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International Medical Device Regulators Forum

EU2023
EUROPEAN UNION Chair

Orphan Medical Devices Challenges and Tools

Donal B O'Connor MD FEBS

HPRA, Ireland & EU- MDCG Orphan Device Task Force

September 25, 2023

European Commission

Funded by the European Union

Orphan Medical Devices

Challenging to define

- Medical device intended to benefit patients in the treatment or diagnosis of a rare disease or condition

Challenging to develop and regulate

- Clinical Evidence
  - How to generate & demonstrate
  - How to evaluate pragmatically

Significant public health concern

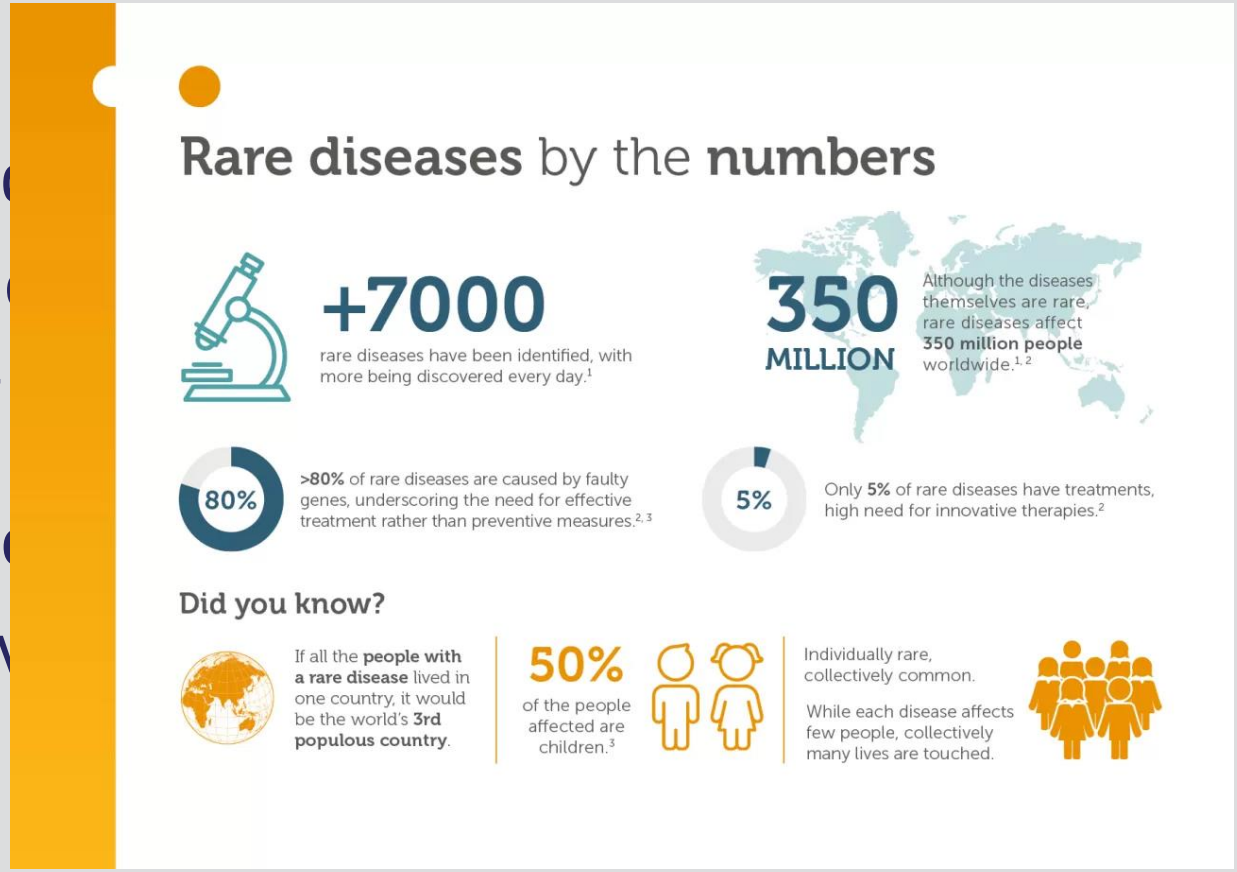
Orphan Medical Devices

Challenging to

- Medical d
  treatment
  condition

Challenging to

- Clinical Ev



Significant public health concern

Unique challenges for Orphan Medical Devices

Development and Assessment challenges

- Clinical Evidence
  - What's required for safety
  - What's required for performance*

Multifactorial barriers

- Economic

Tools for Orphan Medical Devices

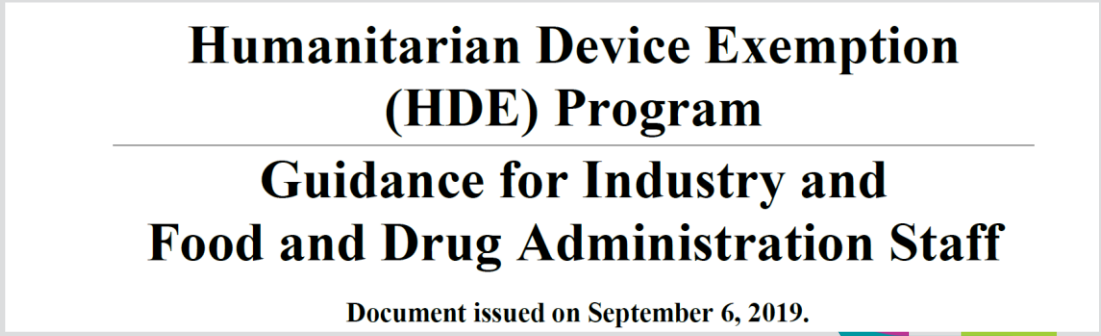
Specialised pathways e.g. US FDA

- Define and designate
  - Principle of potential benefit
  - Proportionate assessment


Guidance for Industry and Food and Drug Administration Staff

Humanitarian Use Device (HUD) Designations

Revision 1 issued: September 5, 2019


Humanitarian Device Exemption (HDE) Program

Guidance for Industry and Food and Drug Administration Staff

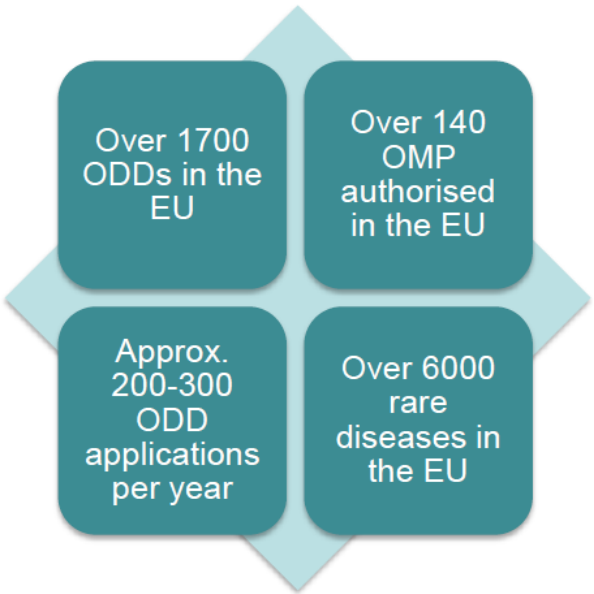
Document issued on September 6, 2019.

Tools for Orphan Medical Devices

Specialised pathways

EU - Medicinal products model

- Orphan designation
  - Orphan medicinal products
    - Defined incentives
    - Regulatory assessment similar



Tools: Clinical Evaluation Guidance
(EU –in development - MDCG ODTF)

CORE–MD
Coordinating Research and Evidence for Medical Devices

Definitions & Designations

- Populations & subpopulations
  - Indications and intended use
    - Epidemiology –EU working def. – in progress….
    - Other factors impacting designation & benefit/risk considerations
      - Alternatives
      - Potential safety/benefit

Clinical Evidence & Evaluation

- Study methodology
  - Endpoints & surrogates
    - Supporting data
    - Extrapolation
- Leverage the product lifecycle
- PMCF
  - Maximise RWE
  - Registries
  - How to capture off-label use
- Uncertainty

Tools: Clinical Evaluation Guidance
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Definition

- Popula
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Definitions & Designa

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& surrogates

ch uncertainty is acceptable?

e product lifecycle

- PMCF
  - Maximise RWE
  - Registries
  - How to capture off-label use
- Uncertainty

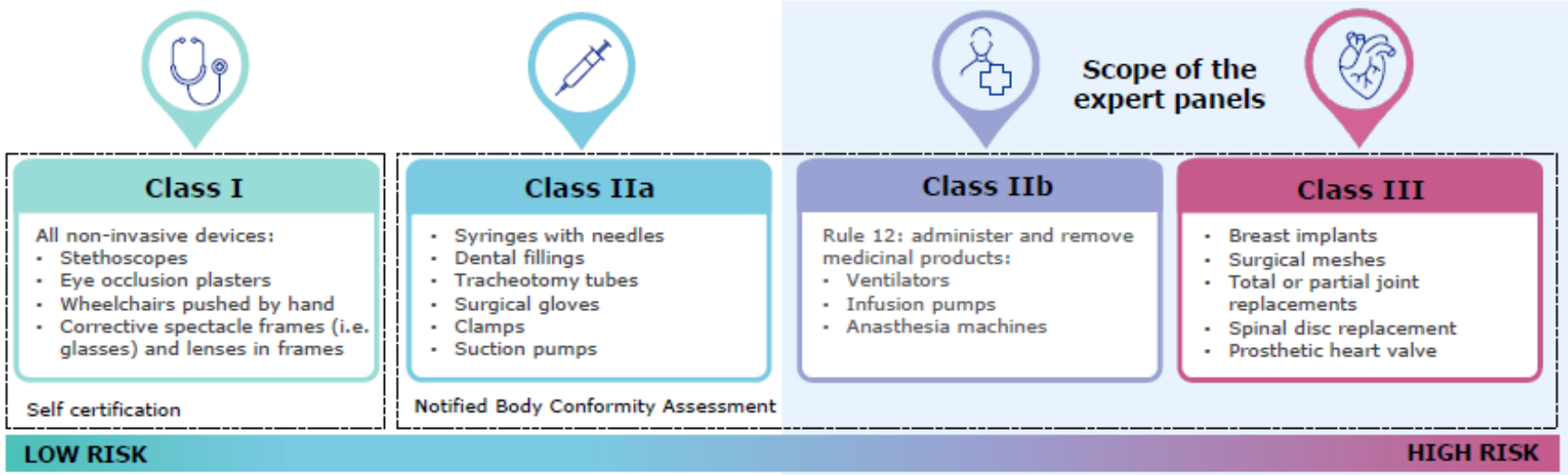
Centralising regulatory science principles – EU Expert Panels

MEDICAL DEVICES

Overview of the types of medical devices

Medical device classification rules adopts a risk-based approach taking into account the risks associated with the use, technical and manufacture characteristics of the device.

The MDR (EC) 2017/745 divides the devices into 4 risk classes and 22 rules on classification of medical devices.



Centralising Principles : EU Expert Panels Scientific Advice

Pilot Scientific Advice - Prioritisation Criteria

EUROPEAN MEDICINES AGENCY

The following criteria will be considered – No priority order

- **Devices intended to benefit a relatively small group of patients** in the treatment or diagnosis of a disease or condition (e.g. "orphan devices" and devices for paediatric use)

-> Description of the target population of patients and quantitative estimate of this population in the EU

- **Devices for unmet medical needs** i.e., devices for medical conditions that are life threatening or cause permanent impairment of a body function AND for which current medical alternatives are insufficient or carry significant risks (see definition of "breakthrough devices" in MEDDEV 2.7/1 rev.4, Appendix 8)

-> Description of the disease(s)/condition(s) and the current standard medical treatments or diagnosis

- **Novel devices with a possible major clinical or health impact**

-> Assessment of the novelty of the device and the expected clinical and/or health impacts resulting from that novelty cf. EC guidance for the medical device expert panels on the consistent interpretation of the decision criteria in the clinical evaluation consultation procedure

Centralising Principles : Expert Panels

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Centralising Principles: EU Expert Panels

EUROPEAN MEDICINES AGENCY

Expert Panels – Activities

- Activities of the Expert Panels on medical devices started with the implementation of the **mandatory consultation procedures**
  - Clinical Evaluation Consultation Procedure (CECP) in April 2021
  - Performance Evaluation Consultation Procedure (PECP) in September 2021
- In addition to the CECPs and PECPs, the Medical Device Regulation (MDR) foresees for the Expert Panels ***ad hoc* activities** depending on needs, that include Scientific Advice (SA) to manufacturers

Opportunities to help Orphan Medical Devices

IMDRF

- What has worked
  - What can be harmonised
  - What can be improved

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Japan's Efforts to Promote Development of Orphan Medical Devices

Tetsuya Kusakabe, MPH, PhD

Pharmaceuticals and Medical Devices Agency (PMDA), JAPAN

25th September 2023

European Commission

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OVERVIEW

Regulatory Authorities in Japan

MHLW

(Ministry of Health, Labour and Welfare)

- Law Enforcement
- Final Authorization
- Publishing Guidelines
- Advisory Committee
- Supervising PMDA

etc.

