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REVIEW

Orphan Medical Devices and Pediatric Cardiology – What Interventionists in Europe Need to Know, and What Needs to be Done

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Abstract

Medical devices include a great diversity of technologies, which are evaluated and approved in the European Union (EU) according to a revised law that came into effect on 26 May 2021, known as the Medical Device Regulation or MDR (EU 745/2017). It has a transition period that allows products that were approved under the previous rules (the EU Medical Device Directives) to continue to be marketed until 26 May 2024 at the latest. As a result of a series of unforeseen factors, there is a possibility that the MDR may result in products becoming unavailable, with the consequent risk of a loss of some interventions that are reliant upon those devices. Devices that are used for orphan or pediatric indications are particularly vulnerable to this. There is an urgent need for policy to be developed to protect essential medical devices for orphan indications and for use in children, to ensure that necessary interventions can continue, and to ensure a more sustainable system in Europe over the longer term. Pediatric cardiologists in Europe need to be aware that particular medical devices may become unavailable over the next two years, and they should contribute to plans to mitigate this risk, so that they can continue to deliver the best possible care for their patients. This commentary examines the factors which have contributed to this issue and suggests ways that policy can be developed to address it.

Keywords Medical device · Regulation · Rare disease · Orphan product

Introduction

Medical devices range from simple wound dressings to complex products such as pacemakers. Their approval is determined by their risk classification and by the system that applies in each jurisdiction. In Europe, the regulations concerning medical devices have recently been subject to significant changes.

Medical devices used in children and those used for the treatment of rare diseases (therapeutic orphan devices) have very different market dynamics, characterized by low sales and a reduced return on investment, when compared to general medical devices. These products are therefore particularly vulnerable to being withdrawn from sale if additional barriers arise, for example from increased regulatory requirements and costs or from longer approval times. Already, many interventions in pediatric cardiology are heavily reliant on the 'off-label' use of medical devices intended for adults, often in different anatomical locations or organ systems [1].

In this paper, we review the regulatory changes that have occurred in the European Union (EU) and discuss their potential impact on the availability of orphan or pediatric devices. We examine the types of support that are provided in other regulatory systems, and we recommend how policy makers and clinicians can ensure that risks to patients are mitigated as much as possible.

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The Background—Medical Device Regulation in Europe

The first laws concerning medical devices in Europe were published in 1990 for active implantable medical devices [2] and in 1993 for general medical devices [3]. These were European Union Directives, which had to be transposed into national law by each member state.

Before these Directives, it was necessary to comply with the national standards in each country. These often had different requirements concerning product testing and manufacturing, which introduced technical barriers that made it difficult to trade medical devices across borders in Europe. The European Union therefore applied its 'new approach' legislative framework to medical devices, which introduced the principle of shared 'essential requirements' for all products in place of differing national standards. Once a product complies with the essential requirements and satisfactorily undergoes a review known as a 'conformity assessment', conducted by a notified body, then it can be affixed with a CE-mark and sold anywhere within the European Union. This new approach policy succeeded in establishing a single market for medical devices in Europe.

It is important to note that the primary motivation behind the directives for medical devices was to facilitate trade, and that there was minimal focus on clinical evidence requirements. As a result, the directives allowed high-risk devices to enter the market without pre-market clinical studies, by using non-clinical test methods, or by claiming equivalence to another device. The emphasis on trade was very different from the rationale for the first European regulation for medicinal products, which was designed much more to protect public health and which mandates clinical trials and a demonstration of therapeutic efficacy [4]. A summary of important differences that persist between drug and device regulation is presented in Table 1.

Taken from Fraser AG, Nelissen RGHH, Kjærsgaard-Andersen P, et al. Improved clinical investigation and evaluation of high-risk medical devices: the rationale and objectives of CORE-MD (Coordinating Research and Evidence for Medical Devices). EFORT Open Rev. 2021;6:839-849.

As a 'light-touch' regulatory system, the EU Directives led to some high-profile failures of medical devices, [5, 6] and they resulted in more safety alerts and recalls than occurred when devices were first approved in the USA [7]. One benefit of the light-touch EU system, however, was that it tended to be supportive of innovative product development.

