporting registries and standards for post-marketing surveillance including off-label use.

competent authorities, such as Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) in France have begun making listings of devices subject to shortages publicly available [8].

OPDs have a variety of purposes, including prediction, diagnosis, treatment, management, monitoring, and rehabilitation. Examples of unique devices that may be needed for specific rare diseases at different stages of their clinical course include:

- Therapeutic devices such as microvascular plugs, which can be used for closure of patent ductus arteriosus in premature babies [9].
- Monitoring devices such as electroencephalogram (EEG) devices combined with artificial intelligence algorithms to detect seizure activity in neonates [10].
- Supportive devices such as exoskeletons used to assist mobilization in patients with conditions such as spinal muscular atrophy, or Duchenne muscular dystrophy [11].
- Diagnostic devices such as genetic tests used for the diagnosis of many rare diseases; these are in-vitro diagnostic tests subject to a separate but similar regulation to medical devices in the EU [12].

Some uses are within the scope of the manufacturer's intended purpose, in which case information is provided on the label. Many OPDs, however, are adapted or repurposed to suit a pediatric or rare disease use, depending on the clinical needs [13].

For some clinical specialties such as pediatric cardiology, a majority of interventions are dependent on off-label use [14]; the variety of ways in which an OPD can be used off-label include:

- Different anatomical locations or organ systems – for example placing an adult bile duct stent into the vasculature of a child to treat pulmonary arterial stenosis, coarctation of the aorta, or other conditions.
- Different combinations of devices – for example using a stent in the right ventricular outflow tract before placing a percutaneous valve [15].
- Treatment of different conditions – for example the use of a microvascular plug intended for occlusion of the peripheral vasculature in adults, for pulmonary flow restriction in neonates with congenital heart disease [16].

Manufacturers must provide information about their medical devices to ensure that the clinician, patient and device user can understand how to implant or use the device in a safe and effective way. This is typically communicated in the Instructions for Use (IFU; a document required by the EU legislation), but labeling is not the only way to provide relevant information in clinical practice. Off-label use is often supported informally within clinical communities by sharing information at conferences, in the scientific literature, in clinical guidelines, during clinical training, and at other fora. This information may be sufficient to maintain safe practice, but data arising from these uses may not be collected systematically, and/or the data available may be considered insufficient for regulatory purposes.

The objectives of this paper are to provide a narrative review of the regulatory, policy and practice landscape for the use of OPDs, and to propose high-impact changes that are needed to maintain public health benefits arising from the current use of OPDs, including off-label use of devices that have been approved for other indications.

2. Methodology

This paper is based upon the experience of the authors who work in pediatrics (BVK, MAT, MD), pediatric cardiology (DK, MG), rare disease (AHJ, MD) and regulatory policy (AGF, TM). The authors contributed to the Medical Device Coordination Group Task force on Orphan devices (TM, MD, BVK, MAT, AGF, MG, AHJ); to the International Rare Disease Research Consortium Working Group on Medtech for Rare Disease (TM, MD, AHJ); and to the CORE-MD project (www.core-md.eu) which examined clinical evidence for high-risk medical devices used in pediatrics (TM, AGF, BVK) [17,18]; and from their engagement with clinical communities and orphan device manufacturers via the Biomedical Alliance (TM, BVK, MG, AGF).

3. An introduction to the regulatory process for the introduction of a medical device in the European union

Device developers (termed 'manufacturers' in the MDR) initiate the regulatory process related to the development of their product. This includes its design, verification and validation, which may be followed by pre-market clinical investigations. In the pre-market phase, the design of a clinical investigation requires assessment and approval by a national competent authority and by a research ethics committee (MDR, Article 62(4)). To achieve market approval, manufacturers must thereafter apply to a notified body (for all devices except those in the lowest risk class). This process, known as 'conformity assessment,' typically consists of review by the notified body of the technical documentation, clinical evaluation and quality management processes of the manufacturer of the device. Once this is successfully completed, the device may be CE (Conformité Européenne) marked. The CE mark allows a medical device to be sold freely in the EU single market without further technical

barriers to trade, and without any legal restrictions on their use by physicians. The CE-mark is also used or relied upon by many other jurisdictions worldwide.