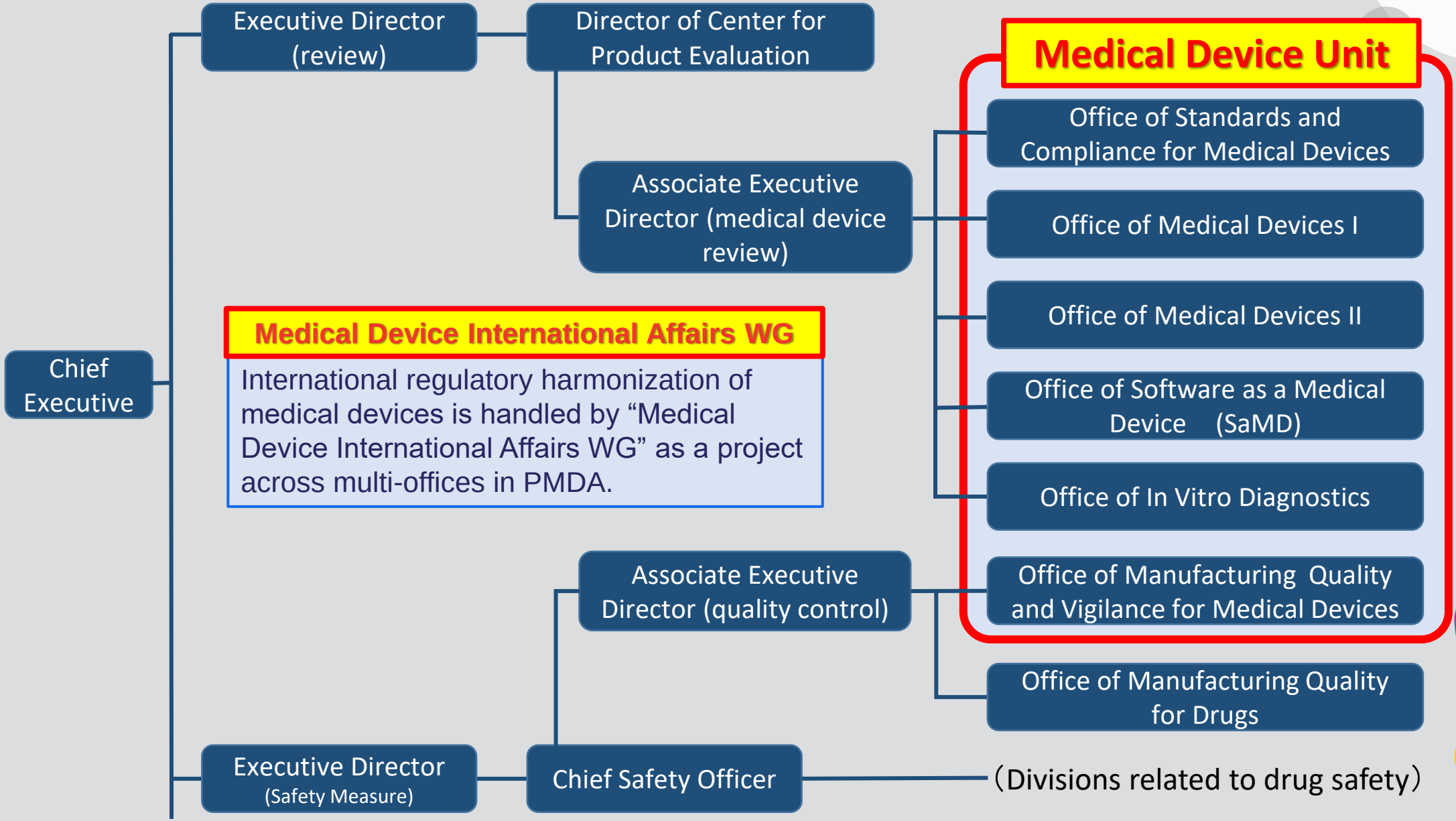
PMDA

(Pharmaceuticals and Medical Devices Agency)

- Scientific Review
- Post Market Safety
- GCP, QMS Inspection
- Consultation on Development Strategy

etc.

PMDA Organizational Structure



Designation Criteria for Orphan MD

1. Small number of patients

- < 50,000 in Japan (Prevalence Rate < 3.9 in 10,000 people)
- Or designated intractable disease

2. High medical needs

- Unmet needs (No alternative medical intervention is available)
- Significant benefit (Significantly improved efficacy and/or safety expected compared to existing products)

3. High probability of successful development

- Strong rationale to use the product, and an appropriate development plan

(Source) Article 77-2-1, Pharmaceutical and Medical Device Act (PMD Act)

Incentives for R&D Promotion

1. Grant-in-Aid for R&D Expenses

- Up to ½ of direct expenditure up to 3 yrs. from NIBIOHN*

2. Administrative and Scientific Advices

- Pre-submission meeting/advices by MHLW on the application for orphan designation
- Administrative and scientific advices by PMDA (Priority Consultation) and NIBIOHN* on R&D after the designation

* NIBIOHN: National Institutes of Biomedical Innovation, Health and Nutrition

https://www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/orphan_drug.html
https://www.nibiohn.go.jp/nibio/part/promote/files/orphan_guide.pdf

Incentives for R&D Promotion

5. Premium for Medical Device Pricing

- Orphan medical devices are given the 10% premium
- The premium is up to 1.5 times of average price in foreign countries (cf. up to 1.25 times for standard new MDs)
- Unaffected by the market price of other similar medical devices for a period of time

https://www.mhlw.go.jp/content/10800000/001073851.pdf

Incentives for R&D Promotion

3. R&D Tax Deduction

- 20% of R&D expenses excluding grant-revenue for orphan products during granted period (up to 3yrs.) is deductible in corporate taxation

4. Priority Review

- Priority review (Fast-track review) by MHLW/PMDA
  - SAKIGAKE Designation System, Conditional Early Approval System for Innovative Medical Device Products, etc.
  - 9 months (cf. 12 month for standard new MDs)

https://www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/orphan_drug.html
https://www.nibiohn.go.jp/nibio/part/promote/files/orphan_guide.pdf

Designated and Approved Orphan MDs

(Nov. 1993 – Jan. 2023)

Orphan MDs	Products
Designated	32
(Approved)	(22)

https://www.nibiohn.go.jp/nibio/part/promote/files/ph_orphanlist_medicaldevice_JP.pdf

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Contact Us | Pharmaceuticals and Medical Devices Agency (pmda.go.jp)

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Saving Orphan Medical Devices a manufacturer perspective (MDD to MDR regulatory change example)

Leo Hovestadt, Elekta

September 25, 2023

European Commission

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World-wide overview of orphan regulations

(Simplified)	US	Japan	Australia	EU	Brazil
Orphan regulation	Drugs & devices	Drugs & devices	Drugs	Drugs (& devices in development)	Drugs
Incidence	Rare disease	Rare disease	Rare disease	Rare disease	Rare disease
Indication	NA	**Serious** disease	**Serious** medical condition	**Life-threatening /** chronically debili-tating conditions	**Serious** debilitating condition

World-wide focus for orphan devices is on:

- Rare diseases
- Mostly for serious / life threatening indications

Major **regulatory improvements**, like the MDD to MDR transition (and other past major regulatory improvements):

- Cause most orphan devices under the legacy devices,
- and mostly for non-serious conditions

The transition from the MDD to MDR is associated with orphan devices and shortages

Regulatory improvements cause orphans devices, but why?

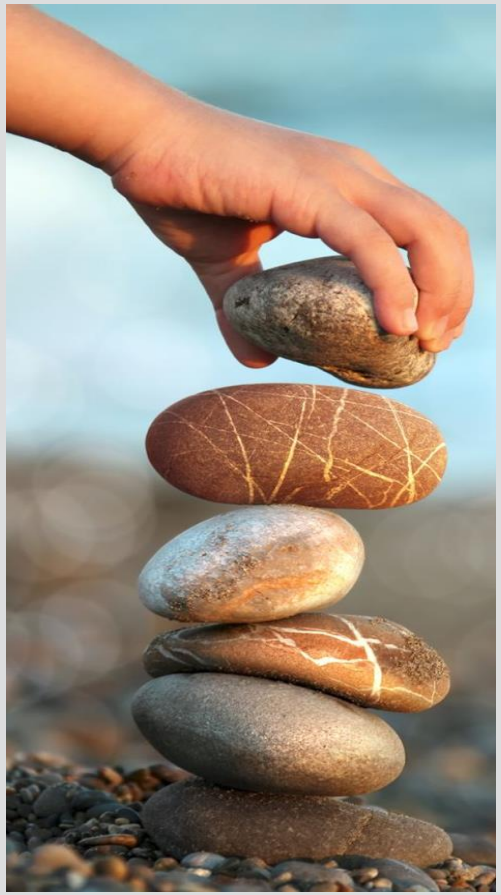
- New requirements for clinical evidence, pediatric indications, etc
- Significant increase in certification cost and time
- Shortage of Notified Body capacity and recertification time ✓
- Avalanche of other new regulations (concers keep the patient first instead of last)

For manufacturers removing the device / indication from the market is currently the major possibility when encountering recertification issues, leading to orphan devices and shortages.

Possible convergence for rare disease and orphan devices, such as might be possible :

- Accelerated regulatory pathways WIP
- Support in performing clinical study for serious diseases WIP

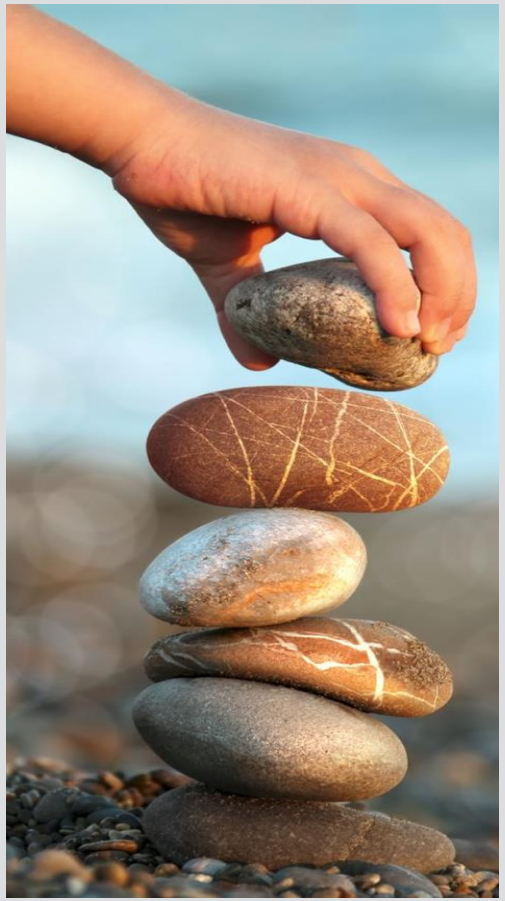
Opportunities for saving for orphan devices



- New requirements for clinical evidence, pediatric indications, etc
  - A. Review and if acceptable promote other sources of evidence, such as:
    - Real world evidence
    - Pre-market investigator initiated studies

- B. Avoid orphan indications for legacy devices (in addition to A.):
  - If possible mitigate clinical evidence issues through transparency in the manual (note, legacy devices are assumed to have a history of safe use)
  - If possible mitigate through a professional use statement requirement
  - Allow a proper risk / benefit assessment including all evidence sources for orphan indications
  - Example: Allowing a pediatric indication for a smaller size adult needle, in case the amount of clinical evidence is insufficient, since there are not enough pediatric patients to deliver the evidence

Opportunities for saving for orphan devices



- Significant increase in certification cost and time:
  - A systematic review if cost and time for MDR certification activities contribute enough to safe and performing devices.
  - Example: Periodic Safety Update Reports are very time consuming to create and review. However the purpose is the same as the Post Market Surveillance system. So are reductions in time spent possible ?