On 26 May 2021, the Medical Device Regulation (EU 745/2017) (MDR) entered into force. A Regulation applies directly in each member state of the EU. The MDR maintained the 'new approach' of the Directives but introduced some important changes, particularly to strengthen the quality of clinical evidence for high-risk devices [8]. Although it is very detailed, with 123 Articles and 16 Annexes, the MDR does not include any special pathways for the regulatory approval of orphan medical devices. An orphan disease is defined by the European Medicines Agency (EMA) as occurring in < 1 in 2000 people, so a similar definition for orphan medical devices would apply to many technologies used in pediatric cardiology. For example, the prevalence of transposition of the great arteries is < 1 in 3000, and that of tricuspid atresia < 1 in 9000 (both possible indications for emergency balloon atrial septostomy, see below).

This leaves medical devices in the EU in a very different position from drugs, since pathways were developed for orphan medicinal products in 2000 [9] and for pediatric medicinal products in 2006 [10]. In 2007, the European Commission undertook a public consultation on the

Table 1 Some key differences between the regulatory evaluation of pharmaceutical products (drugs) and high-risk medical devices in the European Union

	Pharmaceutical products	Medical devices
Organization responsible for granting market access	European Medicines Agency (about 90%) National authorities (≈ 10%)	Notified bodies
Types of organizations which bring products to market	Mostly large and established pharmaceutical companies	Variable: many start-ups and small and medium enterprises, as well as large medical technology companies
Time when clinical evidence is generated	Generally pre-market	Both pre- and post-market studies
Clinical development phases	Highly standardized (phases 1–4)	Less standardized Product-dependent
Clinical study design	Highly standardized. Double-blind randomized controlled trial expected.	Less standardized Pivotal trials often done after CE-marking
Irreversible effects on study subjects	Rare	Common, particularly with permanent implants

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possibility of adopting legislation for orphan or pediatric medical devices, but it did not proceed [11]. The US Food and Drug Administration (FDA) has pathways such as its humanitarian device exemption scheme [12] and the breakthrough device program [13], which together with other activities provide support for research and innovation of novel medical devices for pediatric indications [14].

Why has the Marketing of Orphan and Pediatric Products Become More Challenging in Europe?

In order to understand the challenges arising from regulatory changes, it is helpful to understand the nature of the medical device sector in Europe. There are approximately 34,000 medical device manufacturers in Europe [15] and estimates suggest that 95% are small and medium-sized enterprises (SME) [16]. The number of manufacturers of orphan or pediatric devices and the number of these products are not known in Europe as there is no central database.

When the FDA introduced the first legislation in the USA for medical devices in 1976, it allowed the continued use and marketing of devices that had been available before the entry into force of the law (an approach known sometimes as 'grandfathering'). In Europe, we are making significant changes to a system that is already running—the equivalent of fixing an engine while the plane is in the air—without any provision for some legacy devices to be exempt from the new provisions.

Orphan or pediatric medical devices may be developed as customized devices or as smaller versions of a device that is already manufactured for adults, such as an implantable heart valve, or they may be developed de novo and not based upon similar products in general use. Companies which develop new products are often small businesses with few experts in regulatory affairs, which makes the burden of compliance more difficult to manage than it would be in a larger organization. Some of the additional burden relates to increased requirements for technical documents, particularly plans and reports relating to clinical evidence and post-market data. This is not simply an initial exercise, but one that requires ongoing maintenance and resources from the manufacturer throughout the duration of marketing of its product.

The MDR has increased the general requirements for clinical data, but in the absence of EU technical specifications for particular types of devices it can be difficult for a manufacturer to understand if further clinical studies are needed. This can be particularly challenging because it is impossible for a company to receive advice from a notified body prior to making its submission [17]. That is very different from the USA where the FDA offers a Q-Submission process in which developers can ask questions before their regulatory submission, so that they can then design studies and provide clinical evidence that will make the pathway to the market more predictable [18]. In the EU, product developers are faced with a new set of legal requirements but have to wait for the assessment of the notified body. The assessment process is highly formalized, and the notified body will reject an application after a number of rounds of interaction (typically three) if non-conformities have been raised but it remains unsatisfied with the corrective plans that the manufacturer has submitted in response. For a high-risk device the whole process can take up to 18 months.

