Clinical Evaluation of Orphan Medical Devices

MDCG 2024-10 Guidance

Richard Holborow

2024-09-27

Background to the Creation of the MDCG 2024-10 Guidance…

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REVIEW

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

Melvin T[1] · Kenny D[2] · Gewillig M[3] · Fraser AG[4]

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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.

✉ Melvin T
melvinto@tcd.ie

Kenny D
damien_kenny@icloud.com

Gewillig M
marc.gewillig@uzleuven.be

Fraser AG
fraserag@cardiff.ac.uk

[1] School of Medicine, Trinity College Dublin, Dublin, Ireland
[2] Children's Health Ireland at Crumlin and Mater Hospital, Dublin, Ireland
[3] University Hospital Leuven, Leuven, Belgium
[4] Department of Cardiology, University Hospital of Wales, Cardiff CF14 4XW, UK

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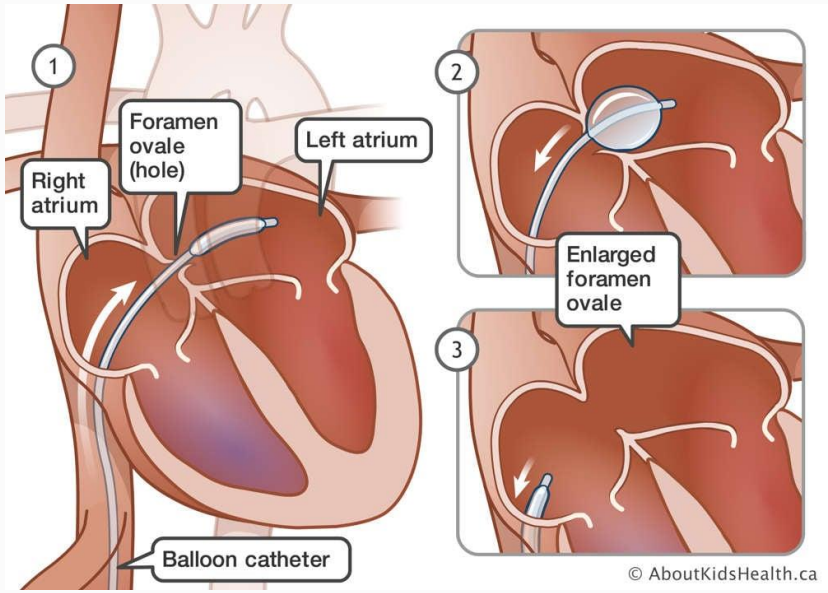