- Avalanche of other new regulations (where the patient comes last (Note: the MDR is overruled):
  - The new regulations do not have indications for use, risk – benefit assessment, risk management, state of the art, etc. Making it often difficult / impossible to bring the medical devices to the market.

Thanks for listening and your help to keep the orphan Medical Devices on the market is much appreciated !!!

THANK YOU / QUESTIONS

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Orphan or Urgently-needed Medical Device Supply Policy

Ahram Cho, Deputy Director, Ministry of Food and Drug Safety

2023.9.25

European Commission

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Orphan or Urgently-needed Medical device Supply Policy of MFDS

Background

- **(Issue)** Supply shortage or a lack of substitutes for medical devices used in treating rare/intractable diseases has affected patient care.
- **(Solution)** In compliance with the law, the government designates, directly imports, and provides 'Orphan or urgently-needed' medical devices crucial for treating patients with such diseases that lack alternative treatment options.

Law (Effective as of June 2019)

- **Article 15-2 Paragraph 1 of the Medical Devices Act**

The Minister of the Ministry of Food and Drug Safety may domestically supply medical devices falling under the following categories (referred to as "orphan or urgently-needed medical devices") by means of importation or other methods to expand treatment options for patients with rare/intractable diseases, manage such diseases, and more effectively serve public health.

1. Medical devices without substitutes in Korea intended for diagnosing or treating rare diseases meeting the criteria under Article 2, subparagraph 1 of the「Rare Disease Control Act」.

2. Medical devices recognized by the Minister of the Ministry of Food and Drug Safety or requested by the head of the relevant central administrative agency as urgently needed for public health reasons or requiring stable supply support.

Selection Criteria for Orphan or Urgently-needed Medical Devices

- **(Substitutability)** Necessity for treating rare/intractable diseases and the absence of a substitutable medical device in Korea.
- **(Safety)** Proof of approval and a record of sales/usage from the manufacturing country
- **(Supply Availability)** Availability of sustainable supply with the overseas manufacturer's agreement on domestic supply.

Designation Procedure of Orphan or Urgently-needed Medical Devices





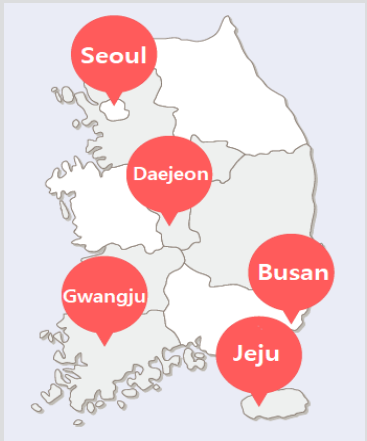
STEP01	STEP02	STEP03	STEP04	STEP05
Regular demand-survey	Basic research	Academic advisory and deliberation committee	Opinion inquiry of related ministries and organizations	Designation
Demend-survey **biyearly** Applicants: Medical institutions, Patients, etc	Approval status of similar domestic products, Sales status and clinical safety/efficacy in major countries, Disease information, Price information, and more	(Academic advisory) - Gather opinions on need for domestic supply and the availability of domestic treatment methods (Deliberation committe) - Discussion on the need to designate orphan or urgently needed medical devices	Gather opinions of Ministry of Health and Welfare(MOHW), Health Insurance Review and Assessment Service(HIRA), and other related organizations	Designation of orphan or urgently-needed medical devices

Product List (30 products, August 2023)

No.	Manufacturer	Product Name	Designated Date	No.	Manufacturer	Product Name	Designated Date
1	Gore	VASCULAR GORE-TEX STRETCH GRAFT	`19.7.10	16	Bentley	Begraft Peripheral	`20.1.9
2	Gore	VASCULAR GORE-TEX STRETCH GRAFT - Large Diameter	`19.7.10	17	Jotec	E-vita open plus	`20.1.9
3	Gore	GORE-TEX SUTURE	`19.7.10	18	Gore	PROPATEN® Vascular Graft configured for Pediatric Shunt	`20.5.29
4	Gore	GORE-TEX® Soft Tissue Patch	`19.7.10	19	Cook Medical	Zenith t-Branch Thoracoabdominal Endovasulcar Graft	`21.1.26
5	Gore	GORE® ACUSEAL Cardiovascular Patch	`19.7.10	20	Cook Medical	Zenith Universal Distal Body Endovasulcar Graft	`21.1.26
6	Gore	GORE® PRECLUDE® Pericardial Membran	`19.7.10	21	Jotec	E-vita open NEO	`21.1.26
7	Getinge Group	Avalon Elite Bi-Caval Dual Lumen Catheter	`19.10.2	22	Medcomp	SPLIT CATH III	`21.7.14
8	Andramed	Andra Stent	`19.10.2	23	Abbott	Masters Series Mechanical Heart Valve	`21.12.22
9	Numed	Covered mounted CP stent	`19.10.2	24	REPER-NN LTD	MIOL-Iris	`22.4.25
10	Numed	BIB® Catheter	`19.10.2	25	GWSG	Jones Tube	`22.4.25
11	Numed	Atrioseptostomy catheter	`19.10.2	26	FCI S.A.S	Ptosis Probe	`22.5.30
12	Cook Medical	Flexor® Introducer	`19.10.2	27	Bentley	Begraft Peripheral Plus	`22.9.23
13	Cook Medical	Performer® Introducer and set	`19.10.2	28	OptiMed	sinus-SuperFlex-DS	`22.12.23
14	Merit medical	HeRO 1000	`19.10.2	29	Edwards	KONECT RESILIA aortic valved conduit	`23.6.30
15	Merit medical	Surfacer	`19.10.2	30	Medtronic	DLP Pediatric One-Piece Artery Cannulae	`23.7.31

Procedures for Supplying Orphan or Urgently-needed Medical Devices

STEP01	STEP02	STEP03	STEP04	STEP05
Import and Customs clearance	Securing domestic stock	Application for supply	Supply Products	Billing
Purchase medical devices according to supply plans	(Central storage office) Seoul (Local storage centers) Daejeon, Gwangju, Busan, Jeju	Patients or medical institutions submit supply applications	(Logistics companies) Delivery on the requested date	Charge for Product cost plus tax and distribution cost Use to purchase other orphan or urgently-needed medical devices



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Humanitarian Device Exemptions (HDE)

April Veoukas, Abbott for GMTA

25 September 2023

European Commission

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Humanitarian Use Devices (HUD) for Rare Diseases.

In the U.S.

- A disease or condition that affects fewer than 200,000 people is a rare disease
- HUD is a medical device intended to benefit patients in the treatment of a disease or condition that affects or is manifested in not more than 8,000 individuals

Review Standard for HDE

To foster innovation and availability to patients with rare diseases the HUD is exempt from the requirement of establishing a reasonable assurance of effectiveness.

Rather the HDE is based on a determination of safety and probable benefit.

That is, evidence demonstrates the HUD will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from use of the HUD outweighs the risk of injury or illness from its use taking into account the probable risks and benefits of currently available devices or alternative forms of treatment.

Pathway Stages

Designation/Application Contents

HUD Designation

- Description of rare disease
- Why therapy is needed
- Device description
  - Proposed indication
  - Scientific rationale for device
- Authoritative references

HDE Application

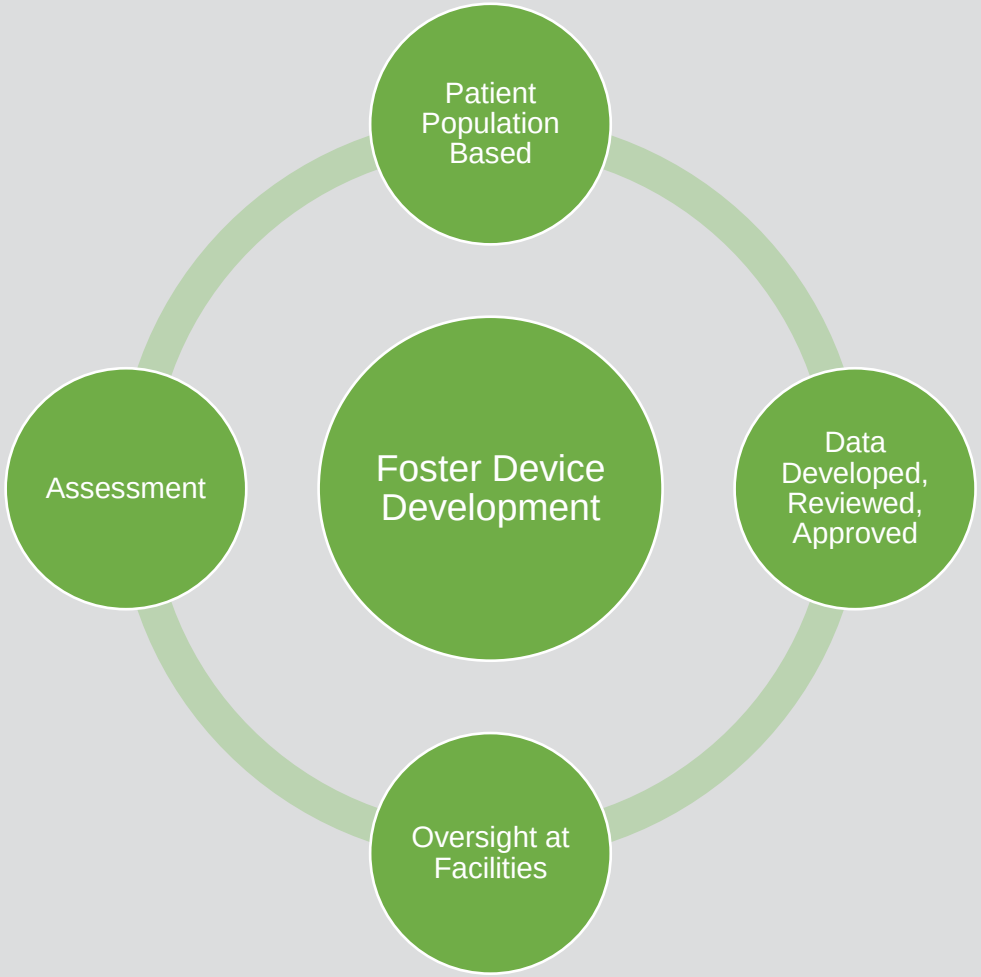
- HUD designation
- Why device would not be available unless HDE
- No comparable device available
- Assessments of Risks/Benefits
- Nonclinical, Clinical Data and/or summaries
- Labelling

HDE Post Approval

Requirements

- Available only in facilities having IRB oversight
- IRB approval before HUD can be used at a facility for clinical care
- Supplements for changes affecting the safety or probable benefit of the device
- Periodic reports
  - Annual patient population assessment
- Additional (e.g., recalls, adverse event)

Foster Device Development and Treatment Availability



THANK YOU / QUESTIONS

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Pediatric medical devices: US regulatory perspective

Kenneth J. Cavanaugh Jr, PhD **US FDA**

September 25, 2023

European Commission

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Why develop pediatric devices and labeling?

- Promote pediatric-specific device designs
- Establish pediatric-specific training programs
- Allow pediatric-specific advertising and claims
- Clearly delineate the populations in which safety and effectiveness has been established
- Denote that risks to pediatric patients were evaluated and found to be outweighed by the benefits
- Provide the treating physician with available evidence that may inform individual patient treatment

Why not develop pediatric devices and labeling?