These challenges are compounded by lack of capacity in the notified bodies, which are the independent commercial organizations that conduct conformity assessments to allow CE-marking and marketing of a product. All notified bodies which were active under the device directives are required to be redesignated by their national regulatory agency to evaluate devices according to the new MDR. By July 2022 only 31 have been approved, compared with a total of 96 at one time under the directives. The representative group for notified bodies (TEAM NB) issued a report based on their 2021 activity which demonstrated that there is insufficient capacity to assess all products currently available under the Directives before time runs out under the transitional rules in May 2024 [19]. Only 1069 new certificates have been issued out of a total of at least 24,073 that need to be renewed [20].

As a result of these various factors, some medical device manufacturers may restrict the range of devices in their portfolios as they convert to the MDR, in order to prioritize their more profitable products for notified body assessment. It is very difficult to estimate the risk that important products may be withdrawn, affecting clinical practice.

The challenges of system capacity and readiness have been known in Europe for some time now, but it is only recently that the possible consequences have been assessed by surveys. One questionnaire to industry found that 89% of respondents now prefer US rather than EU market entry for innovative devices, due to the increased predictability of regulatory requirements [21]. The European trade association MedTech Europe published results of a questionnaire of medical device manufacturers which found that over half of respondents plan portfolio reductions, and that 33% of these companies' medical devices are currently planned for discontinuation [22].

Finally, it is important to note that many of the products used in Europe for orphan or pediatric interventions are used 'off-label', meaning that the products are marketed for one indication but used differently. For example, for stenting of coarctation of the aorta, in many cases stents developed for biliary or renal interventions may need to be used, despite limited data on long-term outcomes. Manufacturers who are reassessing their product portfolios may not realize that by

removing some products with low-volume sales, they may in fact be withdrawing products with important orphan or pediatric indications.

Why are Orphan and Pediatric Products at Particular Risk?

The regulatory challenges mentioned above affect all medical device manufacturers, but those of orphan and pediatric products are particularly vulnerable to additional costs and regulatory hurdles. The US FDA conducted a survey of clinicians in 2018 which described a range of obstacles and their relative magnitudes. This survey found that 'costs of development' and 'lack of profitability to industry' were the two largest independently perceived impediments to new devices becoming available [23].

What Could be the Consequence of this?

The public health risk is the potential loss of necessary interventions, due to withdrawal of the products needed to conduct them. Two examples are provided below to highlight how this can lead to changes in treatment.

Example 1—the Rashkind Balloon Catheter.

Dr William Rashkind developed balloon atrial septostomy in 1966 [24], using a balloon catheter to dilate an existing atrial communication in order to improve atrial mixing. This has been a well-established and potentially life-saving intervention for cyanotic congenital heart disease for many years. The procedure is typically carried out on neonates or young infants.

Three years ago, at least three alternative devices were available, from Edwards Lifesciences (Edwards Lifesciences LLC, Irvine, California, USA), Medtronic (Medtronic Inc., Minnesota, USA) and NuMed (NuMed Inc., Texas, USA). Recently, recalls were required for two of these products [25, 26] due to technical problems, so now only one remains available in Europe (insofar as the authors are aware). In the event that the last available device is withdrawn, then it would no longer be possible to perform balloon atrial septostomy.

Having to use a device with which they are unfamiliar and that may have different characteristics (requiring insertion over a wire) means that some interventionists now prefer to undertake the procedure in the catheterization laboratory rather than at the bedside under transthoracic echocardiographic guidance.

The manufacturer of the remaining device has shared its comparison of the regulatory costs and timelines for their current and the planned next versions (Table 2).