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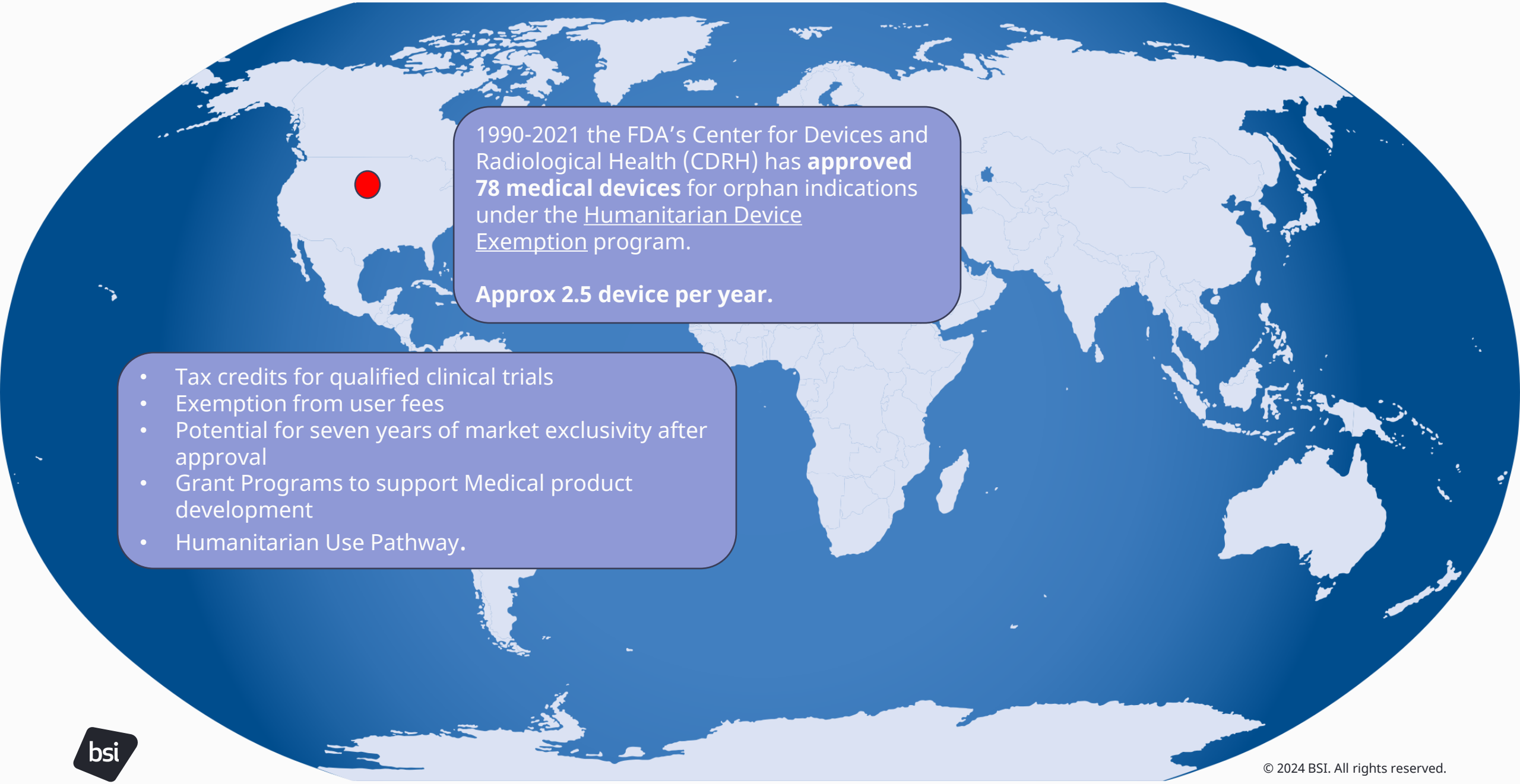
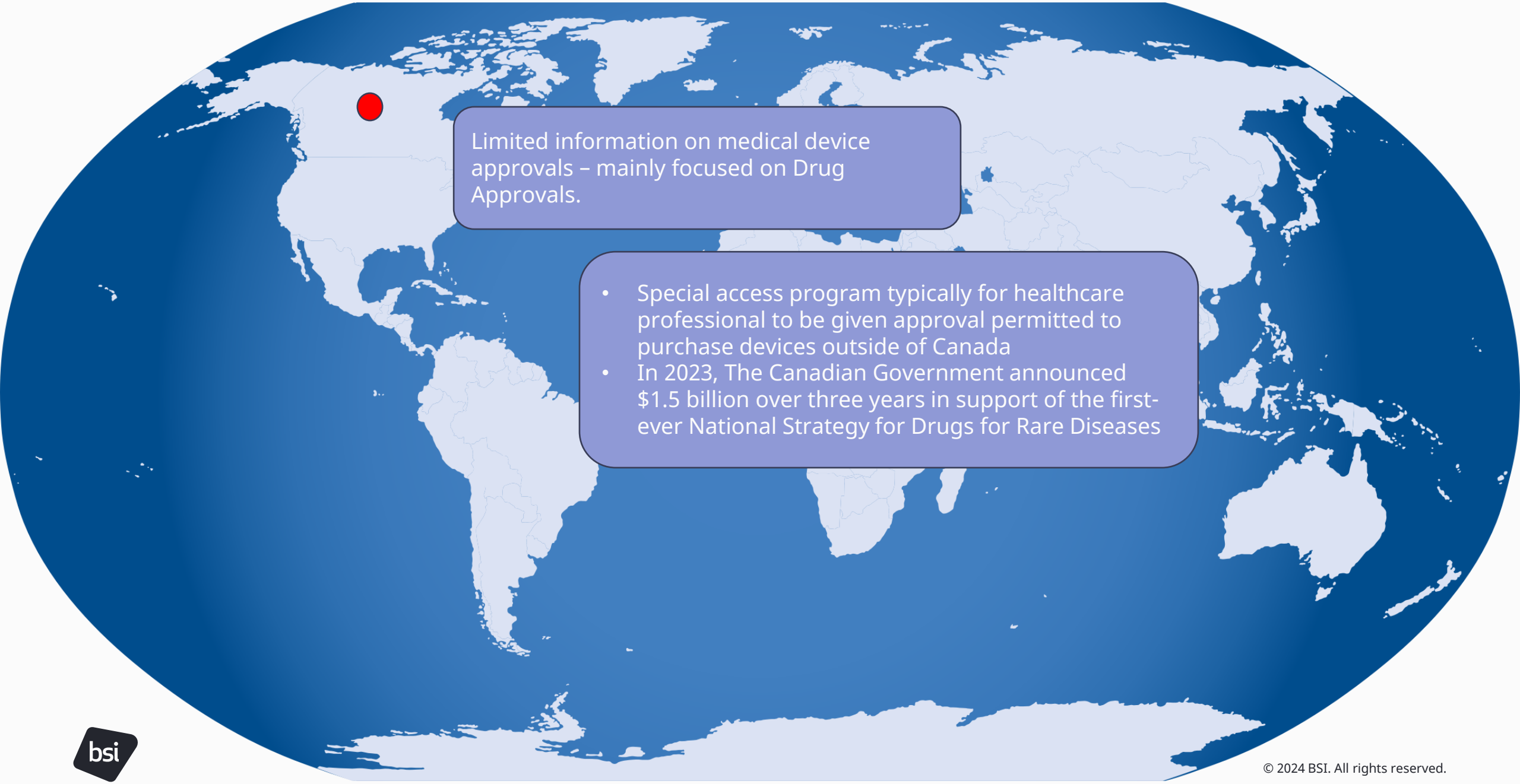


1990-2021 the FDA's Center for Devices and Radiological Health (CDRH) has **approved 78 medical devices** for orphan indications under the Humanitarian Device Exemption program.

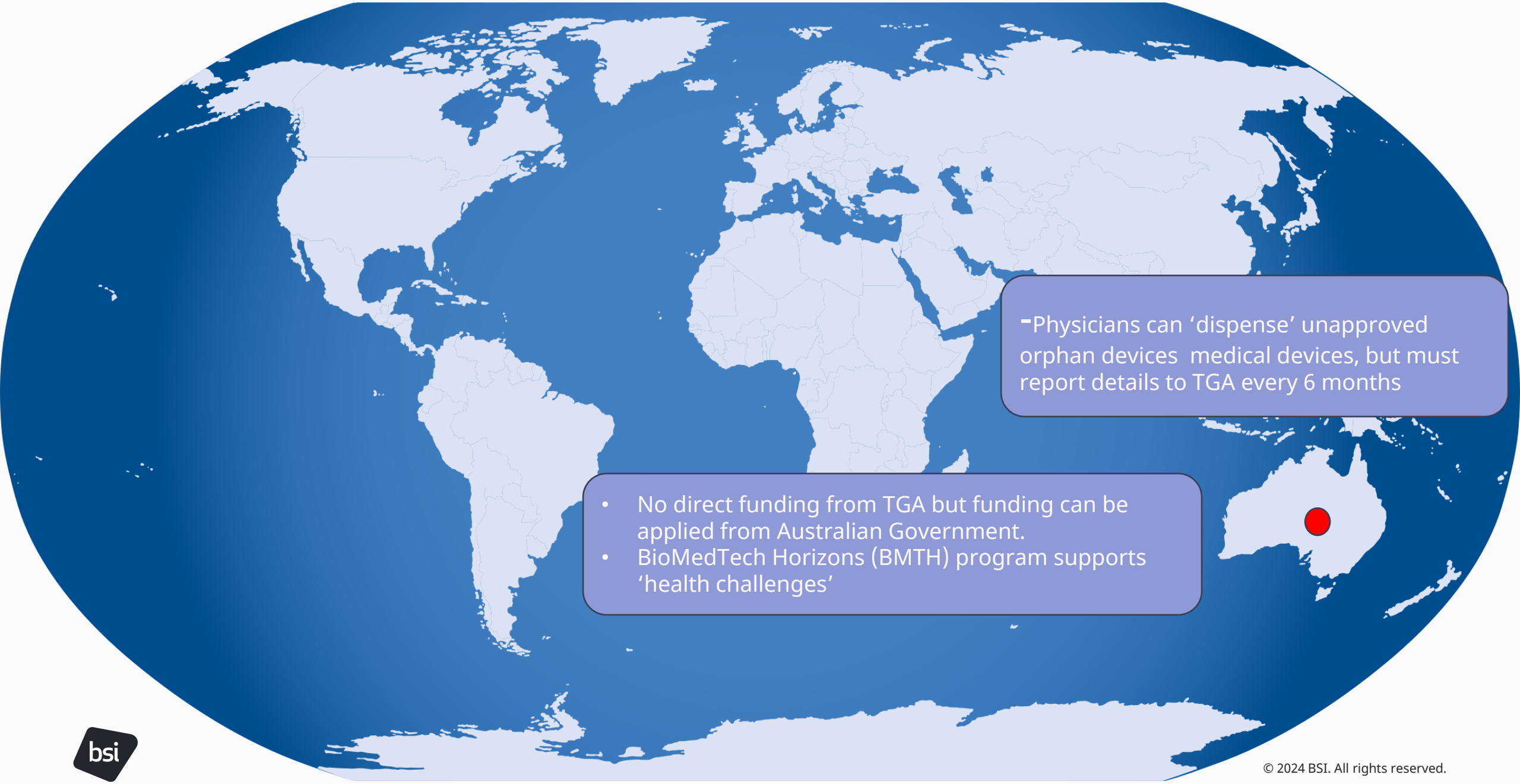
Approx 2.5 device per year.