- Unique design considerations
- Small market / sample size
- Ethical considerations
- Lack of pediatric device development infrastructure

- Frequently a low return on investment
- Evidence generation can be challenging

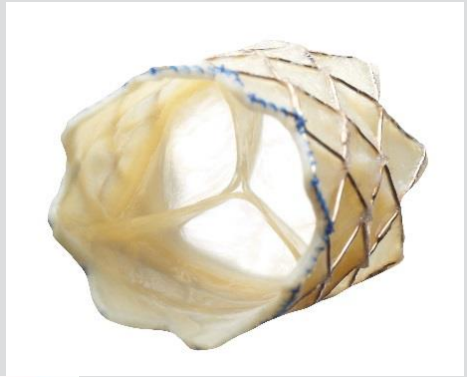
What regulatory programs can facilitate access to pediatric devices in the US?

Humanitarian Use Devices (HUD)

- Medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in not more than 8,000 individuals in the United States per year
- Devices designated as HUD by FDA are eligible for marketing via *Humanitarian Device Exemption (HDE)* pathway
  - Demonstrate safety and probable benefit (not effectiveness)
- Potential (not required) option for pediatric devices

Stepwise approval: HDE ⟶ PMA

- Medtronic Melody Transcatheter Pulmonary Valve
  - HDE approval: 2010
  - PMA approval: 2015
- Berlin Heart EXCOR Pediatric VAD
  - HDE approval: 2011
  - PMA approval: 2017



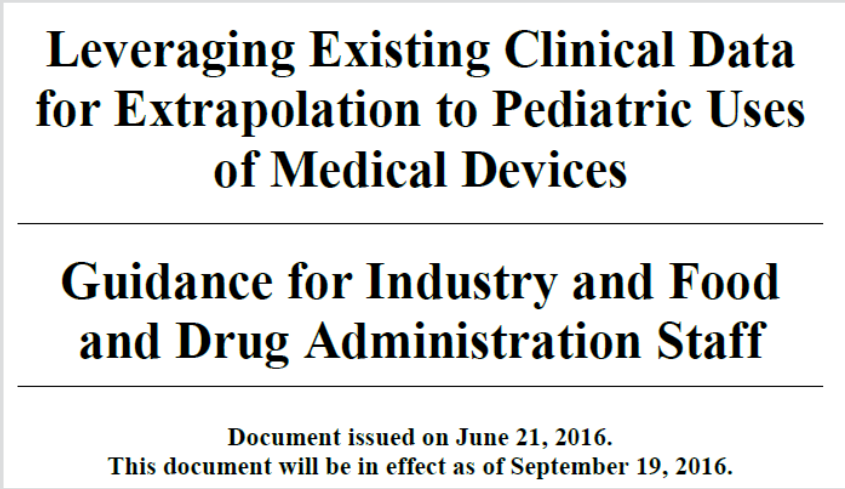
Leveraged continued follow-up data from clinical study plus post-approval study data to demonstrate effectiveness for PMA

Financial factors

- No fee for pediatric-only marketing submissions
- Ability to sell pediatric HDE devices for profit
- Potentially more favorable reimbursement for on-label pediatric device use
- FDA-funded **Pediatric Device Consortia Grants Program**

Regulatory policy

- Guidance on extrapolating clinical data to pediatric uses
- Initiatives to promote access to safe and effective devices addressing unmet needs
  - Breakthrough device
  - Benefit-risk considerations
  - Pre-market vs post-market balance



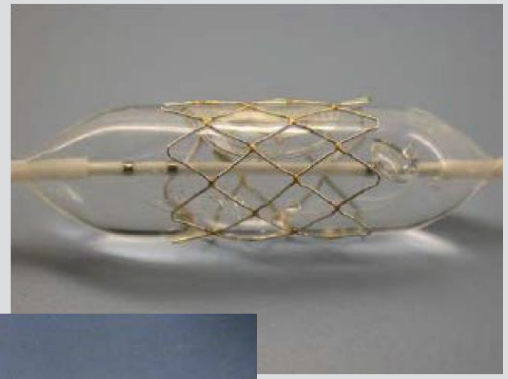
Leveraging Existing Clinical Data for Extrapolation to Pediatric Uses of Medical Devices

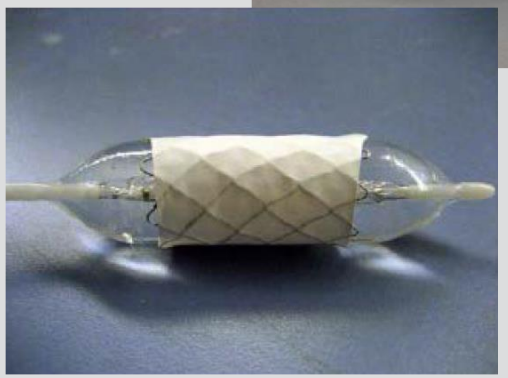
Guidance for Industry and Food and Drug Administration Staff

Document issued on June 21, 2016.
This document will be in effect as of September 19, 2016.

What are some examples of FDA-approved pediatric devices?

NuMED Cheatham Platinum Stent System





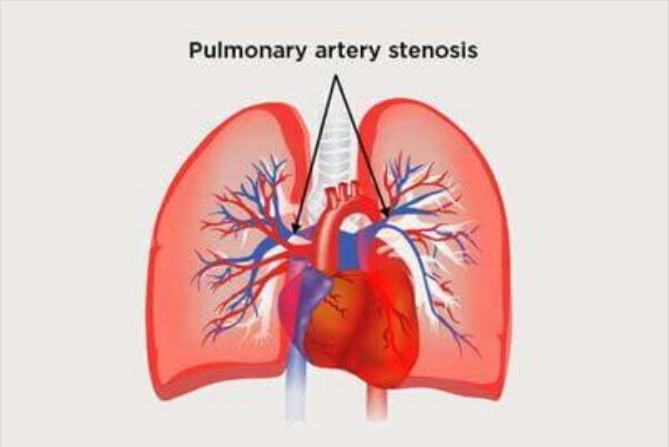
Indicated for treatment of native or recurrent coarctation of the aorta

- Supported by 192 subjects from multiple clinical investigations
  - Majority of subjects were pediatric
- Studies were sponsored by *academia*

Cordis PALMAZ MULLINS XD Pulmonary Stent

Indicated for non-emergency treatment of pulmonary artery stenosis in pediatric patients who are at least 10 kg in weight with two ventricle anatomy

- Supported by data from 108 subjects captured in cardiovascular registry
  - 74% pediatric subjects
- Safety and effectiveness assessed via *real-world clinical evidence*

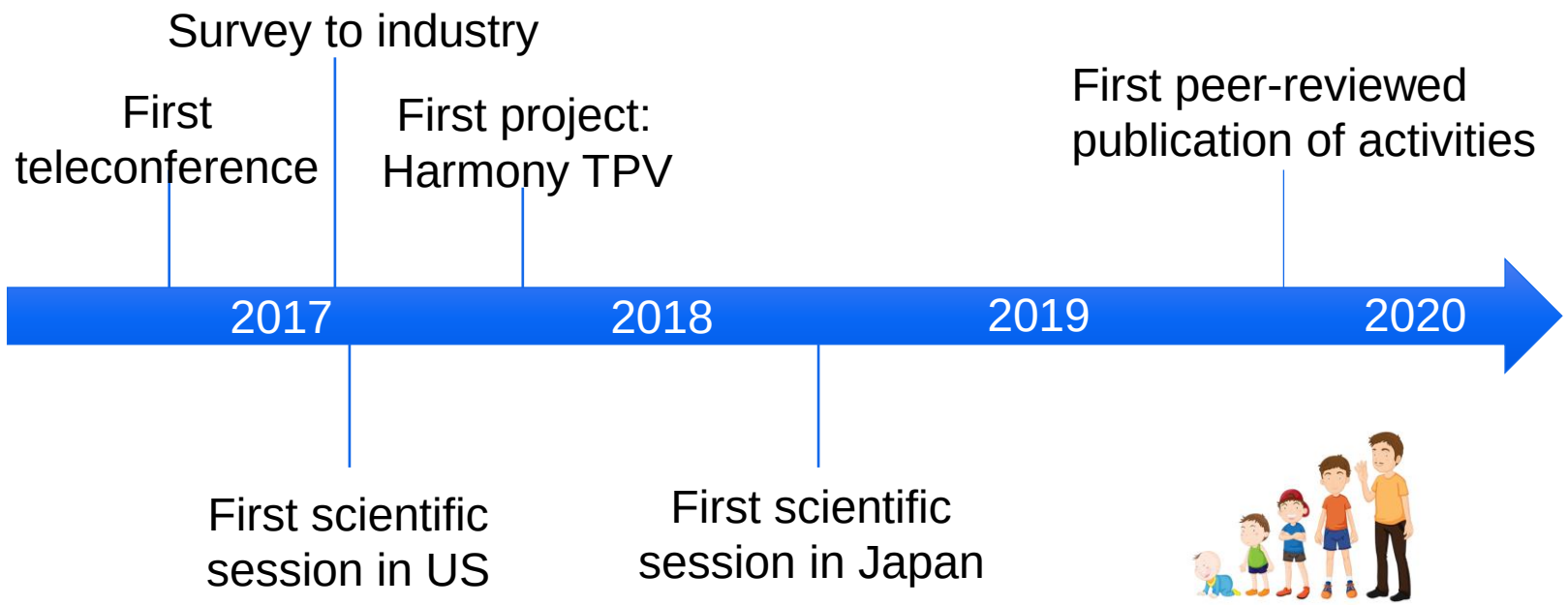


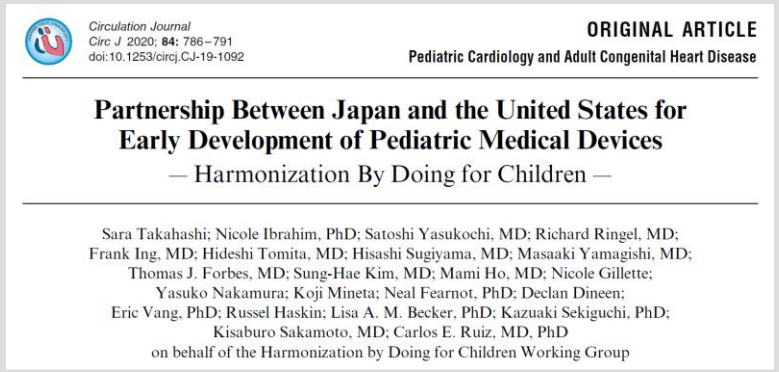
Medtronic Harmony Transcatheter Pulmonary Valve System

Indicated for management of pediatric and adult patients with severe pulmonary regurgitation and a native or surgically-repaired right ventricular outflow tract

- Supported by 71-patient clinical study
  - 38% pediatric subjects
  - Clinical sites in US, Canada, Japan
- Part of US-Japan *Harmonization by Doing* initiative

US-Japan Harmonization by Doing (HBD) for Children





Circulation Journal
Circ J 2020; 84: 786–791
doi:10.1253/circj.CJ-19-1092

ORIGINAL ARTICLE
Pediatric Cardiology and Adult Congenital Heart Disease

Partnership Between Japan and the United States for Early Development of Pediatric Medical Devices
— Harmonization By Doing for Children —

Sara Takahashi; Nicole Ibrahim, PhD; Satoshi Yasukochi, MD; Richard Ringel, MD; Frank Ing, MD; Hideshi Tomita, MD; Hisashi Sugiyama, MD; Masaaki Yamagishi, MD; Thomas J. Forbes, MD; Sung-Hae Kim, MD; Mami Ho, MD; Nicole Gillette; Yasuko Nakamura; Koji Mineta; Neal Fearnot, PhD; Declan Dineen; Eric Vang, PhD; Russel Haskin; Lisa A. M. Becker, PhD; Kazuaki Sekiguchi, PhD; Kisaburo Sakamoto, MD; Carlos E. Ruiz, MD, PhD
on behalf of the Harmonization by Doing for Children Working Group

Facilitate identification and pursuit of actual, practical applications of harmonization

Next steps?

