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Regulatory Frameworks for Orphan Medical Device: A Comparative Review of USFDA and EU Approaches

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ABSTRACT

Approval and development of medical products dealing with rare illnesses, referred to as orphan devices, present special regulation and clinical issue because of small patient requirements, significant development expenses, and low commercial appeal. The paper entails a comparative evaluation of the regulatory standards implemented by the United States food and drug administration (USFDA) as well as the European Union (EU) in dealing with these challenges. The USFDA has now created specific methods to accelerate orphan devices with their Humanitarian Use Device (HUD) and Humanitarian Device exemption (HDE) programs, which have more relaxed standards of clinical evidence and ease of entry of an orphan to the market by utilizing Institutional Review Board (IRB)-approved use. By comparison, the EU covers the subject of orphan devices with the Medical Device Regulation (MDR) 2017/745, not giving them a specific orphan pathway, which requires a stricter procedure of conformity assessment and increased amount of premarket clinical evidence. This paper presents the definitions, the approval methods, post-marketing surveillance requirements, and challenges peculiar to each of the regions. Although the US system focuses on faster access among limited data, the EU system prefers high safety and performance requirements. The review comes to the conclusion that harmonization, or mutual learning of these regulatory systems, may promote both innovation and patient safety especially concerning the SMEs and patients with rare medical conditions.

INTRODUCTION

The characteristics of rare diseases are largely connected with the small number of patients and insufficient expertise. This type of medical products will hereafter be defined as the term orphan devices as the term orphan drug is applicable relating to these kinds of medical products, in that, they are less likely to be developed since they are small products in terms of market, and their research and development costs are normally not recoverable by the revenues generated by the market.

The FDA groundbreaking initiative Humanitarian Use Device (HUD)/Humanitarian Device Exemption (HDE) was specifically intended to fast-track the market introduction of orphan devices on the basis of their continued multiple authorization of local investigational review board… Since no similar regulatory course is introduced in the EU, one arises, whether any of the aspects of the FDA approach can be used as an example of the modelled legislation in the EU (Worringen U.,2015)

The rules on medical devices in the European Union (EU) altered in May 2021. The Medical Device Regulation (MDR) was created to guarantee the performance of the internal market of the medical devices and guarantee the health of the users and patients. But the MDR, too, delivered unplanned consequences, and resulted in an impairment in the development of medical devices to treat rare diseases Orphan Device (n.d.) in the EU". Medical equipment includes instruments, implants, assistive devices and diagnostic equipment. When many medical devices have to be developed across the globe, there is a lack of devotion to the development and availability of the medical device used in the rarest diseases. (Potman K.,2024)

Rare diseases have been referred to as chronic debilitating or life-threatening diseases that occur in a rate of up to 5 out of 10, 000 people and less (Worringen U.,2015)

The European Union medicines legislation characterizes rare diseases to be those having a prevalence of less than <1/2,000 of the population. The number of known rare diseases ranges between 6,000 and 8,000, which means such diseases cause a problem to 30 million people in the EU, and therefore the overall effect they have on the society is much beyond what the term rare disease reflects (. Melvin T et al., 2024)

This thesis is an attempt to examine details of the regulatory pathways in European Union (EU) and United States (U.S.) towards

medical devices to be used in rare diseases and conditions. The market dynamics are drastically different in medical gadgets applied in children and medical gadgets applied in treatment of rare diseases (therapeutic orphan devices), as compared to general medical devices, that is, the sales are low and the rate of return is low. This is in effect what makes these products highly susceptible in case there is an increase in the number of barriers such as additional regulatory requirements and costs or delay in the approval process (Sutherell JS et al., 2010)

Ⅰ.Orphan Medical Device development and approval process of USFDA:

2.Definition:

A Humanitarian Use Device (HUD) is a division of medical equipment in which the United States Food and Drug Administration (USFDA) categorized it under Safe Medical Devices Act of 1990, controlled as in 21 CFR 814.3-(n). The USFDA outlines that a HUD is expressly supposed to have the effect of benefiting patients by diagnosing or treating a disease or condition that does not impact or appear in greater than 8,000 people yearly in the United States. The regulatory pathway refers to the intervention aimed at encouraging innovation and availability of medical devices that would address rare or orphan diseases, the low number of patients, which could not constitute an adequate commercial incentive to the development of traditional premarket approval (PMA).Clue regulatory considerations of an HUD are:The condition should be afflicted or represented in 8,000 or less persons per year in the United States,The machine should be safe and likely on a benefit and The application is expected to contain adequate scientific evidence to substantiate the planned use, but is not under the same intensive set of requirements of effectiveness as would be needed to obtain a PMA.(USFDA 814.3,2025)