Personal communication from NuMed, reproduced with permission.

The costs in the EU are at least tenfold higher than for the equivalent assessment in the USA or Canada. Due to the anticipated long timeline for assessment in Europe, and the date of expiry of their current CE certificate, the manufacturer may lose market access for their device from July 2023 for at least one year.

Alternative interventions could be static balloon dilation, an emergency arterial switch operation, or extracorporeal membrane oxygenation (ECMO) followed by surgery. These alternative interventions may not be as effective and they may be associated with a higher rate of complications, in addition to being more resource intensive.

Example 2—the Cook Medical 414 stent.

The Cook Medical Formula 414 Stent (Cook Medical LLC, Indiana, USA) is a balloon expandable renal stent system that was available in Europe until last year. This stent was used 'off-label' for interventions such as coarctation of the aorta in newborns [27] or for stenting of

Table 2 Comparison of costs and duration of regulatory assessment in Europe and North America, for the Z-5 and Z-6 Atrioseptostomy catheters manufactured by NuMed

	EU MDR 2017/745	US FDA	Health Canada
Cost of assessment	€135,844 ($142,832) every 5 years	€3,030 ($3,186) One payment (Small Business Fee)	€7,412 ($9,964 CAD) One-off payment for license amendment of €7412 ($9,964 CAD), and annual license renewal cost of €283 ($381 CAD)
Duration of assessment	18–24 months review time	30-day review under Special 510(k) process	License Amendment Review, received within 47 days

EU MDR European Union Medical Device Regulation; *US FDA* Food and Drug Administration of the United States of America; *CAD* Canadian dollars

the right ventricular outflow tract in neonates and young infants [28]. These are complex interventions for which alternative treatments may include balloon angioplasty or surgery. Although Cook Medical offer other size conformations of this stent type, they have thicker guidewires and may be less suitable for use in neonates. This is an example of a portfolio change by a manufacturer for renal stenting which has potential consequences for treatment options in pediatric cardiology.

If we Start to See More Product Withdrawals, Does the Regulatory System have Checks and Balances to Counteract this?

For products which are not CE-marked, it is possible to apply for a derogation [29]. This is an exceptional approval in which the national competent authority steps in on a national basis, to allow marketing in place of the usual assessment by a notified body. This procedure is more complex and less predictable, however, than the usual notified body assessment, and a separate application may be required for each patient or at the least in each EU member state. It is legally possible for the European Commission to apply a derogation on an EU-wide basis, following the issuing of a derogation by one member state, but that has never happened despite a number of national derogations being issued during the COVID-19 pandemic. National regulatory agencies and the European Commission could coordinate to set a policy for the use of derogations in a more systematic way, but it might be vulnerable to legal challenge as it would create a loop-hole in the free market. Derogations are unlikely to provide a realistic solution to the current challenges.

When faced with the added burden of COVID-19, the European Commission delayed the date of application of the MDR from May 2020 to May 2021, in order to prioritize activity related to the pandemic [30]. Two of the largest national trade associations for medical devices recently called for a further delay to the MDR, in order to avoid 'disaster for patients' [31]. That would achieve a stay of execution, but not a definitive solution to the challenges described above.

These factors leave policy makers in Europe struggling to maintain the availability of current products, rather than striving to provide extra incentives and supports to ensure that innovative and safe products are available for special populations.

What Can Medical Device Policy Makers in Europe Learn From Elsewhere?

The European Commission has dedicated significant resources to developing policies for orphan drugs, noting that 'patients suffering from rare diseases deserve the same quality of treatment as other patients within the European Union' [32]. Tools have been introduced by legislation for both orphan diseases [9] and pediatric products [10]. The FDA has also adapted more policy and regulatory tools to support these populations with the devices that they need.

The EU regulatory system for medical devices could learn a lot from the special provisions for devices in the USA and for drugs in the EU, both in terms of effective incentives and requirements or 'carrots and sticks'. Some examples that might increase the availability of products are provided in Table 3.