Opportunities to facilitate global pediatric device development and access by:

- **Communicating** with regulatory authorities early and often
- **Collaborating** with external stakeholders, including international partners
- **Continuing** to generate and utilize clinical evidence from multiple sources

Sharing lessons learned and developing best practices can further stimulate the global pediatric device ecosystem

FDA resources

- Humanitarian Use Device (HUD) designation
  - https://www.fda.gov/media/130442/download
- Humanitarian Device Exemption (HDE) program
  - https://www.fda.gov/media/74307/download
- Extrapolation of clinical data for pediatric use
  - https://www.fda.gov/media/91889/download
- Pediatric Device Consortia Grants Program
  - https://www.fda.gov/industry/medical-products-rare-diseases-and-conditions/pediatric-device-consortia-grants-program

THANK YOU / QUESTIONS

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PEDIATRIC DEVICES

Joel Batts, Sr. Vice President | Clinical & Regulatory Affairs | OrthoPediatrics

Monday, September 25, 2023

European Commission

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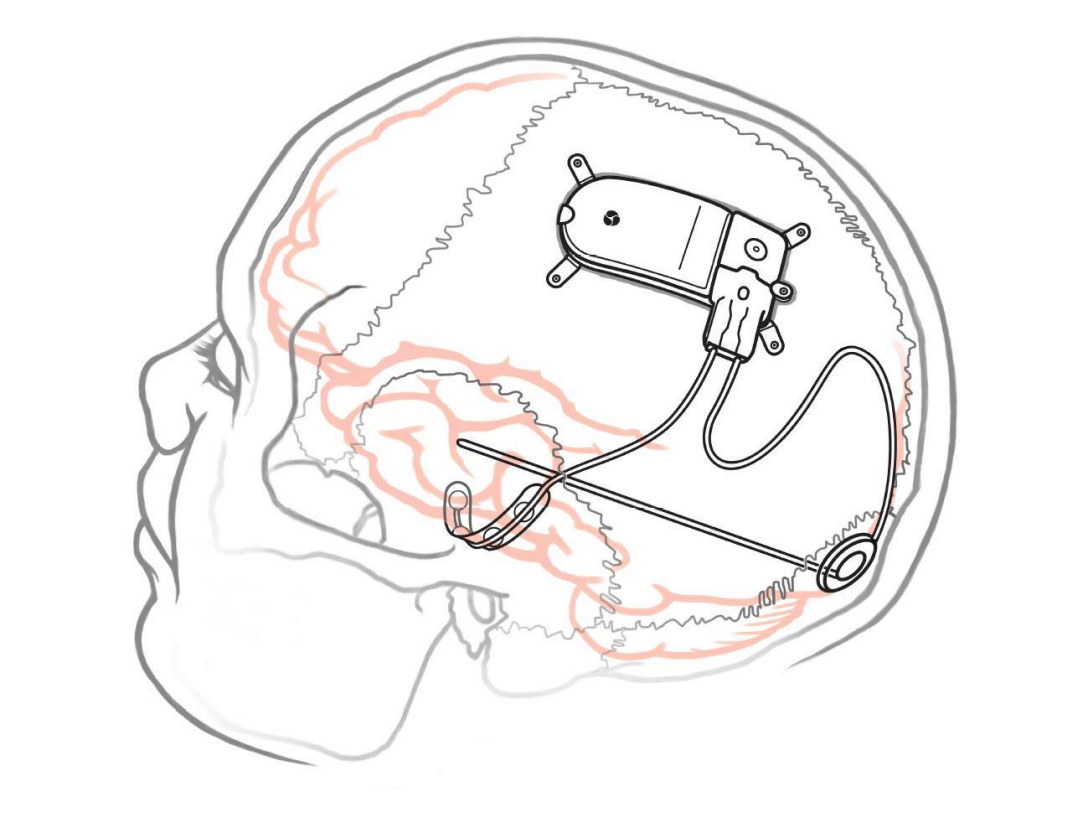
PRESENTATION OUTLINE

- Background
- Challenges
- Opportunities

BACKGROUND

- FDA reports over the past decade, less than a quarter of PMA or HDE devices were approved for pediatric use
- Adult devices frequently used off-label in children
- Adult devices frequently modified or "jerry-rigged" for individual use in children

REAL WORLD OF THE OPERATING THEATRE



- No neurostimulator device is sized for kids
- Pain pumps are not sized for children
- RNS* limited to teens—device is too large

*responsive neurostimulation: a technology that has reduced seizure incidence by 82% and decreased sudden death rate

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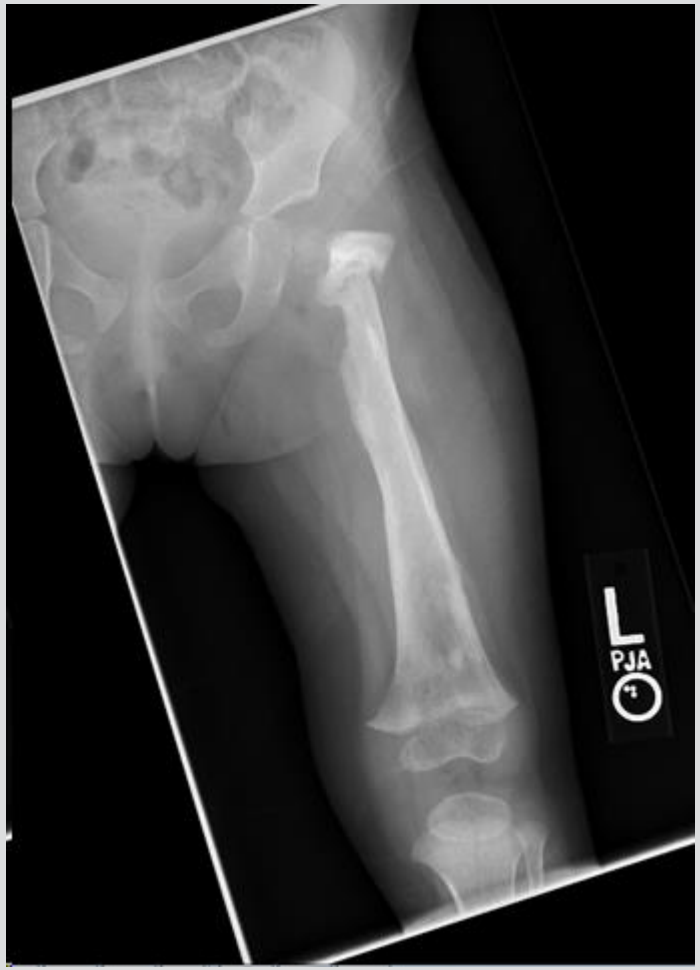
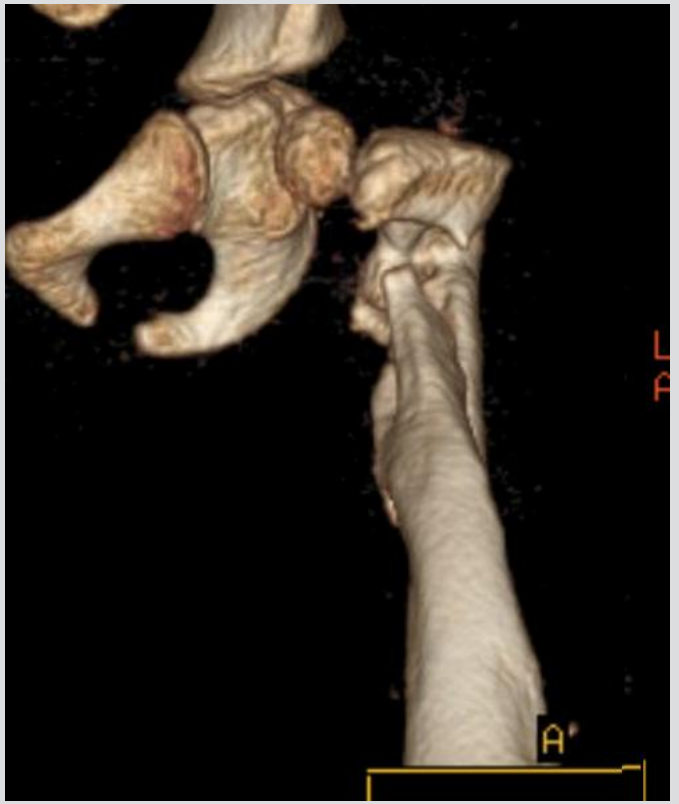
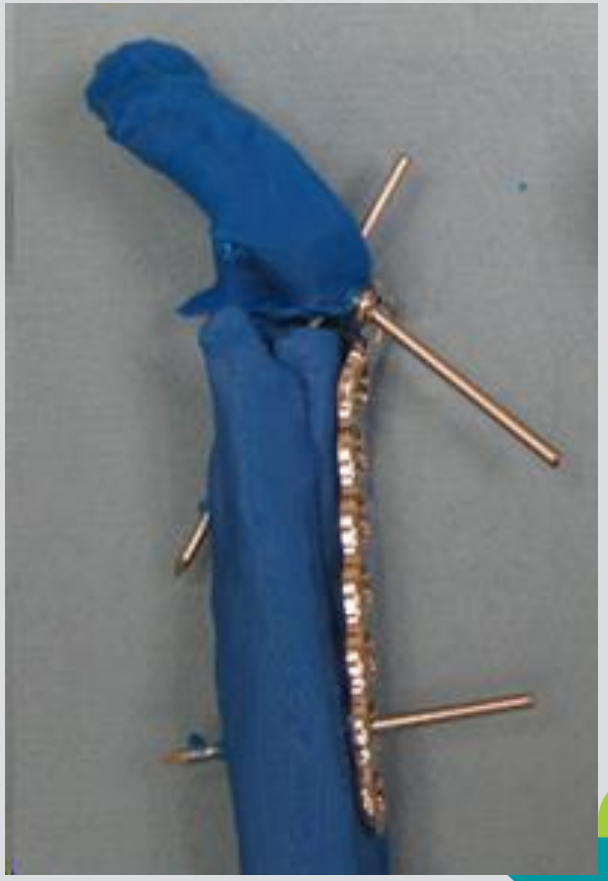
REAL WORLD OF THE OPERATING THEATRE







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PEDIATRIC DEVICE CHALLENGES

Challenging regulatory pathways and related evidence requirements

- Conduct of traditional controlled trials difficult and costly due to:
  - Small, orphan populations
  - Heterogeneous
  - Geographically dispersed pediatric populations
  - Reluctance of parents to enroll children in trials

PEDIATRIC DEVICE CHALLENGES

Challenging regulatory pathways and related evidence requirements

- Review teams do not always appropriately factor in the following in pediatric benefit/risk analyses:
  - Lack of an on-label pediatric device,
  - Off-label use of adult devices in pediatric populations, or
  - Modifying or jerry-rigging of adult devices for individual use in pediatric populations

PEDIATRIC DEVICE CHALLENGES

- Challenging reimbursement landscape
  - In U.S., little or no reimbursement for many pediatric devices unlike for adults
- Little investor interest in small markets with high R&D costs, and challenging regulatory and reimbursement pathways

REGULATORY OPPORTUNITIES

Establish small/orphan population regulatory pathway:

- Ensure appropriate benefit/risk analyses to drive achievable evidence requirements via consultation with clinical experts
- Facilitate use of Real-World Evidence/ Real-World Data in pediatric submissions
- Balance pre-market and postmarket requirements by requiring small confirmatory trials followed by robust postmarket follow up via registries or other PS

REGULATORY OPPORTUNITIES

- Use of pediatric specific reviewers/teams to ensure expertise on unique issues associated with pediatric populations
- Permit extrapolation of adult data or data from different device sizes to pediatric populations where appropriate[2]
- Allow use of general device claims where appropriate rather than requiring specific device claims for each pediatric age bracket

[2] *See Leveraging Existing Clinical Data for Extrapolation to Pediatric Uses of Medical Devices, Guidance for Industry and Food and Drug Staff, September 19, 2016*

REGULATORY OPPORTUNITIES

- Pediatric diseases and conditions can have life-long impact on health, qualifying pediatric devices for breakthrough consideration
  - For regulatory systems with breakthrough device designations, provide automatic designation of devices with pediatric intended use to:
    - Expedite clearance/approval and
    - Assure regulatory expertise is brought to bear to bring products to market

OTHER OPPORTUNITIES

Development of entity and ecosystem to facilitate pediatric device development – i.e., **S**ystem of **H**ospitals for **I**nnovation in **P**ediatric **M**edical **D**evices (SHIP-MD)

- **Objectives:**
  - Establish a non-profit public private partnership (PPP) to provide non-binding advice to innovators
  - Reduce uncertainty in pediatric medical device development by de-risking regulatory & payment processes and accelerating development process
  - Create clinical trial network of Children's Hospitals (Hubs) and connected facilities (Spokes) w/single IRB & contract process to expedite trials

OTHER OPPORTUNITIES

- **SHIP-MD Continued:**
  - Foundation for the National Institutes of Health (FNIH) will lead 18-month design phase to develop and implement the PPP and plan for a sustainable infrastructure for pediatric medical device (PMD) development & commercialization

OTHER OPPORTUNITIES

Once established, the concept could be expanded to include an international clinical trial network to:

- Further expedite collection of diverse pediatric data
- Expedite pediatric patient access to safe and effective medical devices

CONCLUSION

Given the multiple challenges in developing pediatric medical devices, a public private partnership comprised of regulators, industry and clinicians is an important path forward to encourage pediatric device development.