3.Regulatory Framework:

3.1 United States: The Humanitarian Device Exemption (HDE)

When the U.S. Congress passed the concept of humanitarian use device/ humanitarian device exemption in 1990, the Safe Medical Devices Act of 1990 (P. L. 101-629) fixed a regulatory framework by the U.S. federal law governing the obligation of unusual restraints and financial burdens of medical devices in development that was aimed at targeting the rare disease populations.

Finally, the U.S. Congress came to know of the barriers of the approval threshold of potential medical devices with new technologies regarding the health care value including in rare diseases as well. A non-standard premarket procedure, also known as HUD/ HDE pathway was adopted in order to avoid leaving patients having a rare disease or condition behind to access the technical innovation adopted as well as the associated previous technical innovation adoption benefits under the standard premarket procedure adopted by the product sponsor company or corporation.(Worringen U.,2015)

A manufacturer of an orphan device must first send a Humanitarian Use Device (HUD) designation request to the FDA Office of Orphan Products Development. In order to get this designation, the manufacturer has to show that the device fits the definition of an orphan device as well as must provide a rationale of how they intend to use the device and why the population group that they are prescribing it to needs the device. Having been awarded the HUD status, the manufacturer may go further and make a Humanitarian Device Exemption (HDE) application and request for permission to market the product.(USFDA,2016)

HDE will be accorded to a device that satisfies three requirements namely:

1.The device must not create greater or high risk of disease and crippling to the patients and the benefits to health must outweigh the risk.

2.There must be no other choice or alternative in treating or diagnosing a specific disease/condition, there must be no access by the individuals to the device outside the HDE and no similar device to treat or diagnose the same disease/condition.

3.The machine is used to treat or diagnose a disease / condition that affects a population of not more than 8,000 people. (USFDA,2019)

4.Approval and Development of Humanitarian Use Device (HUDs)

Humanitarian Device Exemption (HDE) program in the U.S. Food and Drug Administration (FDA) regulates the development and approval procedure of the so-called Humanitarian Use Devices (HUDs) and are stipulated by the Title 21 of the Code of Federal Regulations (21 CFR Part 814, Subpart H). This was identified in the Safe Medical Devices Act of 1990, and subsequent improvements on the same introduced in the Food and Drug Administration Modernization Act (FDAMA) of 1997, as a means to jump start innovation in the field of medical devices concerning conditions which exhibit small numbers of patients.

4.1 Rare Condition and Unmet Medical Need identification

The initial phase of the creation of a HUD is the identification of a rare disease or condition that does not have more than 8,000 individuals affected by the given condition each year in the United States. Developers need to prove that there exists a medical need that is not satisfied or that the therapeutic alternatives are insufficient and inappropriate, consequently qualifying the potential advantage of the specified device. (USFDA,2022)

4.2 Clinical and Preclinical Development

Despite the streamlining of the burden of proving effectiveness incorporated by the HUD pathway, manufacturers do need to carry out:

- Bench testing, Biocompatibility etc. (preclinical studies)
- Clinical studies, frequently conducted with smaller trial or case series to obtain safety data and some preliminary evidence of likely usefulness.

The aim is to show the device:

- Does not create a high risk to the patient which is not reasonable
- Will be to bring clinical benefit to the targeted patient group.(USFDA,2019)

4.3. HUD designation (humanitarian use designation)

In order to move forward the HDE pathway, manufacturers have to file the application designation to Humanitarian Use Devices (HUD) to the Office of Orphan Products Development (OOPD), which will be followed by the FDA. Such application should contain:

- An Explanation of an illness or a disorder.
- The projected number of victims in U.S.
- A description of the evidence that indicates how the device diagnoses the condition.(USFDA 814.102, 2025)

4.4. Request of Humanitarian Device Exemption (HDE) Request

After the HUD designation is issued, the manufacturer files EC with the FDA Center of Devices and Radiological Health (CDRH) or the Center of Biologics Evaluation and Research (CBER). HDE application should include:The device description and the details of manufacturing it Preclinical and clinical safety information, Likely benefit, v. risk analysis, Labeling and instructions of use and Plans of post-market surveillance (when needed)

In contrast to the Premarket Approval (PMA) process, the HDE application has no need in proving the effectiveness regarding the outcome of large-scale randomized trials.(USFDA 814.104, 2025)

4.5. FDA Review and Approval

The FDA checks the HDE application in order to determine:

- The safety report of the device.
- The expected good to the targeted patient population.
- The question of whether the device qualifies to be categorized as a Humanitarian Device Exemption.