- Tax credits for qualified clinical trials
- Exemption from user fees
- Potential for seven years of market exclusivity after approval
- Grant Programs to support Medical product development
- Humanitarian Use Pathway.



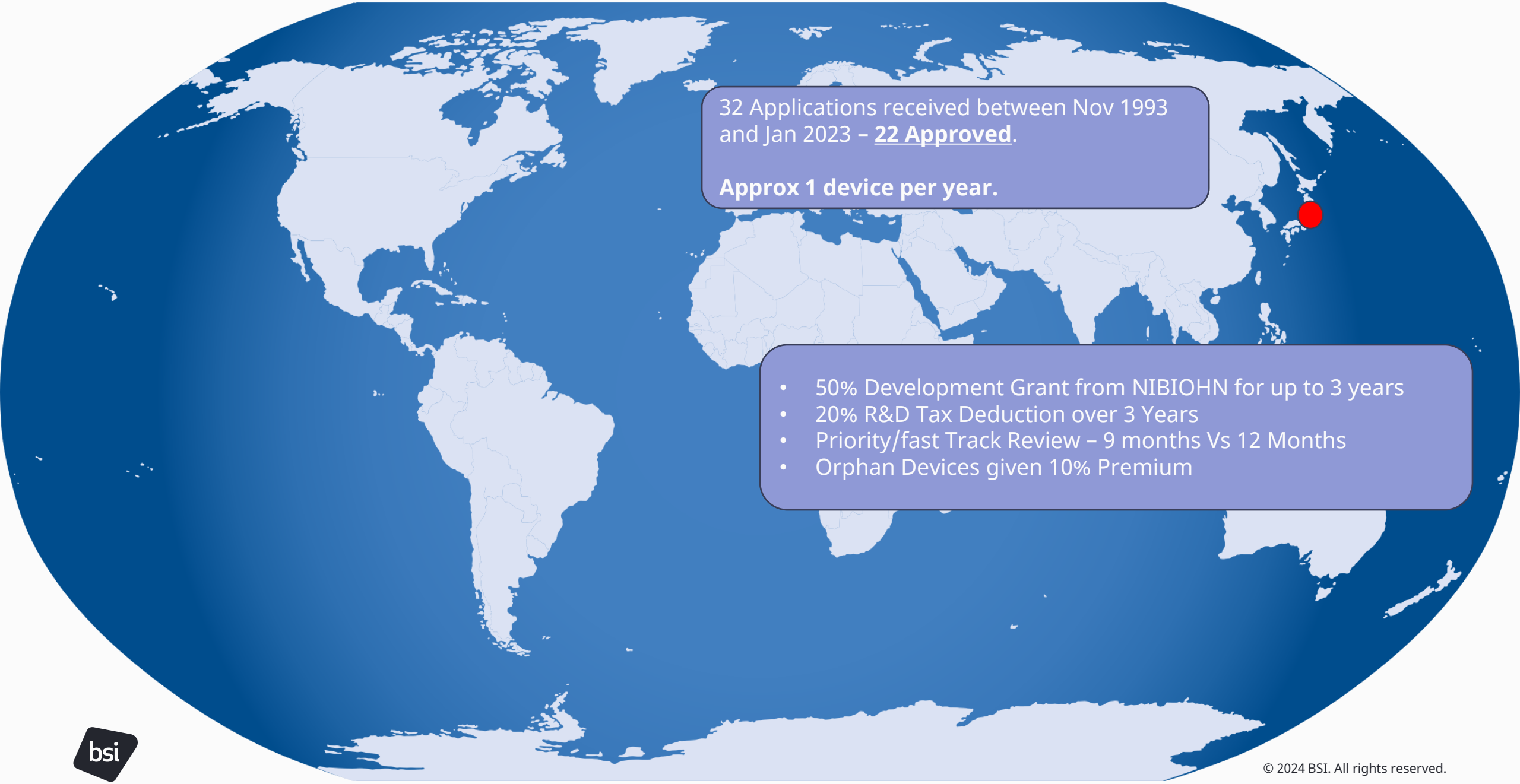
Limited information on medical device approvals – mainly focused on Drug Approvals.

- Special access program typically for healthcare professional to be given approval permitted to purchase devices outside of Canada
- In 2023, The Canadian Government announced $1.5 billion over three years in support of the first-ever National Strategy for Drugs for Rare Diseases



-Physicians can ‘dispense’ unapproved orphan devices medical devices, but must report details to TGA every 6 months

- No direct funding from TGA but funding can be applied from Australian Government.
- BioMedTech Horizons (BMTH) program supports ‘health challenges’



32 Applications received between Nov 1993 and Jan 2023 – **22 Approved**.

Approx 1 device per year.