In Figure 1, we present an overview of the regulatory pathway, summarizing opportunities and recommendations relating to the on-label and off-label use of OPDs.

4. The European Union regulatory context relating to OPD and off-label use

The marketing of medical devices is regulated in the European Union by the Medical Device Regulation (EU) 745/2017 (MDR). It replaced Directives which had introduced European regulation of medical devices in the 1990s, in order better to protect public health and patient safety [19]. Under the Directives, medical devices were subjected to 'light-touch' requirements for clinical evidence, which *de facto* made the European system supportive of introducing new products: the barriers to market access were relatively modest, although with some possibility of unsafe or ineffective devices entering the market. A series of scandals, mainly relating to safety, accelerated revision of the legal framework, with more onerous requirements for clinical evidence under the MDR.

We are currently still in a transition between two regulatory systems for medical devices in the EU – that of the previous Directive and the MDR. There is no 'grandfathering,' i.e. automatic market access cannot be based on the prior approval. The transition period was planned to be completed in 2024, but full application of the MDR has been postponed until 2027 or 2028, depending on the risk classification of the medical device. Reasons cited for this prolongation included a lack of assessment capacity of notified bodies, in addition to the risk of loss of essential medical devices [20]. To benefit from the extra time, manufacturers were required to have submitted an application to a notified body by May 2024, and to establish a contract with a notified body by September 2024. This means that OPD companies which have not applied to their notified body will not be able to keep their device on the market after by September 2024.

The MDR has only one mention of off-label use, in the section concerning manufacturers' post-market responsibilities. Medical device manufacturers are required to identify 'possible systematic misuse or off-label use of the device, with a view to verifying that the intended purpose is correct' (MDR, Annex XV, Part B, section 6.1(e)).

The association for notified bodies, TEAM-NB, produced a position paper which provides an insight into the way that notified bodies perceive off-label use of devices and how the clinical data associated with off-label use are likely to be assessed [21]. The guidance notes that clinical data arising from off-label use could be presented as clinical data to support the marketing of a device under the MDR, but it also cautions regarding the extent to which those data could be be relied upon:

> Off-label data typically does not have 'sufficiency.' Whilst it may hold sufficient quantity, particularly if systematic off-label use has