THANK YOU / QUESTIONS

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Paediatric Medical Devices: Challenges and Possible Solutions

Prof. Dr. Dr. Berthold Koletzko

Dept. Paediatrics, LMU University of Munich, Germany

European Academy of Paediatrics - CORE MD Project Task Leader

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Declarations

- Sincere thanks to EU / IMPDRF for inviting a Physician Scientist
- I declare NO CONFLICT of interest *(no funding provided by any company related to medical devices)*
- My work in this area was financially supported in part by EU Horizon 2020 research and innovation programme, project CORE-MD *(Coordinating Research and Evidence for Medical Devices, grant agreement 965246)*
- On behalf of the European Academy of Paediatrics, I led the work within the CORE-MD consortium on developing ***"Recommendations on high-risk medical devices in children"***

European Union funded CORE-MD project: Purpose

- Improved methods for **clinical investigation** and **evaluation** of high-risk medical devices (MD)
- To build better **knowledge bases** amongst **clinical** & **regulatory** communities
- Offer suggestions for **ways forward**
- *Approach: systematic reviews, CE mark with conditions, hierarchy of evidence, ethical principles, review of clinical guidance & standards, et al.*

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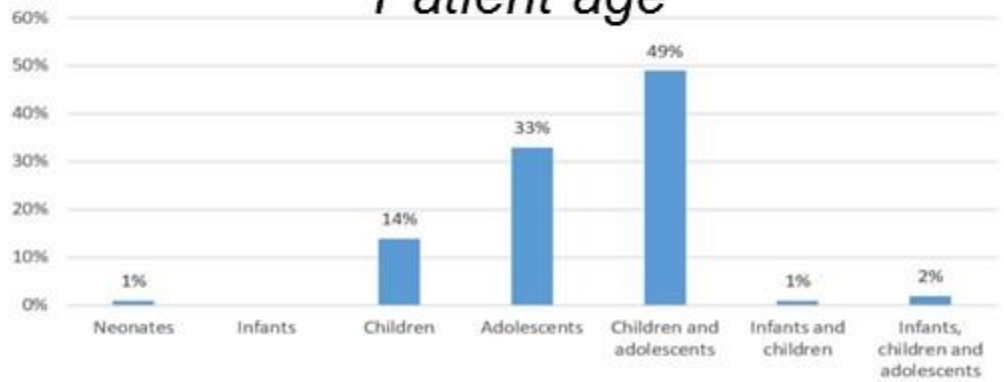
Background

- The EU MDR 745/2017 aims to strengthen clinical evaluation and safety, particularly of high-risk MD
- EU MDR **markedly increases time & costs** for bringing MD to or keeping them on the market; particularly challenging for MD sold in small numbers
- **Paediatric and orphan MD increasingly disappear** from the EU market
- **Loss of essential MD** needed for appropriate care of sick children and other patients with orphan disease

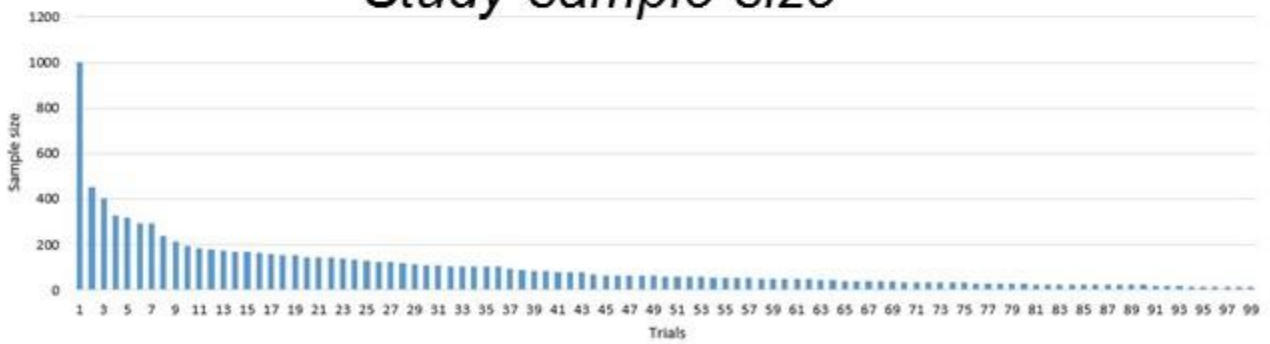
Systematic review, paediatric clinical trials on MD

- Scoping review on clinical trials investigating selected high-risk paediatric medical devices in patients aged 0-21 yrs, published 2017- 2022
- Mostly **small sample size** *(median 59; 65% <100)*
- Most studies *(≈90%)* in children with **diabetes** *(common disease, ≈same MD as adults)*, but **few in other disorders**
- Studies in **infants & young children lacking**

Patient age



Study sample size



Gürlich K et al. Evidence from clinical trials on high-risk medical devices in children: a scoping review. Ped Res 2023, in press

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Recommendations on clin. investigation & evaluation

DOI: 10.1111/apa.16919

ACTA PÆDIATRICA NURTURING THE CHILD WILEY

European expert recommendations on clinical investigation and evaluation of high-risk medical devices for children

Experts from various child health specialties, representatives of **24 medical associations** (Eur Acad Paediatrics, Child Health Foundation-Stiftung Kindergesundheit, Assoc Eur Paed Congen Cardiol, Biomed Alliance Eur, Cardiovasc Intervent Radiol Soc Eur, conect4children, Eur Ped Dialysis WG, Eur Ped Surgeons Assoc, Eur Rare Kidney Dis Ref Network, Eur Ref Network Rare Endocrine Conditions, Eur Ref Network Hereditary Metabol Disorders, Eur Soc Cardio, Eur Soc Developm Perinatal Paed Pharmacol, Eur Soc Emergency Med, Eur Soc Endocrinol, Eur Soc Ped Nephrol, Eur Soc Paed Neonatal Intens Care, Eur Soc Paed Gastro Hepatol Nutrition, German Soc Paed Adolescent Med, Int Ped Nephrol Ass, Royal College Paed Child Health UK, Royal College Physicians Ireland, Int Ped Nephrol Assoc, Soc Study Inborn Errors Metabol) a **regulatory authority** (Health Products Regulatory Authority Ireland) and the **European Commission** Directorate General Health and Food Safety - Health Technology Unit B6

Gürlich K et al. European expert recommendations on clinical investigation and evaluation of high-risk medical devices for children. Acta Paediatr. 2023 Jul 24. doi: 10.1111/apa.16919.

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Clinical investigation: recommendations

- No “one size fits all” solution – one and the same approach to clinical investigation of all MD intended for children patients cannot be applied
- **Different levels of clinical evidence** are required depending on
  - specific research question
  - type of MD
  - identification of potential hazards and expected risks
  - nature and prevalence of conditions treated with the MD
  - intended age group

Gürlich K et al. European expert recommendations on clinical investigation and evaluation of high-risk medical devices for children. Acta Paediatr. 2023 Jul 24. doi: 10.1111/apa.16919.

Clinical investigation: recommendations

The approach to clinical investigation of MD in children should consider

- **RCTs are the gold standard** for evaluating therapeutic benefits of medical interventions and should be performed whenever feasible.
- **RCTs in children are mostly not feasible** to evaluate MDs for ethical or practicality reasons. Other study designs must be considered to generate clinical data on device performance and safety. Generally, one should **strive for the highest level of clinical evidence** that is achievable

- Hierarchy of evidence: 1) RCT (highest level); 2) Comparative prospective study with concurrent controls (experimental or observational); 3) Comparative study without concurrent controls (e.g. with historical control); 4) Prospective case series with documentation of either post-test or pre-test/post-test outcomes

Gürlich K et al. European expert recommendations on clinical investigation and evaluation of high-risk medical devices for children. Acta Paediatr. 2023 Jul 24. doi: 10.1111/apa.16919.

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Clinical investigation: recommendations

- **Mixed population studies** (both adults & children) can optimize sample sizes and resource use in case of a shared indication for MD use (include subgroup analyses)
- **Extrapolation** of data obtained from trials in adultscan be considered for devices with the same intended use in children, if the condition being treated is similar and if there is no indication for different effectiveness and safety of the device in children
- For post-marketing surveillance, European **patient registries supervised by competent paediatric associations** systematically collecting relevant and informative data on paediatric patients treated with MD of interest
- **Define and enhance quality** of existing registries, establish new registries
- **Funding** to be secured from public and private sources

Gürlich K et al. European expert recommendations on clinical investigation and evaluation of high-risk medical devices for children. Acta Paediatr. 2023 Jul 24. doi: 10.1111/apa.16919.

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Clinical evaluation: recommendations

- Establish an **expert panel on paediatric MD**, with **paediatric experts** to provide scientific and clinical advice
  - to developers of new and high-risk MD according to MDR Art. 61(2)
  - to EU MD Coordination Group with respect to consistent application of the MDR on MD for children according to MDR Art. 106
- **Require notified bodies** certifying paediatric MD to **seek advice from competent paediatric experts**
- **Transparency** needed regarding 1) **advice** of expert panels re clinical evidence expectations provided to MD developers according to MDR Art. 61(2), and 2) **clinical data** relied upon by manufacturers for paediatric MDs to ensure predictable evidence requirements, and clinicians have access to MD related data

Gürlich K et al. European expert recommendations on clinical investigation and evaluation of high-risk medical devices for children. Acta Paediatr. 2023 Jul 24. doi: 10.1111/apa.16919.

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Clinical evaluation: recommendations

- **Designation of "orphan MD" status** should be based on a case by case evaluation, taking the following criteria into account
  - Intended use in a life-threatening or chronically debilitating disease with a prevalence of <1 per 2,000 people, based on the accepted definition of rare diseases in the EU
  - Existence of an unmet medical need, and
  - Absent or insufficient suitable / equivalent alternative therapeutic options with similar clinical safety

Gürlich K et al. European expert recommendations on clinical investigation and evaluation of high-risk medical devices for children. Acta Paediatr. 2023 Jul 24. doi: 10.1111/apa.16919.