During this review process the FDA may also solicit advice of external advisory panels.(USFDA 814, 2025)

4.6. Control of the Institutional Review Boards (IRB)

Through HDE, the devices can only be deployed in facilities with Institutional Review Board (IRB) permission in order to provide constant ethical monitoring of usage of the device in provision of medical care to the patients.(USFDA 814.124, 2025)

4.7. Marketing and Post-Market Surveillance

Once approved:

The machine can be sold to generate the targeted rare indication. The manufacturer is required to undertake post-market surveillance by reporting the adverse events to the manufacturer in addition to the stipulated conditions that may be introduced by FDA.

Under section 520(m) of the FDCA, the device is generally not permitted to be sold at a profit unless the particular conditions (like use of such a device by pediatrics) are indicated.(USFDA,2025)

Figure 1. Approval process for Humanitarian Use Device

5. USFDA Clinical Evidence and Performance Requirement

The products used by the rare disease population need postmarket studies to provide up-to-date and comprehensive device data as in technical terms, the authorization of the products will be granted in the initial phase with only partial information.

General exemption of the premarket demonstration of effectiveness of an orphan device should be coupled with a life cycle robust approach. This might not suffice in a situation where the technical limitations are not significantly strong, and the generation of efficacy data would be possible, but it is financially prohibitive.

Considering that there are no other methods of treatment available, and considering extreme conditions of the malady, initial data must be acceptable, should it suit. Only in these kinds of situations should it be appropriate that different levels of protection be extended to patients, which otherwise would be a cause of concern to the community in their perspective as it relates to health and safety.

The fact that the devices are labeled as ascertained as HUD, and they could be used in the clinical setting only after they are approved by an institutional review board, does not pay off the risk of using a new device, frequently placed inside the body itself, with some unknown level of benefit, simply because it would be too expensive to create substantive data.(Worringen U.,2015)

The Humanitarian Use Device (HUD) regulation is an effective program that helps to expand access to medical device to patients with rare diseases or conditions whose conditions are unlikely to generate a standard market incentive to lead to the invention of new devices. Through the granting of an approval avenue with minimal clinical evidence support, HUD program enables the availability of life-saving /life-promoting devices that may help in treatment of small numbers of patients. Nonetheless, this method has also some disadvantages. This nature of clinical evidence requirements being less than standard device approvals naturally implies that there are usually little data on safety and efficacy at the point of approval. This has the possibility of subjecting patients to unforeseen danger which poses insecurity to patient safety in the instance of not having a formidable premarket clinical testing. (Potman K.,2024)

6. Requirements on Labelling and Regulatory Disactivate of Humanitarian Use Devices (HUDs) in US FDA Regulations

Section 502(a) [21 U.S.C. 352 (a)] of the Federal Food, Drug, and Cosmetic Act (FD&C Act), which covers all devices produced or introduced into commerce, including Humanitarian Use Devices (HUDs), requires that all accompanying labelling and promotional material be true and not misleading. This condition makes sure that information that is presented does not mis publicize the safety, efficacy, or other intended use of such a device. A misbranding under this section is to have an untrue or misleading labelling in one way or the other (USFDA,2018)

In the case of devices cleared through Humanitarian Device Exemption (HDE) pathway, a certain disclaimer in the labelling of the device is required by the code of federal regulations [21 C.F.R. SS 814.104(b)(4)(ii)]. It is expected that this disclaimer will alert both the medical community and the consumer of the fact that the efficacy of the device has not been proved categorically with the help of the traditional large-scale clinical trials. This should be stated that: Humanitarian Device. Indicated under the Federal law to be used in the [treatment or diagnosis] of [specify disease or condition]. The functionality of such device towards this application has not been established. (USFDA 814(b)(4), 2025)

This labelling guarantees the transparency of the fact that the clinical evidence of the device is rather limited, which is a cornerstone of the HDE regulatory framework that helps to get access to devices designed to treat rare conditions.