- 50% Development Grant from NIBIOHN for up to 3 years
- 20% R&D Tax Deduction over 3 Years
- Priority/fast Track Review – 9 months Vs 12 Months
- Orphan Devices given 10% Premium

The EU Solution…

- The task force involved Member States, Notified Bodies, Clinicians and the European Commission.
- Notified Bodies were asked to contribute to find a solution within the current legal framework that can be easily adopted.

The EU Solution…

Medical Devices

Medical Device Coordination Group Document MDCG 2024-10

MDCG 2024-10

Clinical evaluation of orphan medical devices

June 2024

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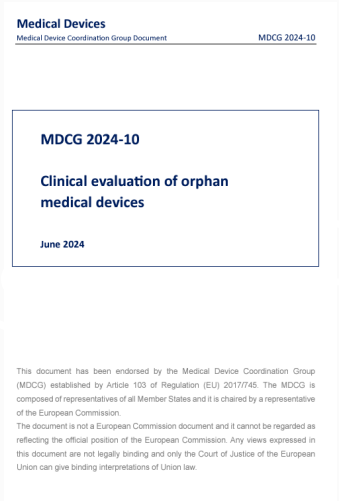
Link to MDCG2024-10

Scope of MDCG 2024-10



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This document provides guidance to manufacturers and notified bodies on the clinical evaluation pursuant to the MDR of medical devices and accessories for medical devices that qualify as 'orphan devices' (OD) and medical devices ***and accessories*** *for medical devices that have* ***an orphan indication,*** *within the meaning of this guidance.*

Custom-made devices, in-house devices, products without an intended medical purpose listed in MDR Annex XVI and in vitro diagnostic medical devices are outside the scope of this guidance.

Please note, this document gives guidance on the clinical evaluation of orphan devices which require clinical data to demonstrate conformity with GSPRs. ***Guidance is not provided*** *in this document for those specific circumstances where* ***MDR Article 61(10)*** *applies to an orphan device.*

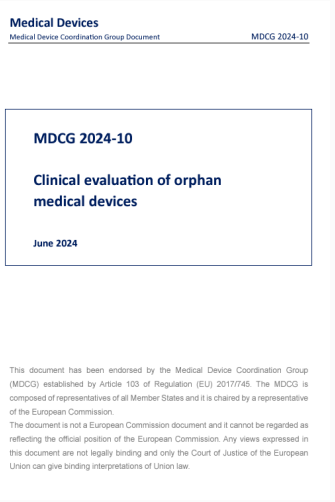
MDCG 2024-10 Guidance Structure

The guidance is set in three parts

PART A – Clinical evaluation considerations

PART B – Procedural considerations

There are three appendices to this document.



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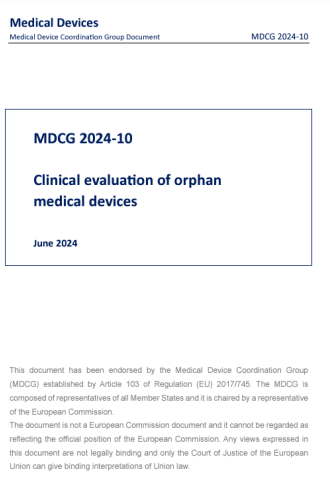
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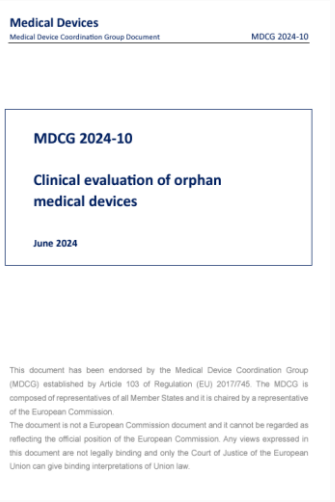
PART A – Clinical evaluation considerations

- The acceptability of limitations in pre-market clinical data for orphan devices,

- Key considerations on the clinical evaluation of new and legacy orphan devices,

- Generating post-market clinical data for orphan devices, including PMS and PMCF.

MDCG 2024-10 Guidance Structure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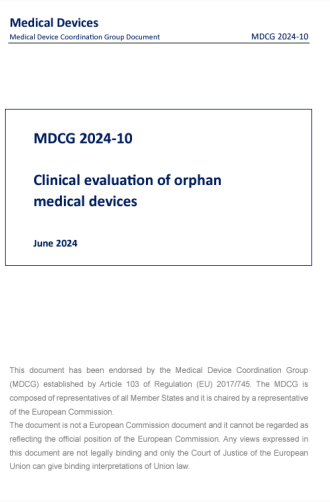
The guidance is set in three parts

PART B – Procedural considerations:

- Guidance for notified bodies on the assessment of orphan devices,
- The role of expert panels in the context of orphan devices.

MDCG 2024-10 Guidance Structure

The guidance is set in three parts



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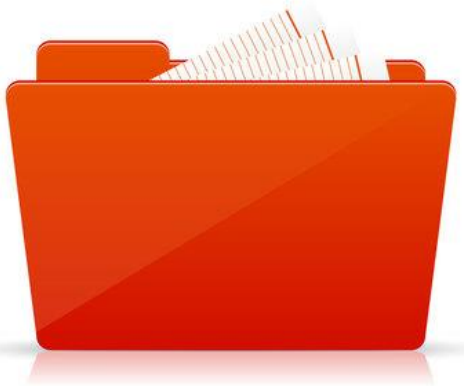
There are three appendices to this document, which include guidance on:

- OD-specific factors to include in the clinical evaluation report,
- Consideration on clinical investigations of orphan devices,
- Extrapolation of clinical data to orphan indications.



What defines a medical device as an Orphan Device (OD)?

What defines a medical device as an Orphan Device (OD)?

A medical device or an accessory for a medical device should be regarded as ‘orphan device’ (hereafter also referred to as ‘OD’), if it meets the following criteria:

- the device 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**[5]; 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.

What defines a medical device as an Orphan Device (OD)?