Interim solutions for paediatric and orphan MD

- **Ensure continued access** to essential paediatric and orphan MD
- Establish systematic monitoring on MD that are about to disappear or have already disappeared from the market
- Implement efficient & fast process to assign a “paediatric device” or “orphan device” status, leading to a simplified, fast and low-cost conformity assessment
- Proactively support bringing MDs to market also for small and particularly vulnerable patient groups, e.g. public funding, other incentives *(cf. drugs for children)*
- Until final solution is achieved: paediatric or orphan MDs that have been marketed for at least 3 years without reported problems to get permission for continued use; MDs approved with credible evaluation in other jurisdictions to be permitted for market access, to support patient safety and well-being with access to essential MDs

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Increasing awareness, support political decisions

- Clinical experts to work together with paediatric associations in Europe to increase awareness on consequences of the EU MDR and its implementation for medical care of sick children, due to increasing unavailability of essential MD for children

Open Letter to EU Health Commissioner signed by 27 organizations

copy by e-mail:
cab-kyriakides-contact@ec.europa.eu

Commissioner Stella Kyriakides
European Commissioner for
Health and Food Safety
European Commission
Rue de la Loi / Wetstraat 200
1049 Brussels, Belgium

Date 27/6/2023
Open letter: Urgent action needed to secure continued access to essential medical devices for children and for patients with orphan diseases

Response by European Commission President

Ref. Ares(2023)5981983 - 04/09/2023

EUROPÄISCHE KOMMISSION
Kabinett der Präsidentin Ursula von der Leyen

Berater zum europäischen Grünen Deal

Brüssel, 04. September 2023
Ares (2023) 4514198

Sehr geehrter Herr Professor Koletzko,

Präsidentin von der Leyen dankt Ihnen für die Übermittlung des an Kommissarin Kyriakides gerichteten offenen Briefes, den Sie gemeinsam mit 28 anderen europäischen Verbänden im Bereich der Kindermedizin und der medizinischen Versorgung unterzeichnet haben. Sie äußern darin Ihre Besorgnis über die Auswirkungen der Umsetzung der Verordnung (EU) 2017/745 über Medizinprodukte (MDR) auf die Verfügbarkeit bestimmter Medizinprodukte, insbesondere solcher zur Behandlung von

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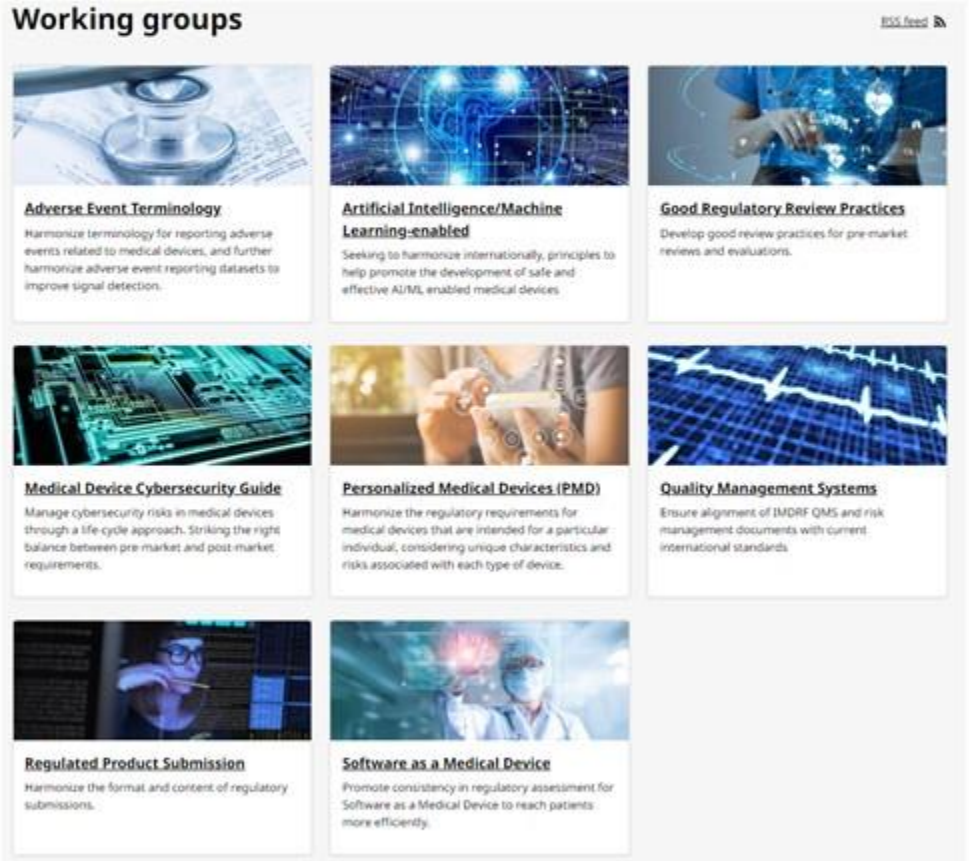
Proposals to IMDRF

- Implement a work item "***Paediatric and Orphan Medical Devices***" to facilitate global regulatory convergence and harmonized approaches towards solving the very large existing challenges
- Establish consistent **involvement and representation of health care professionals** in IMDRF to ensure clinical experience and needs are adequately considered in global regulatory approaches



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THANK YOU / QUESTIONS

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PERSONALIZED AND CUSTOM MADE MEDICAL DEVICES

Mariana Madureira, INFARMED, Portugal

25 September 2023

European Commission

Funded by the European Union

OVERVIEW

MEDICAL DEVICES REGULATION (EU) 2017/745 (MDR)

Custom-made device definition, Art. 2(3)

any device specifically made in accordance with a written prescription of any person authorised by national law by virtue of that person's professional qualifications which gives, under that person's responsibility, specific design characteristics, and is intended for the sole use of a particular patient exclusively to meet their individual conditions and needs.

However, mass-produced devices which need to be adapted to meet the specific requirements of any professional user and devices which are mass-produced by means of industrial manufacturing processes in accordance with the written prescriptions of any authorised person shall not be considered to be custom-made devices;

MEDICAL DEVICES REGULATION (EU) 2017/745 (MDR)

Custom-made device specific requirements:

- Manufacturers obligations / documentation (Annex XIII),
- Person responsible for regulatory compliance
- Conformity assessment procedure (Annex XIII)
- Class III custom-made implantable devices, with the Notified Body involvement, Art. 52(8)

MEDICAL DEVICES REGULATION (EU) 2017/745 (MDR)

In-house devices, Art. 5(5)

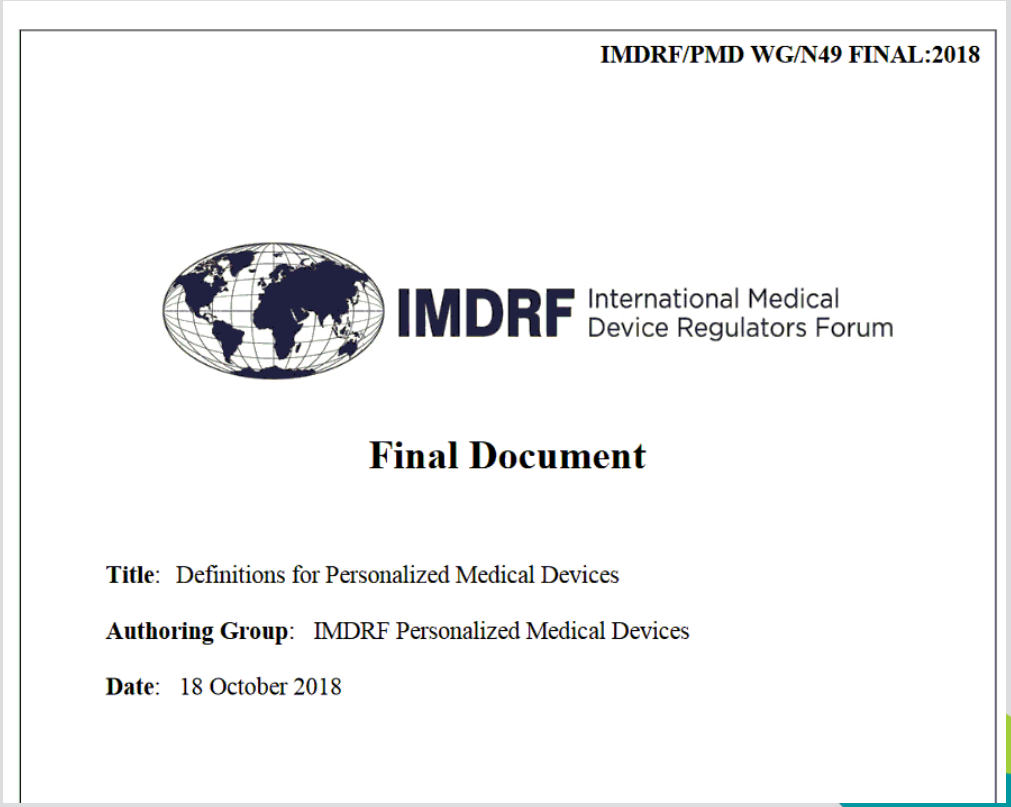
- Devices that are manufactured and used within health institutions
- Manufacture and use of the devices occur under appropriate QMS
- Health institution justification/documentation: that the target patient group's specific needs cannot be met or cannot be met at the appropriate level of performance by an equivalent device available on the market,
- (…)

Health institutions may be required to submit to the competent authority any further relevant information about MD

Not applicable to devices that are manufactured on an industrial scale

DEFINITIONS FOR PMD N49

- Personalised Medical Device (PMD)
- custom-made medical device
  - specific design characteristics
    - DICOM files
- patient-matched medical device
  - specified design envelope
  - batch
- adaptable medical device
  - mass-produced medical device
    - homogenous batch



IMDRF/PMD WG/N49 FINAL:2018

IMDRF International Medical Device Regulators Forum

Final Document

Title: Definitions for Personalized Medical Devices

Authoring Group: IMDRF Personalized Medical Devices

Date: 18 October 2018

PMD – REGULATORY PATHWAY, N58

- Qualification of PMD - Decision Tree
- General requirements: Custom-made MD, Adaptable MD and Patient-matched MD:
  - To demonstrate safety and performance, manufacturer must identify the maximum performance limits and limiting configurations in terms of both parameters and manufacturing variables (e.g. related to device geometry, material properties). To ensure that any medical devices produced within the specified design envelope comply with the relevant Essential Principles.

risk-analysis proces

process validation and/or verification

PMD – REGULATORY PATHWAY, N58

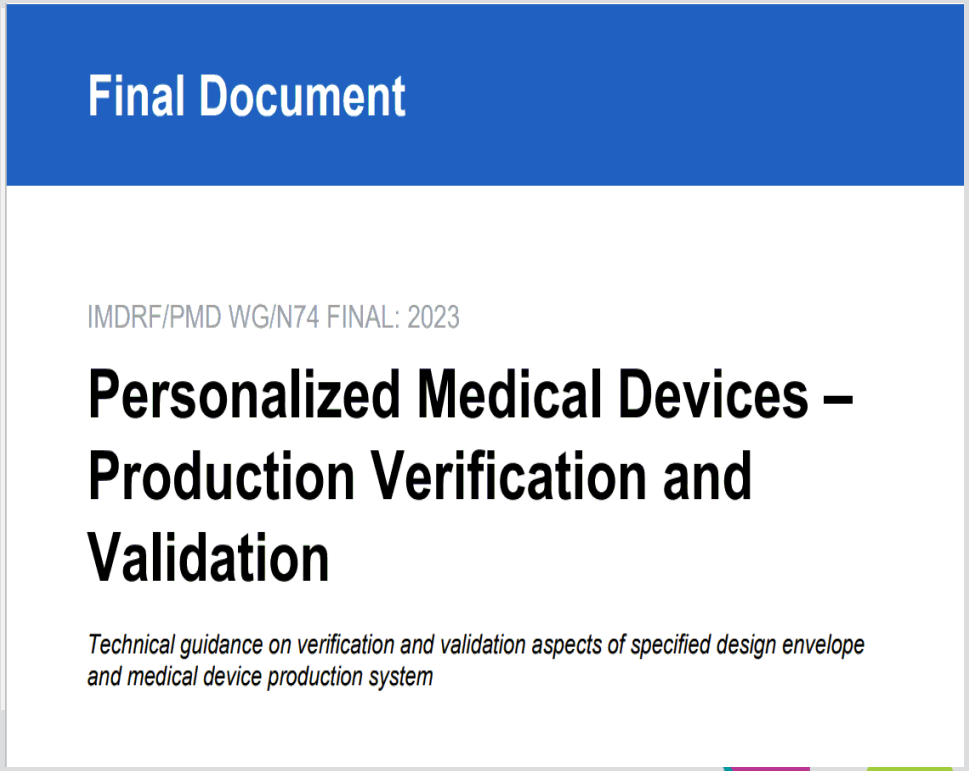
Some considerations for:

- Medical devices produced using Medical Device Production Systems (MDPS) – New concept with broad application
- Materials used in/as medical devices
  - raw materials used for manufacture/materials (MD).
- Considerations for point-of-care manufacture of medical devices (e.g. using MDPS)