Besides this disclaimer, the labeling should also comply with the general requirements as outlined under 21 C.F.R. 814.20 (b) (10) that states that the labeling must include:

- The description of the device and the purpose of usage;
- Warnings, contraindications and precautions;
- Full uses and directions;
- Maintenance, storage, and handling data;
- The list of potential negative effects and complications.

These requirements will guarantee that the information that should be made available to the healthcare professionals and

patients is complete, balanced and necessary so as they make informed choices about using the device. (USFDA 814.20, 2025)

Ⅱ.Orphan Medical Device development and approval process of EU:

7.Definition:

The Medical Device Coordination Group (MDCG) defines the orphan medical devices as: orphan medical devices are products that are specifically designed to diagnose, treat, or prevent a disease or condition that afflicts less than or equal to 14,000 people per year in the European Union. Also, the devices in question can be contemplated when the treatment option is short of existence and/or when they support a probable clinical benefit to existent methods or the prevailing standard of care. The definition appears in the MDCG guidance article on clinical evaluation of orphan medical devices.(MDCG,2024)

8.Orphan Device Status and Orphan Indication

An Orphan Device (OD) in the European Union is a medical device that is particularly designed to prevent, diagnose, or treat a particular disease which is known to affect no more than 12,000 people in a year and either there has been no adequate alternative to this device or the device will offer a promised clinical improvement over other existing alternatives. As opposed to orphan drugs, orphan device has no market exclusivity and more than one device in the same area of treatment may be granted orphan device status. In case of manufacturers with OD designation, there is a need to give a sound scientific rationale, i.e., the epidemiological evidence coupled with device-specific issues, and it is not part of the clinical evidence required as a part of the conformity assessment exercise. Also, an orphan indication of a device may be included in a larger intended use, provided that the device is used in a rare population, or subpopulation that differs significantly with the general use, during which data extrapolation of the non-orphan population may be acceptable, when the populations are similar enough and the data is high in quality, and there is sufficient (high) quality evidence and this extrapolated evidence is scientifically valid and sound.(MDCG,2024)

9.Regulatory Framework:

The medical device regulation (EU) 2017/745 (MDR) became effective on 26 May 2021, replacing the Medical Device Directives. In comparison with the Directives that need to be transposed into national law, a Regulation, e.g., the MDR, is directly applicable and has the legal effect in all EU Member States without involving National laws. The MDR also maintained the key features of the so-called New Approach to which the previous Directives are aimed that is why they are focused on the application of the basic safety and performance demands. Nonetheless, MDR incorporated important changes that are meant to improve the overall safety and performance of medical equipment in the European economy. Among the most significant changes, is the significant increase in the level of clinical evidence requirement, and also in the case of high-risk devices. The MDR focuses more on clinical assessment, post-marked clinical follow-up, and sustained production of information during the entire life of the device in order to guarantee the safety of the patients and efficiency of the device. Such increased demands are aimed to regain the lost confidence of the population, raise the accountability and make sure that only the well-proven safe and clinically useful device is further admitted to the market. (EU,2022)

MDR had a special impact on orphan devices because of these products and market forces. Furthermore, most orphan devices within the EU are frequently invented by the Small and Medium-sized Enterprises (SMEs), which have very poor knowledge and experience in terms of regulatory matters. SMEs can have a difficult time dealing with regulatory changes. This renders orphan devices even more open to market withdrawal.(Melvin D et al.,2023)

Strict regulatory requirements set with the EU Medical Device Regulation (MDR 2017/745) represent a huge challenge to orphan devices. A large number of these devices are invented by the Small and Medium-sized Enterprises (SMEs) and they possess little regulatory affairs skills and resources. SMEs are usually not able to handle the increased cost, complex documentation and requirement of more clinical evidence in the MDR. Consequently, there are possibilities that some of the orphan devices will be discontinued in the market which will lead to a decrease in treatment to rare culprits.(EU,2017)

European regulators have recently paid attention to the approval of OPDs, with the role of MDCG task force on orphan devices created in 2021. MDCG plays the statutory role in respect of the MDR in Europe. This task force has created advice on the clinical assessment of orphan medical devices and procedures to allow them to be approved, and this has suggested recommendations towards notified bodies as well as expert panels (MDCG,2024)