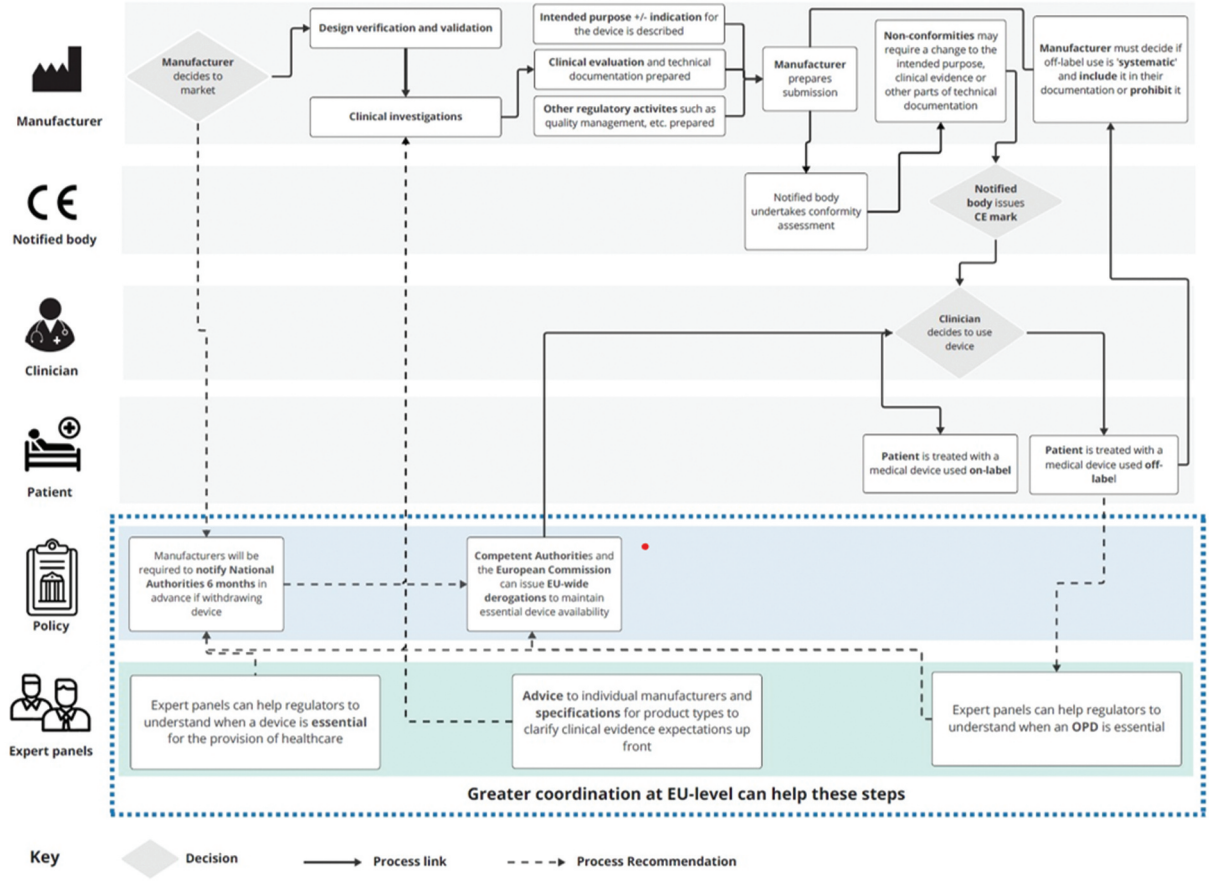

Figure 1. Overview of the regulatory pathway, and recommendations to support the availability of orphan and pediatric medical devices.

> been identified, it however will often fail to have sufficient quality in terms [of] meaningful conclusions. [21]

This wording is understandable, as there would be obvious risks in relying upon deficient data from uncontrolled individual case reports or a retrospective compilation presented as a case series. This TEAM-NB position paper, however, does not describe what would be acceptable or under what conditions more limited evidence might be justifiable for marketing on grounds of public health.

5. Changes in availability of OPDs

Availability of sufficient OPDs has always been a challenge, and it has been noted that the development of medical devices for rare diseases significantly lags behind the development of orphan medicines [22]. An analysis in the United States concluded that the creation and development of entirely new device products was the most important need from the perspective of clinicians, and that the costs of development and the lack of profitability to industry are the two largest perceived impediments [23]. Similar challenges are likely to apply more acutely in the EU since the MDR has changed market dynamics. We do not yet know how many OPDs may be withdrawn because of the regulatory changes, irrespective of whether they have been used on-label or off-label, and what impact that will have on therapeutic options. Doctors have noticed that some essential medical devices which they use for interventions (i.e. the only device available for a particular intervention) are no longer available [24]. The clinical community has identified devices that have already disappeared or are at risk of leaving the market [25]. This includes both devices that are used on-label and those that are used off-label for rare diseases or orphan indications.

6. What are the policy and practice challenges associated with off-label use?

While off-label use of OPDs is common in clinical practice, there is a strong regulatory reticence to create regulatory policy relating to off-label use. An overly permissive policy for off-label use could disincentivise manufacturers from gathering the necessary clinical data for their device. A device could be marketed for one indication but predominantly sold for a variety of other uses which may have limited evidence to support them. This could expose patients to risks and experimentation outside of the typical protections of a clinical study. For OPDs, this needs to be balanced against limited alternative options and the potential for significant clinical benefits expected from an off-label use. No high-risk medical device can be used without some risk, and higher risks may be acceptable in the case of rare diseases or orphan indications. A current lack of evidence can be mitigated over time by increased requirements for the systematic collection of post-market data in order to identify any unsuspected risks as soon as possible.

Another challenge in creating policy for off-label use is that it is intimately related to the practice of medicine. The decision of a healthcare practitioner to adapt a medical device or to use a medical device in an off-label manner is part of the art and practice of medicine, which may even become essential to solve an unexpected technical problem or clinical complication arising during an interventional procedure. The United States Food and Drug Administration (US FDA) recognizes this by stating clearly that it does not regulate the practice of medicine, by which it means that it does not comment on the discretion of healthcare practitioners to use medicines or devices according to the needs of individual patients [26].