- *the device 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**[5];*

Guidance Note: It is important to note that the status as an **orphan device does not confer market exclusivity for that device**. For the sustainable development of orphan devices (and retention of legacy orphan devices), the criteria should not be interpreted so as to prevent more than one device in a given therapeutic area being designated as an OD.

Similarly, the **existence of an OD in a specific therapeutic area is not alone a reason to prevent a manufacturer from justifying OD status** for another similar device intended for use in the same disease or condition.

What defines a medical device as an Orphan Device (OD)?

Extrapolated from the population estimate criteria for Humanitarian Use Device (HUD) designation established by the U.S. Food and Drug Administration (FDA) and calculated on the basis of an EU population of 447 million.

What defines a medical device as an Orphan Device (OD)?

*There is **insufficiency of available alternative options for the treatment, diagnosis, or prevention of this disease/condition**.*

Point of Clarification over Interpretation:

The word *'insufficiency'* was used over a 'single option' or 'no other alternatives' to recognise that whilst there may be multiple options, they are limited in terms of availability and clinical evidence.

What defines a medical device as an Orphan Device (OD)?

- 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.

What defines a medical device as an Orphan Device (OD)?

- 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.

Points of Clarification over Interpretation:

Note the word 'expected' as the assumption of clinical benefit may be limited to scarce evidence or to pre-clinical data.

'Expected'

The Statement *compared to available alternatives or state of the art* also ensures that additional options can be available to orphan devices and to avoid market exclusivity.

What is expected of manufacturers?

Manufacturers are expected to evidence the qualification criteria for an Orphan Device.

Section 4.2 and 4.2.1 of MDCG 2024-10

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Manufacturers are expected to evidence the qualification criteria for an Orphan Device.

CHAPTER VI

CLINICAL EVALUATION AND CLINICAL INVESTIGATIONS

Article 61

Clinical evaluation

1. Confirmation of conformity with relevant general safety and performance requirements set out in Annex I under the normal conditions of the intended use of the device, and the evaluation of the undesirable side-effects and of the acceptability of the benefit-risk- ratio referred to in Sections 1 and 8 of Annex I, shall be based on clinical data providing sufficient clinical evidence, including where applicable relevant data as referred to in Annex III.

The manufacturer shall specify and justify the level of clinical evidence necessary to demonstrate conformity with the relevant general safety and performance requirements. That level of clinical evidence shall be appropriate in view of the characteristics of the device and its intended purpose.

To that end, manufacturers shall plan, conduct and document a clinical evaluation in accordance with this Article and Part A of Annex XIV.

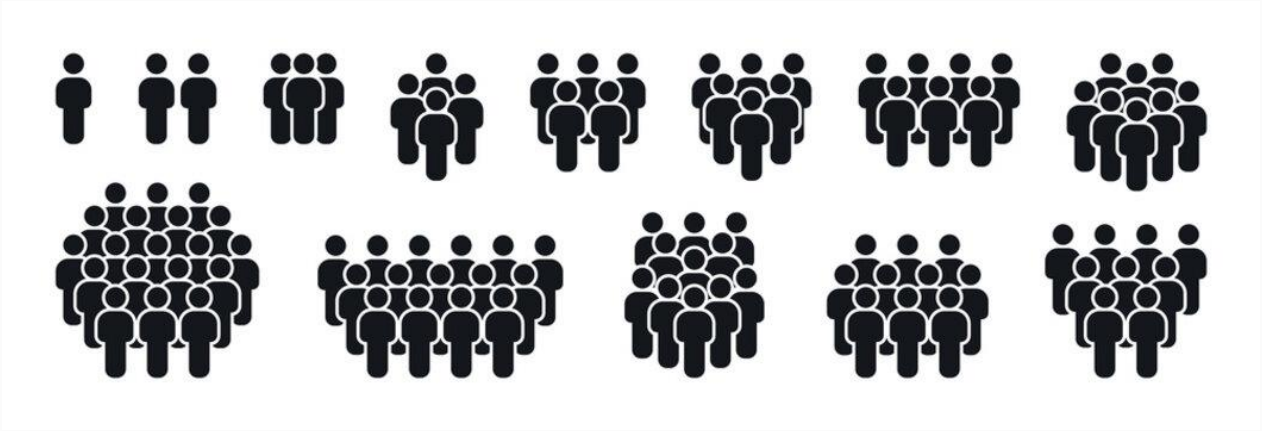
What is expected of manufacturers?

The manufacturer should provide a description of the specific disease condition that presents in not more 12,000 individuals in the EU.

The manufacturer should justify that the device is intended to be used to benefit patients.

- The manufacturer will need to provide evidence of epidemiological status, this could come from publications or medical society guidance, or rare disease registries.
- *The manufacturer may consider including additional supporting data for incidence estimates, for example from national level data, health service level data or from independent clinical experts or medical society consensus statements.*

What is expected of manufacturers?



The manufacturer may wish to pursue specific indications that qualify as an orphan device of a more widely available device or sub populations based on diversity of anatomy e.g. congenital abnormalities.

For orphan subpopulations, the manufacturer should provide information to justify the existence of a valid orphan subpopulation for the purpose of justifying OD status for a device used in a disease/condition that presents in more than 12,000 individuals per year. This can include providing a scientific rationale for why the device is only intended for use within that subpopulation and the intended use would not be appropriate for the wider population with a non-rare disease/condition.

What is expected of manufacturers?

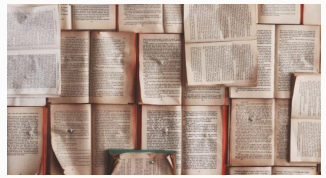
An explanation should be provided as to why the device would provide an expected clinical benefit compared to available alternatives or state of the art for the treatment, diagnosis or prevention of the disease/condition.

What is expected of manufacturers?

Information from medical literature (for example clinical treatment guidelines) or consensus statements from clinical experts or medical societies, which may include patient representative groups, may be used to support the justification of the expected clinical benefit, for example where they detail relevant gaps in clinical management of the disease in the existing state of the art and why the therapeutic option to be provided by the proposed OD is needed.

What is expected of manufacturers?

Relevant non-clinical and preliminary clinical data on the device, and/or data on similar devices, may be used in support of a statement that the OD will provide an expected clinical benefit.