In other regulatory regimes, ambiguity is reduced by a clear advice being given on clinical evidence requirement (such as the Q-submission advice process by the US FDA). The consultation of an expert panel in regards to an orphan device discussed in this section is optional/voluntary and not based on the clinical evaluation consultation procedure (CECP) established in MDR Article 54(1).As said, the European advisory frameworks are in their infancy, though there is the pilot project whereby the EMA would have expert panels to offer advice, and special interest is on OPDs. (Melvin T et al.,2024)

10. EU Approval Process of orphan device:

10.1. Qualification and Classification of devices

In Annex VIII of The Medical Device Regulation (EU) 2017/745 (MDR), first manufacturers are required to establish whether their product is likely to be considered as a medical device by evaluating its planned medical use, with references to MDR Article 2(1). Upon confirmation, classification of the device into one of the risk categories namely, the device categorized as Class I (low risk), device categorized as Class IIa and Class IIb and Class III (highest risk) should be done on agreement factors such as invasiveness of the device, duration of using the device and effects of the device working with the human body. In the case of orphan devices, especially those that want to be used to treat rare genetic diseases or those that involve implantation technologies the most would be categorized as Class III since they are considered high risk and required to be subjected to a comprehensive process of conformity assessment and overview by a Notified Body prior to being subjected to the market.(EU,2017)

10.2. Conformity Assessment Procedure

The main approval process is conformity assessment. Depending on the type of the device, the process would be as follows: 1.Class III and Class IIb: Manufacturers should apply to a Notified Body (NB) to subject to a complete technical file review and clinical evaluation. NB considers the General Safety and Performance Requirements (GSPRs) provided in the Annex I of MDR. 2. When the devices are new or pose high risk (as many orphan devices):Article 54 of the MDR requires the consultation with a panel of experts, especially when the clinical evaluation is using new technologies. (EU,2017)

10.3. Clinical Evaluation and Evidence Generation

The Medical Device Regulation (EU) 2017/745 (MDR) poses one of the most complicated issues in the process of developing and allowing orphan devices because small patient samples make it difficult to establish strong clinical evidence. Following Article 61 of the MDR, the manufacturers will be required to create a Clinical Evaluation Report (CER) with data found in clinical investigation, literature, and post-market to prove the device to be safe and perform well. Nevertheless, the peculiarities of rare conditions are being considered in Article 61(10) of the MDR that proposes significant flexibility as clinical investigations may not be required when sufficient clinical evidence is present and the exemption can be justified scientifically because of the rarity of the condition. The damage is of great importance to orphan devices, in which traditional randomized clinical trials would be impractical or ethically difficult in many cases. To ensure that the clinical evaluation of the cases is supported, manufacturers can consider other sources of evidence such as the expert opinion, registry data, or real-world evidence as long as they are scientifically sound and reasonably justified (EUARTICLE61, 2017)

10.4. Technical Documentation Preparation

The manufacturers of the medical device, and this would include orphan devices, have to make detailed documentation that would show they have complied with the medical device regulation (EU) 2017/745 (MDR). Among the documents that will have to be provided, there is the Technical File according to Annex II, which contains detailed reports on the description of devices, the

design, the manufacturing process as well as risk analysis, and a checklist of General Safety and Performance Requirements (GSPR). They will also be required to compile Clinical Evaluation Report (CER) in accordance with Annex XIV to illustrate clinical safety and effectiveness of the device. Another requirement is a Post-Market Surveillance (PMS) Plan which is necessary in order to monitor the device performance continuously until it goes in the market. Based on the ISO 14971, the Risk Management Plan covers the recognition and elimination of either possible risks during the life span of the device. Moreover, the Instructions to use (IFU) should be prescribed completely and the labels should be appropriate and correspond with the safe and efficient usage by healthcare providers or patients.(EU,2025)

10.5. Interaction with a Notified Body

The manufacturer provides documents to a specific, designated Notified Body.It considers:Technical documentation,Clinical evaluation (especially in limited-data situations),Quality management system (According to ISO 13485),Evidence of conformance to Annex I (GSPRs).Notified bodies also produce a design examination certificate (Annex IX) in the case of Class III devices.(EU,2017/745)

10.6. Expert Panel Consultation (if required)

In cases in which:There is no much clinical data,Technology is one of a kind,The risk-benefit is difficult to establish.According to Article 54, the NB might initiate a complaint leading to an EU-level Expert Panel by the coordinating role of the European Commission.(EU,2017/745)

10.7. CE Marking

After the confirmation that the device meets all the requirements of MDR:

- The CE Certificate is issued by Notified Body.
- The CE marking should be affixed to the product, in this case the NB identification number should be added to it (e.g., CE 0123).