In comparison, EU regulation or guidance for medical devices directs device manufacturers to monitor off-label use of their products; the focus on manufacturers rather than physicians may be due to the fact that product legislation is an EU competence whereas the regulation of clinical practice is a national one. As a result, medical device regulators have avoided creating a framework for the use of devices off-label. Manufacturers are reluctant to monitor and disclose any off-label use of their devices, and discouraged by regulations because doing so could make them liable for supporting the practice (when their device has been authorized only for clinical indications for which evidence has been reviewed). Outside the EU framework, there are some exceptions, such as guidance for clinicians from the UK regulator, the Medicines and Healthcare Products Regulatory Agency, which makes recommendations regarding the consent process and documentation of use in the clinical records about the patient [27].

Companies pay for regulatory assessment of medicines and of medical devices, but there are some important features in the medical device ecosystem that challenge the development of new policies. Notified bodies are typically private entities working for profit, whereas public entities authorize the marketing of medicines. The EMA has substantial discounts for processing applications of orphan and/or pediatric medicines, but there is no equivalent allowance for orphan device applications in the EU. In the United States and Canada, however, pathways for low-cost conformity assessments have been established for medical devices that are expected to be used only in small numbers.

The EU medical device regulatory system is also distinctive as there is a separation of responsibility between the organizations which provide advice (EMA expert panels), the organizations which approve pre-market studies (national competent authorities), and the organizations which approve market entry (notified bodies). This separation of responsibilities, in a policy sense, has the tendency to create incongruent goals. For example, EMA expert panels may not be confident that their advice will align with the later expectations of competent authorities and notified bodies. Notified bodies may be reluctant to approve an OPD with limited evidence as they may perceive that accepting more limited datasets may lead to repercussions from their designating authority at their next audit.

The decentralized nature of the EU medical device system results in ambiguity about requirements for clinical evidence. It may be unclear to the developer and also to the EMA expert panel, the competent authority, and the notified body what are the exact expectations to support the marketing of an OPD. In other regulatory systems, ambiguity is mitigated by

the provision of clear advice on clinical evidence requirements (for example the Q-submission advice process of the US FDA). European advisory structures are just beginning, however, with the pilot project for EMA expert panels to provide advice, with a specific emphasis on OPDs. Notified bodies are also beginning to provide 'structured dialogs' to increase the efficiency and predictability of their assessments, but the extent to which they can recommend detailed requirements for clinical evidence is unclear. It is unlikely that these structured dialogs would be able to provide advice on how to gain regulatory approval or sanction for an important off-label use for which there may be limited supporting data, since there is currently no formal pathway in the EU for conditional approval of a device. These various EU advisory structures are not aligned or coordinated. Advices given are not summarized or made publicly available, so the 'performance ambiguity' inherent in the system will persist until there is a change in policy.

The off-label use of OPDs is associated with other factors that fall outside the remit of medical device regulation but which can limit the generation of decisive policy. These factors include professional and product liability, reimbursement, insurance, informed consent, and ethical considerations relating to the use of a device in a different way to its approved use.

7. What has been happening to address the regulation of OPDs?

The approval of OPDs has recently received the attention of European regulators, following the establishment in 2021 of an MDCG task force on orphan devices. The MDCG is the statutory body with responsibility for the MDR in Europe. This task force has produced guidance concerning the clinical evaluation of orphan medical devices and procedures for approving them, with recommendations for both notified bodies and expert panels [3]. As already mentioned, the guidance contains the first EU definition of an orphan medical device; in full, an orphan device is one which is "specifically intended to benefit patients in the treatment, diagnosis, or prevention of a disease or condition that presents in not more than 12,000 individuals in the European Union per year; and at least one of the following criteria are met:

- there is insufficiency of available alternative options for the treatment, diagnosis, or prevention of this disease/condition, or
- the device will offer an option that will provide an expected clinical benefit compared to available alternatives or state of the art for the treatment, diagnosis, or prevention of this disease/condition, taking into account both device and patient population specific factors."