What can Interventionists in Europe do

Practicing clinicians who use products for which there are limited alternatives and which may be vulnerable to discontinued marketing, should consider early engagement with product manufacturers. It is important for clinicians to be aware as soon as possible if there are plans to withdraw products, as planning may be needed to transition to alternative products, suppliers or possibly interventions. In some cases stockpiling of products may help to manage short periods of unavailability. For some products, there may be a learning curve associated with the use of alternative devices, so preparing for this in advance is important. This is likely to become most acute in the run-up to May 2024 when the transition period will end.

Engaging with national regulatory authorities via clinical associations and engaging in European initiatives to collect data relating to this issue should be considered. The Association for European Paediatric and Congenital Cardiology (AEPC) has a Working Group on Interventional Cardiology, that is collating information about devices that may be affected.

What do Policy Makers Need to do?

The public health risk associated with a loss of necessary products requires urgent attention. This could start by identifying the products which are at risk of being withdrawn. Because of the absence of any centralized European database, this will require support from medical device manufacturers and their trade associations and from the clinical associations whose members rely most on orphan and pediatric devices. Once identified, these products require support by means of reducing the cost and burden of regulatory compliance in a reasonable way. Expert panels have been active for over 1 year, and a number of opinions on new and high-risk medical devices have been produced. [33] These panels are intended to provide consistent scientific, technical and clinical advice

Table 3 Regulatory incentives and requirements to support orphan products

	European Union	United States of America
Requirement for companies with adult products to assess use in pediatric populations	Yes for pharmaceutical products, established by Regulation (EC) No 1901/2006 on medicinal products for pediatric use	Established by the Medical Device Safety and Improvement Act of 2007
Requirement for regulators to track the products available for orphan / pediatric populations	EU Orphan product legislation provides for a formal designation as an orphan product, which will then be tracked centrally	Established by The Medical Device Safety and Improvement Act of 2007
Market exclusivity as an incentive to develop products	Market exclusivity is provided for in Regulation (EC) 141/2000 on orphan medicinal products	The US FDA has a Pediatric Exclusivity Provision for drug development, but it does not have one for medical devices.[b] The US FDA also has a voucher program to allow for a priority review.[c]
Incentive with public sector funding for research on rare diseases	Orphan diseases are a research priority for European funding in general, but without prominent reference to medical devices.[a]	The US FDA Pediatric Device Consortia Program.[d]
Fee waiver for regulatory assessments	Yes. A total or partial fee reduction is available, once an orphan designation has been granted by the European Commission.[e]	Yes. For a pre-market authorisation (PMA) application for a device intended solely for a pediatric population under Sect. 738(a)(2)(B)(i) of the Federal Food, Drug, and Cosmetic Act

[a]European Commission, Study to support the evaluation of the EU Orphan Regulation, Final report July 2019 https://ec.europa.eu/health/system/files/2020-08/orphan-regulation_study_final-report_en_0.pdf. Accessed 13 June 2022. [b]U.S. Food and Drug Administration, The Pediatric Exclusivity Provision, 21 April 2022, https://www.fda.gov/science-research/pediatrics/pediatric-exclusivity-provision#:~:text=L.,as%20the%20pediatric%20exclusivity%20provision. Accessed 13 June 2022. [c]U.S. Food and Drug Administration, Rare Pediatric Disease (RPD) Designation and Voucher Programs https://www.fda.gov/industry/developing-products-rare-diseases-conditions/rare-pediatric-disease-rpd-designation-and-voucher-programs. Accessed 26 June 2022. [d]U.S. Food and Drug Administration, Pediatric Device Consortia Grants Program https://www.fda.gov/industry/developing-products-rare-diseases-conditions/pediatric-device-consortia-grants-program. Accessed 26 June 2022. [e]European Medicines Agency, Decision of the Executive Director on fee reductions for designated orphan medicinal products, EMA/135645/2020 https://www.ema.europa.eu/en/documents/other/decision-executive-director-fee-reductions-designated-orphan-medicinal-products_en.pdf Accessed 25 July 2022

when needed to support the implementation of the MDR [34] and they could assist policy development for orphan and pediatric devices.