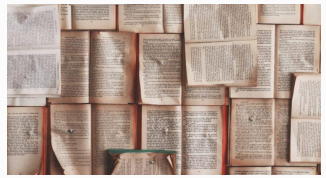


Considerations and Limitations when documenting a Clinical Evaluation on Orphan Devices.

Considerations and Limitations when documenting a Clinical Evaluation on Orphan Devices.

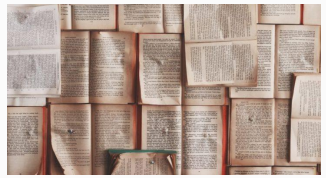
- All available non-clinical and clinical data relevant to the orphan device have been evaluated, and any limitations in clinical data have been identified

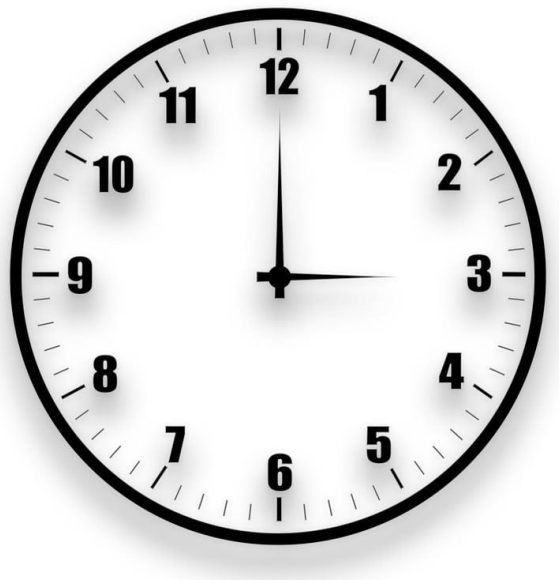
Considerations and Limitations when documenting a Clinical Evaluation on Orphan Devices.



- The existing non-clinical and limited clinical data is sufficient to demonstrate that the relevant GSPRs in Annex I MDR are met,
- That the benefit-risk ratio is acceptable, and that it is expected that the device will provide a clinical benefit taking into account the clinical condition, the state of the art, and the safety of patients.

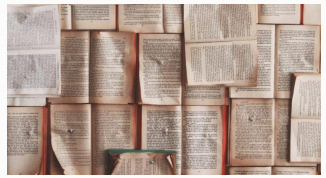
Considerations and Limitations when documenting a Clinical Evaluation on Orphan Devices.





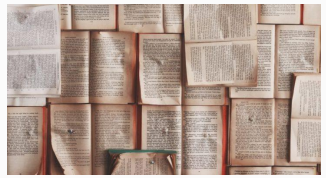
- It is not feasible or proportionate to generate further clinical data within an acceptable time frame in the pre-market setting.

Considerations and Limitations when documenting a Clinical Evaluation on Orphan Devices.



- The manufacturer has an adequate PMCF plan that, once executed, will generate clinical data in an appropriate time frame that will fully address the remaining limitations in clinical data.

Considerations and Limitations when documenting a Clinical Evaluation on Orphan Devices.



- Users of the device will be adequately informed (e.g. by provision of information in the IFU, SSCP (for implantable and class III devices), and/or other accompanying documentation) of the orphan status of the device, the limitations in pre-market clinical data, and instructions to users on how to report incidents, complaints, and other clinical experience to the manufacturer.

The Role of Pre-Clinical Data

- It should be recognised that orphan devices will have limitations in clinical data so the role of pre-clinical data is to help support an understanding of the expected behaviours of the device.
- Where possible these expected behaviours should be verified through post market clinical follow up.

The Role of Pre-Clinical Data

Useful sources of non-clinical data can include:

- Results of laboratory and animal tests;
- Data from computer modelling and simulated use testing, including software-based models, 3D printed models, and other physical models;
- Data from ex vivo studies and cadaveric studies;
- Data from similar devices (per MDCG 2020-5, section 5), for which equivalence is not demonstrated (not qualifying as clinical data per MDR);
- Information with regard to the state of the art of the technology;
- Datasets with previously collected information on patients' health. These can be used to test the device without exposing patients, most commonly to validate software.
- Any other relevant data involving humans, which does not qualify as MDR clinical data.

Are Manufacturers still required to follow the clinical evaluation obligations of the MDR e.g. identify GSPR, PMS, PMCF?

The requirements for the clinical evaluation of medical devices laid down in Article 61 and Annex XIV of the MDR also apply to orphan devices. These include the following steps:

- *establish and update a clinical evaluation plan;*
- *identify relevant clinical data and any limitations in clinical data;*
- *appraise all relevant clinical data;*
- *analyse all relevant clinical data;*
- *generate new or additional clinical data needed to address outstanding issues;*
- *document this evaluation in a clinical evaluation report; and*
- *update the clinical evaluation through PMCF activities.*

Off – Label Use & Legacy Orphan Devices

In such circumstances, with respect to the MDR clinical evidence requirements, it might be acceptable to consider clinical data from off-label use when considering revision or expansion of a device's intended purpose to include this use/indication, provided that (in addition to the guidance stated in this document):

- the decision to not perform a clinical investigation is justified and compliant with relevant MDR requirements;
- the off-label clinical data is of sufficient amount and quality to allow clinical evaluation and notified body assessment; and
- the PMCF plan sufficiently justifies how the limitations in clinical data will be addressed through PMCF activities.

Please note, this scenario is only **foreseen for exceptional cases of legacy orphan devices** or orphan indications with respect to legacy devices and is **not expected to apply to new orphan devices**.

Orphan devices never previously marketed…

- When designing a clinical investigation for orphan devices, potential recruitment challenges and sample size implications should be taken into account.

- Strategies should be considered on how best to recruit and retain patients, considering the geographical distribution and potential logistical challenges.

- Efforts should be made to collaborate with multiple centres where appropriate and proportionate to ensure sufficient participation and to enhance the potential for generalisability of results.