In general, the guidance places an increased reliance on medical device registries, allowing devices to be marketed subject to conditions for example that further clinical data are gathered. It refers to aspects of clinical evidence relevant to OPD such as extrapolation of evidence from a general population. The guidance also contains some detail relating to the use of data from off-label use, noting that off-label data is acceptable only in 'exceptional' cases for 'legacy' devices (i.e. those previously approved under the EU medical device directives) and that it does not apply to new devices.

Regulatory guidance is important to facilitate predictability of regulatory processes, so these current regulatory initiatives are to be welcomed. The procedural considerations note that notified bodies can discuss orphan status as part of a 'structured dialogue' between the manufacturer and the notified body, prior to submission. Expert panels can give early scientific advice to device developers, although the implementation of this procedure is yet to be elucidated. In the next section, therefore, we recommend how expert panels can support the availability of essential OPDs.

Although not specific to OPDs, the European Commission has also introduced legislation that requires all medical device manufacturers to inform national competent authorities when they intend to withdraw a medical device or IVD from the market, at least 6 months in advance [28]. This will give regulators greater oversight of pending problems, in future, but the notification will not be active in time for devices that may exit the system in September 2024.

8. Recommendations to support the essential use of OPDs

Within the current EU regulatory framework for medical devices, there are many initiatives that could be taken without delay since they would not require prior amendments to the legislation. Once products at risk have been identified, then definitive measures to protect these devices are needed. The major disincentives to continued marketing appear to be the duration, cost and unpredictability of assessments for the MDR. Policies to protect OPDs need to be focused on addressing these causes. Communicating the rationales for decisions relating to individual OPDs will be important to support similar decisions in future and to set objectives for the development of new policies when needed.

8.1. A more proactive and systematic approach for identifying devices at risk

Effective policy interventions for OPDs require the earliest possible identification of 'disappearing devices' and in particular of any 'last-in-class' devices. Some national initiatives aim to identify all medical devices that are being withdrawn [8], but their coordination and a specific focus on OPDs are needed. A more proactive, systematic, and EU-wide approach should gather data, as mandated by medical device regulators according to the new 6-month notification applied to all medical devices and IVDs. European clinical associations such as the Biomedical Alliance [25], the European Reference Networks, and some pediatric subspecialty and national societies have conducted surveys, but these were not systematic. Clinicians are likely to become aware of a product withdrawal only long after the commercial decision within the company has been made. Regulators should establish and manage a common portal that all healthcare

professionals in the EU can access to report when they have concerns that an essential device may be withdrawn, and there should be a clear mechanism for regulators to consult medical associations and Expert Panels so that they can advise if special measures are needed urgently to ensure that patients are not disadvantaged.

8.2. Definition of essential medical devices

An analysis to identify essential OPDs should be considered, in a similar way to the priority medical device [29] and essential medicines listings [30] prepared by the World Health Organisation. This should include devices whether used on-label or off-label. Once a preliminary list has been compiled, engagement with the expert panels or with relevant rare disease clinical associations can provide advice to help regulators to understand the consequences of a device leaving the market, so that they may have the opportunity to take proactive measures.

8.3. Increased use of mechanisms for exceptional market approvals

To ensure continued availability of essential OPDs, the use of exceptional market approvals will be necessary. Article 59 of the MDR allows for a derogation from the typical notified body approval, whereby a national regulatory authority steps in and takes the place of the notified body on grounds of public health protection. Derogations can be granted at the level of an individual EU member state, or a referral can be made to the European Commission to allow an EU-wide derogation [31]. A derogation-based pathway would allow for a triage of the devices currently at risk, until more definitive solutions are developed. This could be supported by the relevant clinical associations in Europe, or by the expert panels as provided for in the MDR, but there is currently no procedure to give effect to expert interactions with regulators to support such derogations. We recommend that expert panels are empowered to provide advice to national competent authorities to understand when an OPD is essential. This will allow national competent authorities and/or the European Commission to issue derogations to maintain availability until more definitive solutions are developed. Another MDCG task force is currently considering how notified bodies should apply conditions on certificates, in order to support regulatory approval of needed devices but with requirements for manufacturers to collect more clinical evidence thereafter; the recommendations of that task force will probably be relevant especially for OPDs.