For 'last option' products, where there are no alternatives, the development of definitive policy is of the greatest importance. Manufacturers should seek to identify when their products are being used in a systematic off-label way for an orphan or pediatric indication, and this should be taken into account when assessing their product portfolios. In the longer term, specific legislation and funding support should be considered. Interaction with more mature regulatory systems such as the US FDA has the potential to drive greater harmonization of regulatory requirements and share support for developing important but perhaps neglected products. Clinicians in the United Kingdom and Switzerland, where the regulatory systems have diverged from European Union rules in recent years should be extra vigilant, as product manufacturers may be less incentivized to undertake additional regulatory requirements for these markets. For clinicians who have no option but to use devices in an off-label way for a necessary intervention, a policy of no-fault insurance should be considered.

Conclusion

Awareness is building in Europe that the risk that some essential medical devices may become unavailable is real, which increases the chance that a definitive policy will be developed. The Medical Device Coordination Group (MDCG) is the statutory committee of the European Commission and the EU member states that has responsibility for implementing the MDR [35]. Although it is not listed in the current plans of the Commission [36], the MDCG has established a task force to consider the availability of "niche products".

Clinical and scientific experts are also becoming increasingly involved in medical device policy, and this will help to provide a better research base for policy development. Examples of relevant groups in Europe and elsewhere are listed in Table 4.

Products for pediatric populations or orphan indications are particularly vulnerable to market dynamics, and once a product exits worldwide markets, it is almost impossible to resurrect it. There is an urgent need to develop short-term solutions to avoid the loss of products needed for

Table 4 Initiatives to support orphan medical devices

	European Union	International
Public institution with responsibility for policy development	No specific office for medical devices EMA has a Committee for Orphan Medicinal Products	US FDA has an Office For Orphan Products
Scientific groups examining evidence requirements	CORE-MD project, a Horizon 2020 funded project examining methodologies for evaluating medical devices has a task on pediatric devices	The International Rare Diseases Research Consortium (IRDiRC) MedTech Taskforce with support from worldwide patient representatives, regulators, and scientists
Availability of advice for device developers	None available from European Union institutions including notified bodies Envisaged to be provided by Expert Panels under the MDR, but not yet implemented	US FDA allows requests for Feedback and Meetings for Medical Device Submissions (the Q-submission process)
Multi-stakeholder initiatives to support pediatric device development	None available	SHIP-MD initiative in the USA includes the US FDA, industry, clinical and health system representatives
Funding support	No specific funding scheme to support the development of medical devices Horizon 2020 or forthcoming Innovative Health Initiative may have some support for product development EPTRI is a Horizon 2020 funded project, but it is focused on drug development	US FDA Pediatric Device Consortia Grants Program provides services and funding to device development projects

EMA European Medicines Agency; *US FDA* Food and Drug Administration of the United States of America; *CORE-MD* Coordinating Research and Evidence for Medical Devices; *IRDiRC* International Rare Diseases Research Consortium; *MDR* Medical Device Regulation; *SHIP-MD* System of Hospitals for Innovation in Pediatrics – Medical Devices; *EPTRI* European Paediatric Translational Research Infrastructure

interventions for orphan and pediatric indications. We also need to develop a more sustainable regulatory ecosystem which provides a supportive, rather than a hostile approach to the introduction of new devices in Europe.

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Declarations

Conflict of interest TM reports no financial interest. TM is an unpaid advisory board member for a start-up medical device developer Pumpinheart. TM is a member of the IRDiRC International Rare Diseases Research Consortium Working Group on MedTech for Rare Diseases which is mentioned in the article. DK is a proctor/consultant for Edwards Lifesciences, Medtronic, Venus MedTech and Occlutech. MG is Chairman of the Medical Device Regulation Task Force of the Working Group Interventional Cardiology of the Association for European Paediatric and Congenital Cardiology (AEPC). AGF is Scientific Coordinator of the CORE-MD project, supported by grant 965246 from the EU Horizon 2020 program.

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