Post Market Considerations


Medical Device
Medical Device Coordination Group Document
MDCG 2020-7

MDCG 2020-7

Post-market clinical follow-up (PMCF) Plan Template
A guide for manufacturers and notified bodies

April 2020

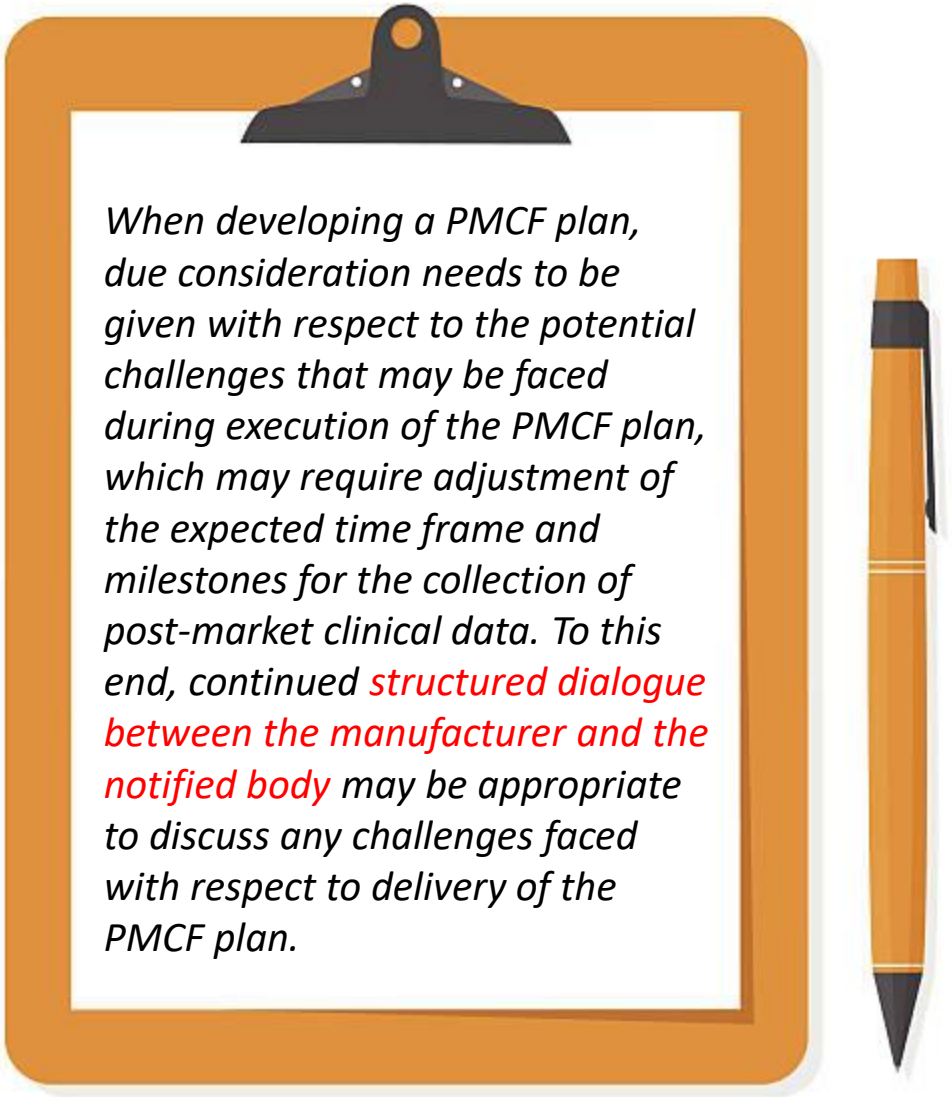
The PMCF plan should include information about:

- All limitations in clinical data identified pre-market, that need to be addressed,

- Justification as to how the PMCF activities will address these specific limitations,

- The type of data to be generated in the post-market phase to further evaluate the clinical performance and safety of the device,

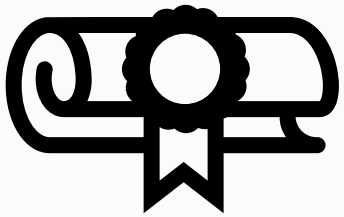
- How these data will be generated in an appropriate time frame, including projections on the numbers of patients that will be managed with the device per year, and pre-defined milestones on the periodic analysis of these data, where appropriate.



There are some obvious practical implications for orphan devices that means they are limited in their ability to collect clinical data in the post market phase.

Novel Devices Vs Orphan Devices – Practical Considerations

There are situations where the ability to gather clinical evidence in the pre-market stage is limited. This may be due to a small need in the market (e.g. Orphan devices) or the limitation of being able to roll out large studies for novel/innovative products



Post Market Pathways

Orphan Devices

Typically Post Market collection of data in Orphan devices remains limited due to low volume/usage. Therefore, data collection activities such as PMCF studies remain unfeasible. Registries can be a good solution.

Novel Devices

Post market data collection for novel devices should include robust PMCF studies and registries as typically there are higher volumes. There does need to be controls in the roll-out of these devices to ensure they are used appropriately, given their early market release and residual risks.

Early Dialogue

While it rests with the manufacturer to demonstrate that its device meets the criteria for orphan device status, the expert panels established in accordance with MDR Article 106 may be requested to provide advice on the orphan device status and the clinical data needed for the clinical evaluation.

The notified body involved in the conformity assessment of a device for which the manufacturer claims an orphan device status may seek advice from an expert panel in accordance with MDR Article 106(11). Before submitting such a request, the notified body should consult the manufacturer, for example to inform them of their plan to request advice from the expert panel and where appropriate to give the manufacturer the opportunity to provide input into the request. Having regard to the limited capacity of the expert panels, notified bodies are advised to reach out to the EMA expert panel secretariat as early as possible to include an envisaged request for advice in the expert panels' planning.

Early Dialogue

*The OD status of the device should be checked by the notified body **as early as possible**, for example as part of structured dialogue before or during initial conformity assessment activities. This should be based on the justification and information provided by the manufacturer and, if applicable, advice provided by an expert panel to the notified body or the manufacturer*

Early Dialogue – Existing clients

1. We advise existing clients to reach out to their scheme manager if the review has not yet started.

2. The Scheme Manager can contact the Clinical Compliance Team and we will ensure that the appropriate team can join a call to discuss the qualification of an Orphan Device.

3. If the review has already been initiated, then the manufacturer can still provide evidence to support the conformity assessment as an orphan device (OD)– Please indicate to the technical reviewer and clinical specialist as part of your review and they will arrange a meeting to discuss the OD Status

Early Dialogue – New clients

New clients can reach out to their sales representative (BDM Team).