8.4. Expert panel for paediatric medical devices

The roles of pediatric experts need to be expanded. The European Commission and the EMA should reconsider their decision not to have an Expert Panel for medical devices used in pediatric patients [18]. A pediatric panel would be able to advise on applications for orphan status for a high-risk device, and on clinical evidence requirements for specific OPDs, in addition to the primary function of providing reviews of Clinical Evaluation Reports submitted by notified bodies. We also recommend that expert panels are empowered to prepare clinical evidence specifications so that the expectations for clinical evidence can be clarified in advance of a regulatory assessment. The eligibility criteria for membership of the panels should reflect the multidisciplinary skills that will be needed to support this work, for example with respect to biostatistics and clinical trial design.

8.5. Consultation with rare-disease communities

Although patients with rare diseases may have a particular need for on-label and off-label use of OPDs, their communities – including patients and their families, and healthcare professionals and providers, in addition to manufacturers and regulators – are under-represented within current structures. To complement clinical expert advice, the voice of patients is vital to ensure that decisions are patient-centric. Rare-disease communities could share responsibility particularly for the off-label clinical use of OPDs, in partnership with regulators and other stakeholders. They could contribute advice related to the promotion of OPDs, and provide a perspective that is unconstrained by any distinction between EU and national competences. A forum to facilitate engagement between stakeholders with an interest in OPDs and expert panels, regulators and manufacturers would support this.

8.6. Regulatory support for medical device registries and standards

The off-label use of devices cannot be avoided. It needs to be supported with:

- compulsory/extensive use of disease-based registries that can document the off-label use of devices (not device-based registries). Such registries should be conducted independently by specialist medical associations or academic institutions. They should apply consistent data standards, and be supported by public funding [18].
- standards for healthcare professionals to develop and implement best practice;
- guidance for healthcare professionals and patients/families about the status and use of off-label devices.

Each element of this recommendation needs to account for the needs and specificities of pediatric patients, where relevant.

8.7. Development of special regulatory pathways

In the longer term, it is clear that a greater centralization would be desirable on public health grounds, to coordinate the pre-market regulation and the post-market surveillance of OPDs, to protect against their possible loss and to support and facilitate their safe innovation. This would help to reduce the discordant objectives of different components within the current system. The development of new special pathways with regulatory convergence with other jurisdictions, will be desirable.

8.8. Special measures to reduce costs

Finally, the issue of the charges made by notified bodies for conformity assessments need to be addressed, with respect to orphan devices. These costs are often very high, and sometimes prohibitive because manufacturers will not bring devices to market when only a small number of products can be sold and hence their costs cannot be recovered. The European Union needs to consider establishing a mechanism for a low-cost conformity assessment of orphan devices, similar to practices established in the United States and Canada, for example by offering conformity assessment for a low fee by the EMA or by a national regulatory authority.

9. Conclusions

When the European Commissioner for Health, Stella Kyriakides, addressed health ministers at the Employment, Social Policy, Health and Consumer Affairs Council (EPSCO) meeting on 9 December 2022, she noted that the development of the MDR followed a series of scandals that put patient safety at risk, and that in some cases caused the loss of lives [20]. Some of these scandals resulted from criminal activity such as using non-medical grade silicone in breast implants [32], something which stricter regulations in the MDR may not be able to prevent. More generally, however, experience has taught us that when regulatory rules are tightened in response to tragedies (such as those related to sulfanilamide or thalidomide), the availability of regulated products for special populations such as children or those suffering from a rare disease conversely can be disadvantaged [33].

Improving regulatory systems is not a simple endeavor, and every attempt comes with foreseeable and unforeseeable consequences. When the MDR was being negotiated, the challenges of making OPDs available were not foreseen, whereas now the risk of losing essential OPDs is increasingly understood. Following the Kefauver-Harris legislative amendments in the 1960s, for the approval of medicines in the United States when for the first time medicines had to demonstrate efficacy, there was an accompanying analysis of all available medicines to understand the difference between current and expected evidence (called the Drug Efficacy Study Implementation, or DESI) [34]. In Europe we understand neither the number of OPDs nor the evidence to support them. If we truly want to protect essential orphan and pediatric interventions, we need the equivalent of a DESI for OPDs in Europe.