This enables the device to be sold legitimately in every place in the European Economic Area (EEA).(EU,2017/745)

10.8. Post-Market Surveillance (PMS) and Vigilance

Continuous monitoring of performance and safety of the device must be done after CE marking and this comprises of:

- PMS Plan (Annex III),
- Periodic Safety Update Report (PSURs) of pattern class IIa and superior,
- Trend reporting, Field safety corrective action (FSCA) where needed,
- Post Market clinical follow up of rare use data collection (PMCF) (31)

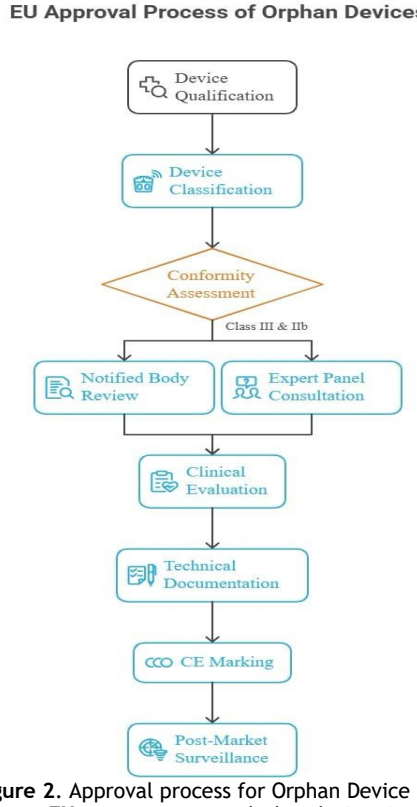

Figure 2. Approval process for Orphan Device in EU

11. Clinical Evidence and Performance Requirements – EU

The MDR has raised the level of clinical evidence based on which medical device can be placed on the market, in particular through a greater number of pre-market clinical investigations in some of the higher risk devices to establish the safety and clinical performance of these devices than is possible with reliance on post-market clinical data. Such more stringent clinical evidence specifications pose a problem to devices strictly to be used in rare diseases/conditions, or in specific indications of rare groups of patients with a otherwise non-rare disease/condition.With respect to the difficulties to provide clinical data (specially in the premarket phase), orphan devices can be admitted into the market with acceptable impairment in the quantity and caliber of pre-market clinical evidence, subject to resources being taken to give assurance to that end, as set out in this document. It should be established with a considerable amount of clinical evidence that a clinical benefit would be achieved as per the expectations and the device is operating the way it is supposed to with appropriate amount of safety.(MDCG,2024)

12.Labeling Requirements and Regulatory Disclaimers for Orphan device under MDR:

12.1.User Information on Orphan Status and Clinical Data Limitations:

These specific conditions or provisions may include, but are not necessarily limited to, directing the manufacturer to implement specific types of PMS or PMCF within a selected time frame to create more clinical data, to satisfactorily alert users of the device about the orphan status of the device, limitations involved in the pre-market clinical information, and to tell users what to do when it comes to reporting incidents, complaining, and other clinical experience to the manufacturer.(MDCG,2024)

12.2.Transparency Obligations:

In that case, the goal here, should be to ensure that the level of transparency afforded to health care professionals, patients, and

the general population is the right one such that they all know the orphan status of the device, any limitation of clinical data used with respect to the device and any conditions and provisions of certification to which it had been subjected. These conditions or provisions can include the examples of manufacturer undertaking specified PMS or PMCF activities within a specified timeframe to generate additional clinical data, appropriate user instructions on how to report incidents, complaints and other clinical experience to the manufacturer and how to be adequately informed of the orphan status of the device and limitations of the pre-market clinical data. The evaluation of Clinical Evaluation Report (CER) prepared by the notified body must MP: describe the details on which the orphan device status has been established and, where appropriate, explain why it has accepted limitations regarding the clinical data available pre-market and the operations that the manufacturer plans to do in its PMS plan and PMCF plan to generate the additional required clinical data. In PMS, the notified body is to take into consideration the PMS data, especially its major findings in the continuation of PMCF and review the benefit-risk profile of the device placed on the market in the framework of agreed surveillance activities and PSUR assessment under MDR Article 86 and confirm that the device can still maintain its previous benefit-risk profile supporting the device being placed on the market. (MDCG,2024)