The Business Development Managers can contact the Clinical Compliance Team and we will ensure that the appropriate members of the team join a call to discuss the qualification of an Orphan Device.

Expert Panels: Advice on Orphan Device Status and Clinical Evidence according to article 61 (2)

Article 61(2) MDR provides the possibility for a manufacturer, prior to its clinical evaluation and/or investigation, to consult an expert panel with the aim of reviewing the manufacturer's intended clinical development strategy and proposals for clinical investigation. The scope of MDR Article 61(2) is limited to class III devices and class IIb active devices intended to administer and/or remove a medicinal product.

Expert Panels: Advice on Orphan Device Status and Clinical Evidence (Late stages of clinical evaluation or completed).

The early scientific advice pursuant to MDR Article 61(2) would be too late for manufacturers who have already drawn up their clinical evaluation report or are in an advanced stage with their clinical evaluation.

In those cases, an expert panel's advice regarding the orphan device status and regarding the clinical data required for the clinical evaluation of a device may be requested by a notified body in accordance with MDR Article 106(11) in the framework of an ongoing conformity assessment procedure.

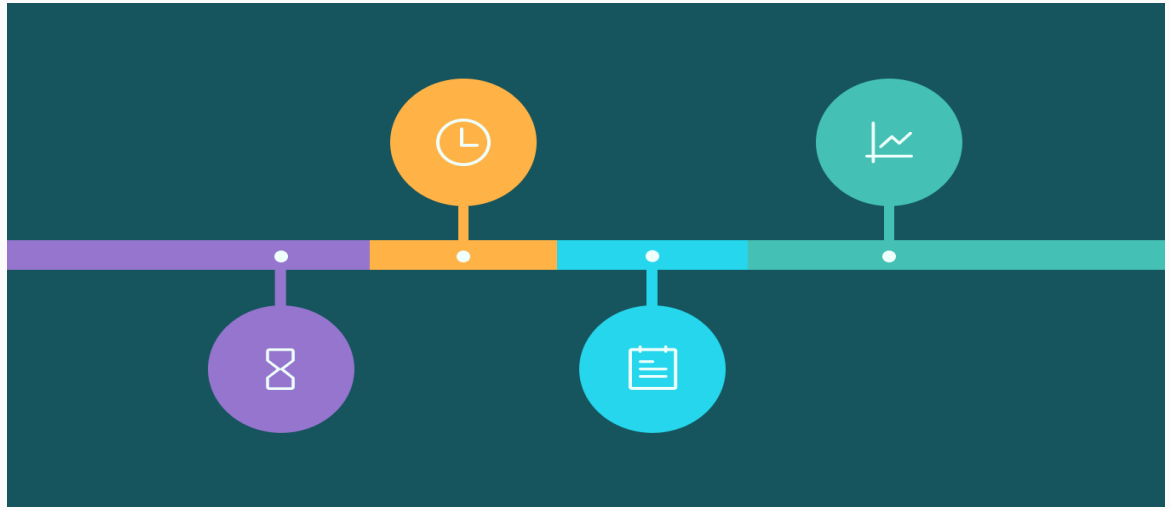
In exceptional cases the manufacturer may request advice from an expert panel on the orphan device status and the clinical data required for its clinical evaluation, even though the clinical evaluation is in an advanced stage or already completed.

Expert Panels: Advice on Orphan Device Status and Clinical Evidence (Late stages of clinical evaluation or completed).

- In these situations, BSI will hold a structured dialogue with the manufacturer.
- An Internal Clinician (IC) will be involved to consider whether the device qualifies as an Orphan Device.
- If there is any disagreement between the manufacturer and the IC, or the IC is unsure, we will contact the expert panels for advice on this question.
- The Clinical Compliance Team will work with the European Medicines Agency (EMA) Secretariate to coordinate the advice.
- BSI has been provided with the details and process from European Medicines Agency to request scientific advice pursuant to article 106.

Surveillance by the notified body

As part of their surveillance activities and post-certification monitoring, notified bodies need to monitor compliance with any conditions/provisions that are binding for the manufacturer and associated with the certification decision, such as updates to clinical data at defined intervals.



Certificates with Conditions

MDCG acknowledged in its position paper MDCG 2022-14, point 17 that the use of certificates with conditions will contribute to increasing the necessary flexibility to apply the reinforced clinical evidence requirements to devices that have a demonstrable track record of safety.

Orphan devices for which the pre-market clinical evidence is deemed sufficient but needs to be completed or confirmed through PMCF, are a good example where notified bodies can make use of the possibility to issue certificates with specific conditions or provisions.

Certificate

Specific conditions or provisions may consist, for example, in requiring the manufacturer:

- to conduct defined PMS or PMCF activities within a specified period of time to generate additional clinical data,

- to adequately inform users of the device of the orphan status of the device, the limitations in pre-market clinical data, and instructions to users on how to report incidents, complaints, and other clinical experience to the manufacturer, e.g. by provision of information in the IFU, SSCP (for implantable and class III devices) and/or other accompanying documentation.

Conclusions.

1. Whilst Orphan Device applications will be rare, they are critical at ensuring small populations continue to have access to diagnosis and treatments.

2. Manufacturers are required to justify the level of evidence to support the incidence of disease and the rationale for orphan device status.

3. The level of clinical evidence will be limited to support the orphan device indication. The evidence will primarily focus on safety and perceived benefit. Pre-Clinical data may be used to support gaps.

4. PMS plans and PMCF plans should be robust, with clearly identified opportunities to gather data to confirm safety and performance.

5. Structured dialogue is critical between all stakeholders. This includes communication between Internal clinicians and manufacturers.

Marketing Resources and Information

There are lots of marketing resources and further information available on our website at:

https://www.bsigroup.com/en-GB/capabilities/medical-devices/

Link to all our Medical Devices webinars:

https://www.bsigroup.com/en-GB/insights-and-media/Search?searchText=*Medical+devices&filterBy=all&pagetypes=webinars&sortBy=1

Follow our Medical Devices LinkedIn Showcase page and keep up to date with all the latest news and resources:

https://www.linkedin.com/showcase/bsi-medical-devices/?viewAsMember=true