In the interim, we simply cannot allow the loss of currently available essential OPDs, regardless of what their labels say. This will require all stakeholders to work together with a decisive policy and with purpose to achieve definitive solutions. This will also require regulatory bodies to move from a narrow interpretation of regulatory responsibility to a broader and more public health-oriented one, in order to implement effective solutions. To develop the necessary protections, regulatory institutions in Europe will need to compromise – patients and clinicians should not be expected to.

10. Expert opinion

The recommendations that we have made have the potential to impact real world outcomes in two ways. Firstly, by identifying and protecting currently marketed devices, at risk of withdrawal, current interventions dependent on these technologies can continue. Secondly, by improving the coordination of actors responsible for OPDs, development of new devices for these populations can be better supported.

Improved regulatory coordination amongst the different experts and organizations who play a role in assessing and supporting OPDs will be central to addressing the challenges which we have outlined, and incorporating the perspectives of the pediatric and rare disease communities. There are also methodological limitations with respect to the clinical evaluation of OPDs. The MDCG guidance on the clinical evaluation of orphan devices (MDCG 2024–10) acknowledges the challenges in conducting pre-market clinical investigations. The development of a methodological framework based on case examples could help OPD developers to understand when the concepts described in the MDCG guidance can be applied. This would help OPD developers to prepare their clinical and market development strategies. Supporting these methodological frameworks and case examples with advice structures would also help developers to apply their clinical and market development strategies with greater confidence.

Now that we have a definition of an orphan device in the EU, research activities can be targeted at this specific sub-type of medical devices. Research to identify these OPDs and to better understand the critical barriers and success factors related to the introduction of these devices in the EU, from both the developers and the regulator perspective would help to further develop this field. Research to understand the prevalence of OPD related data in registries and electronic health records will help to understand the landscape of potentially useful data. Research to understand the optimal way to integrate the patient perspective and the perspective of the pediatric and rare disease communities reliant on these technologies would also help to support a better integration of these perspectives in future regulatory policy.

There are promising areas of research that can support the development of OPDs. The use of computer simulation and modeling (also know as *in silico* methods) for example, has the potential to model the device/patient interaction across the lifespan of a patient. The US FDA have a guideline to support the assessment of the credibility of these models, in order to improve their regulatory utility [35]. There is no such initiative in the EU regulatory framework and this would be an important area for future research and policy.

In the future, a greater reliance on the expertise and decisions of international regulators who have bespoke pathways for orphan and pediatric devices (for example the US FDA) would help regulators internationally to make the best use of finite resources, and it would help developers to avoid duplicative and different regulatory requirements for the introduction of OPDs internationally.

The future of the EU regulatory system for medical devices is currently subject to consideration, with the European

Commission beginning a 'targeted evaluation' of the MDR system later this year [36]. In five years time, the MDR will have completed the transitional arrangements to bring currently available devices approved under the previous Directive system into MDR compliance. This will allow the focus of regulators to shift to supporting new OPD introduction, rather than the current emphasis on avoiding the loss of currently available essential OPDs.

Abbreviations

Agence Nationale de Sécurité du Médicament (ANSM), Conformité Européene (CE), Drug Efficacy Study Implementation (DESI), Electro Encephalogram (EEG), Employment, Social Policy, Health and Consumer Affairs Council (EPSCO), European Database on Medical Devices (EUDAMED), European Medicines Agency (EMA), European Union (EU), Food and Drug Administration (FDA), Instructions for use (IFU), In-vitro diagnostics (IVD), Medical Device Coordination Group (MDCG), Medical Device Regulation EU 745/2017 (MDR), Orphan and Paediatric Devices (OPDs) The European Association of Medical Devices Notified Bodies (TEAM-NB), United States (US).

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Author contributions

TM prepared the first draft and AHJ provided significant suggestions and revisions. MD, BVK, MT, DK, AGF and MG provided comments and suggestions. TM prepared the final draft and all authors approved.

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