13.Comparative Table: Orphan Device Approval – USFDA vs EU

Parameter	USFDA (United States)	EU (European Union)
Definition	Equipment in 8,000 people/year of the U.S. range (HUD classifications)	Medical devices used in treatment of diseases and conditions that 14,000/year or less are affected in the EU, with either non-existent or a limited number of alternatives available, and the expectations of clinical benefit
Regulatory Framework	Humanitarian Device Exemption (HDE) at 2 1 CFR 814, Subpart H	EU Medical Device Regulation (MDR) 2017/745
Designating Body	The Office of Orphan Products Development (OOPD) of FDA	There is no localized orphan designation; it is covered by MDR with assistance of task force of MDCG
Initial Step	Submission of HUD request → review by OOPD	Find out whether it is a medical device, the risk category and its intended use
Risk Classification	No specific risk category however must demonstrate little/no-unreasonable risk	Classified into Class I, IIa, IIb, or III; most orphan devices are Class III (high risk)
Approval Pathway	HDE Application (there is no need to demonstrate full effectiveness); covers safety, probable benefit, and lack of alternatives	Conformity Assessment procedure with Notified Body entailing technical documentation, clinical evaluation and the potential consultation of the expert panel
Clinical Evidence Requirement	Reduced premarket coverage; Clinical prove is acceptable to a minimum; post-market observation is obligatory	Increased expectation; Uncommon to common may be used with the justification, Article 61(10); justification is accepted by real-world evidence or registry data
Expert Consultation	FDA can consult advising groups	A voluntary consultation of an expert panel under the MDR Article 54 of a high-risk or a low-evidence decision
Labeling	Should have the following disclaimer, Humanitarian Device. Low level of evidence of outcome." (21 CFR 814.104(b)(4)(ii))	Having to comply with MDR Annex I GSPR. They should be labeled to full technical extent, and their risks documented, without saying something and putting everything on exclusivity or disclaimer
Post-Market Surveillance	The requirement; the reporting of adverse events included; no profit allowed in some cases except the use of pediatrics	Covers PMS plan, PSURs, trend reporting and post-market clinical follow-up (PMCF)
Profit Restriction	Sale without-profit (except special cases e.g. pediatric products)	Profits are not regulated; there is no discrimination on the marketplace
Challenges	Easy access with minimum evidence → this might result in jeopardizing safety unless strictly observed	Heavy regulation; compliance becomes really hard, especially by SMEs since this poses a risk of major market exit of niche devices
Market Access	Devices were only divisible in an IRB approved establishment	CE marking allows one to avail the whole of EEA when compliance is established

CONCLUSION

The orphan medical devices are crucial in meeting the clinical needs of patients who have rare and in most cases, often life-threatening conditions that cannot be met by ordinary products. Nevertheless, their regulatory mechanisms in development and market acceptance between the European Union and the United States are noticeably different. The Humanitarian Use Device (HUD) and Humanitarian Device Exemption (HDE) programs offered by the USFDA consist of a special and flexible mechanism that offers favorable access to early patients and less clinical evidence. However, in contrast to that, the EU requires strict clinical evaluation criteria, technical documentation, and conformity assessment criteria even in cases of devices supposed to be used with rare conditions via the Medical Device Regulation (MDR).

On the one hand, the US approach promotes innovation and access of the small-scale manufactures to the market; on the other hand, it alleges some fears of safety and efficacy in the long-term perspective because of sparse premarket evidence. Alternatively, the EU model aims at maximizing patient safety and evidence-based performance validation which in most cases prove to be very demanding in terms of compliance requirements thus slowing the access rate particularly among the SMEs.

In order to provide the best experience to the audiences that receive and have rare diseases, a neutral, patient-focused regulatory framework is required, i.e., that provides an innovation design without compromising safety and effectiveness. These gaps can be filled by future regulatory convergence, greater clarity and support to developers in order to increase availability of orphan medical devices globally.

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