PMD – PRODUCTION VERIFICATION AND VALIDATION, N74

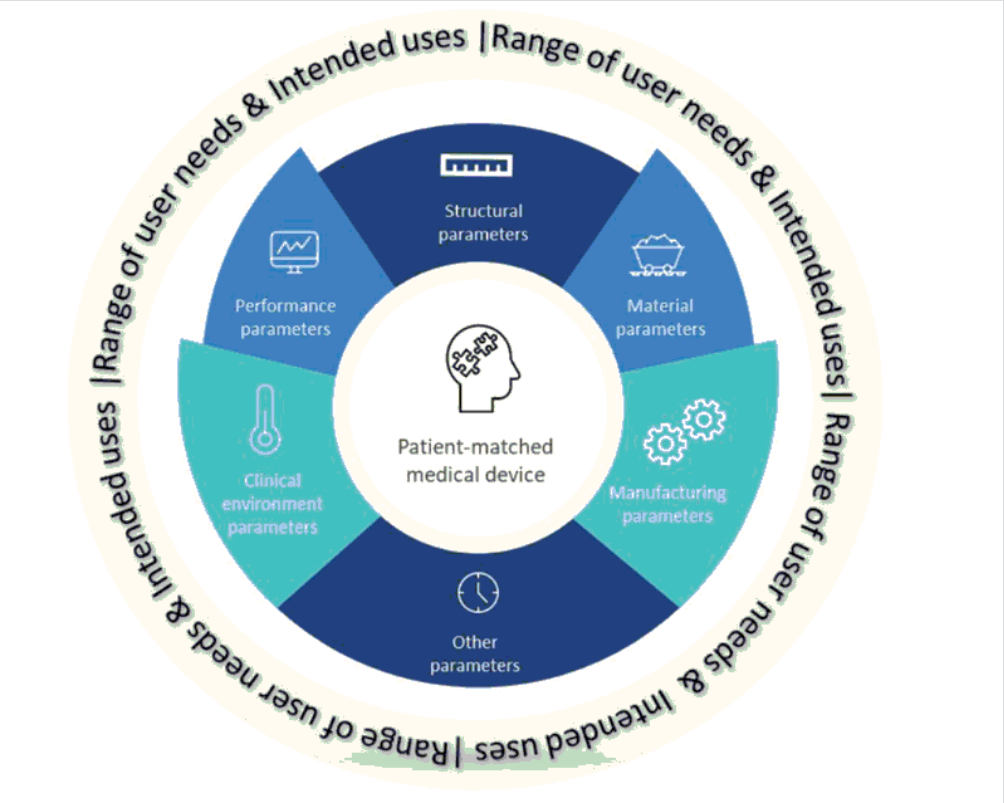
Verification and validation aspects of specified design envelope:

- The manufacturer have to:
  - establish the boundaries for each of the parameters that characterize the specified design envelope
  - demonstrate that devices produced within the bounds of validated parameters of a specified design envelope meets the user needs and the intended uses, and comply with the Essential Principles.



PMD – PRODUCTION VERIFICATION AND VALIDATION, N74

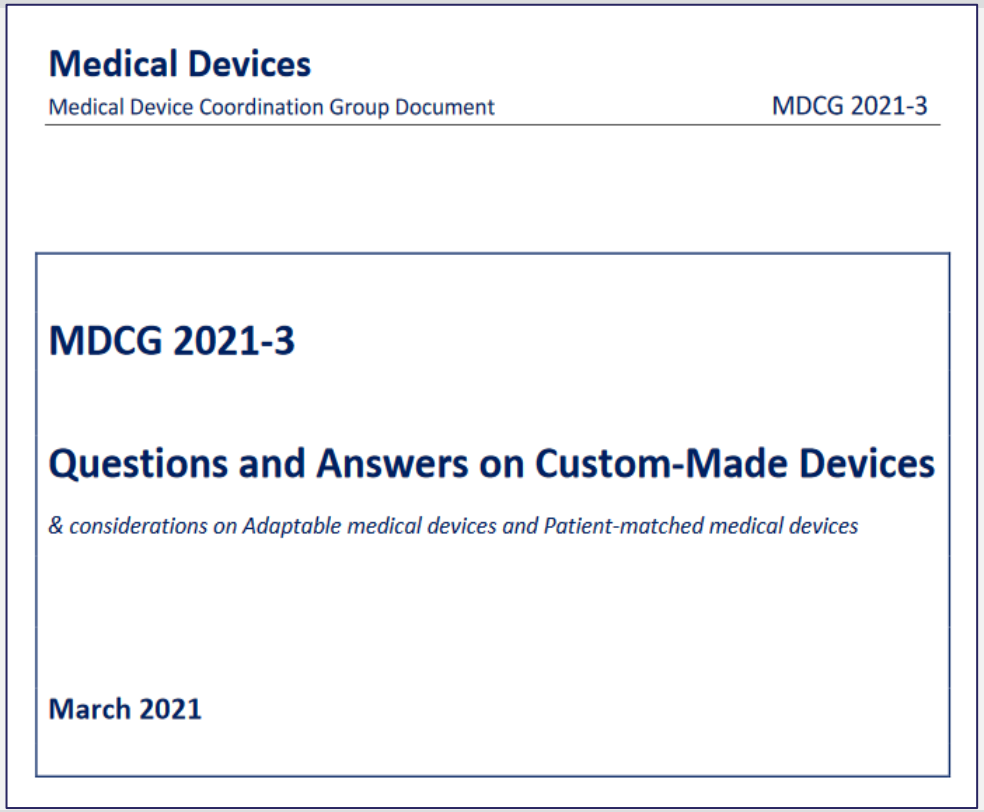
- A specified design envelope can be conceived of as a set of all relevant parameters that characterize a patient-matched medical device for production purposes



PMD – PRODUCTION VERIFICATION AND VALIDATION, N74

- Design verification and validation activities:
  - Risk management activities: the manufacturer should determine the most critical or the worst-case design(s) within the specified design envelop
- Clinical evidence requirements:
  - the clinical evidence should be appropriate to the risk classification, novelty, and parameters (and their reference interval/categories) included in the specified design envelope
  - The investigation of the clinical safety requires an analysis of the worst-case design scenario(s) within the design envelope

QUESTIONS AND ANSWERS ON CMD, MDCG 2021-3



Medical Devices

Medical Device Coordination Group Document MDCG 2021-3

MDCG 2021-3

Questions and Answers on Custom-Made Devices

& considerations on Adaptable medical devices and Patient-matched medical devices

March 2021

Medical Devices

Medical Device Coordination Group Document MDCG 2021-3

Introduction

This Q&A is a high-level document aimed at addressing the most pertinent questions relating to custom-made devices falling under Regulation (EU) 2017/745 on medical devices (MDR). Further guidance on this subject may be elaborated by the MDCG, as appropriate.

In accordance with Recital 5 of the MDR, certain references to International Medical Device Regulatory Forum (IMDRF) guidance documents and terminology included therein have been taken into account under this Q&A. Specifically, the MDR regulatory status of adaptable medical devices and patient-matched medical devices (introduced by IMDRF PMD WG/N49 FINAL: 2018) is clarified in this Q&A.

https://health.ec.europa.eu/system/files/2021-03/mdcg_2021-3_en_0.pdf

QUESTIONS & ANSWERS ON CMD, MDCG 2021-3

- The definition of CMD clarified:
  - Notes defining adaptable MD and patient-matched MD
  - Examples
- The placing on the market of parts, components or materials for PMD, as MD
- Specific considerations/ requirements to be taken into account by those manufacturers

- Qualification of 3D printed device (additive manufacturing)
- Written prescription containing patient specific design characteristics – aspects to consider
- Obligations of CMD manufacturers/ other MD manufacturers
- Implications for manufacturer using CE-marked devices for the purpose of manufacturing a CMD

GUIDANCE ON THE HEALTH INSTITUTION, MDCG 2023-1

- Guidance on terms used in article 5(5) of the MDR/IVDR -> “Industrial scale”
- How to understand the terms ‘manufactured and used’
- Compliance with the relevant general safety and performance requirements
- Legal entity
- Justification that the target patient group’s specific needs cannot be met or cannot be met at the appropriate level of performance, by an equivalent device available on the market

Reference to IMDRF/PMD /N49 -> definition “mass-produced”

Medical Devices

Medical Device Coordination Group Document MDCG 2023-1

MDCG 2023-1

Guidance on the health institution exemption under Article 5(5) of Regulation (EU) 2017/745 and Regulation (EU) 2017/746

January 2023

Other opportunities

- Medical Device Production Systems (MDPS) - new concept at the EU level
- Aspects introduced by IMDRF PMD WG/N74 for verification and validation of the specified design envelope (patient-matched medical device), can be considered for discussion on:
  - clinical evidence for custom-made devices/patient matched medical device

THANK YOU / QUESTIONS

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3D-Printed Personalized Medical Devices

Jan Demol, Materialise

25 September 2023

European Commission

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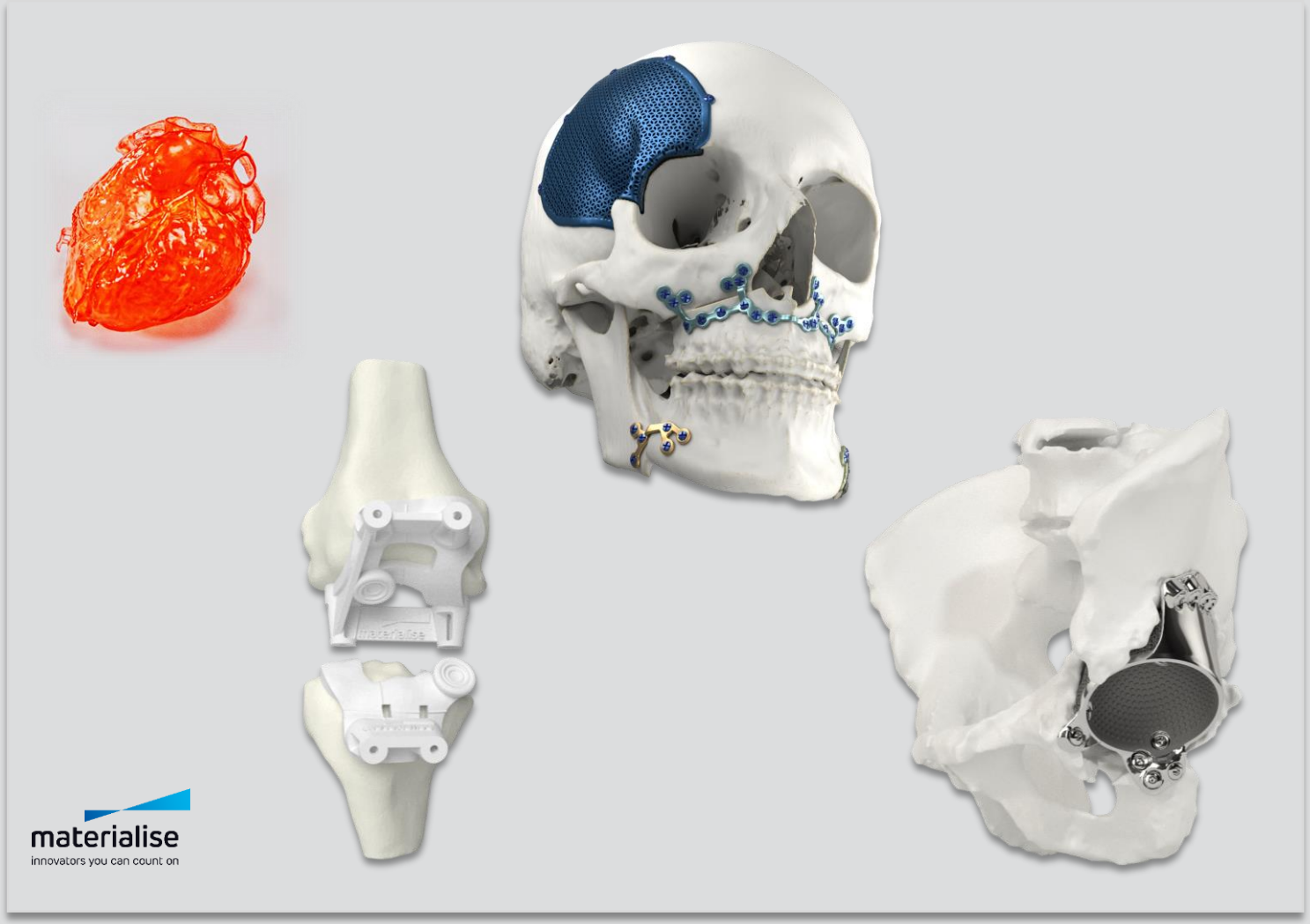
OVERVIEW

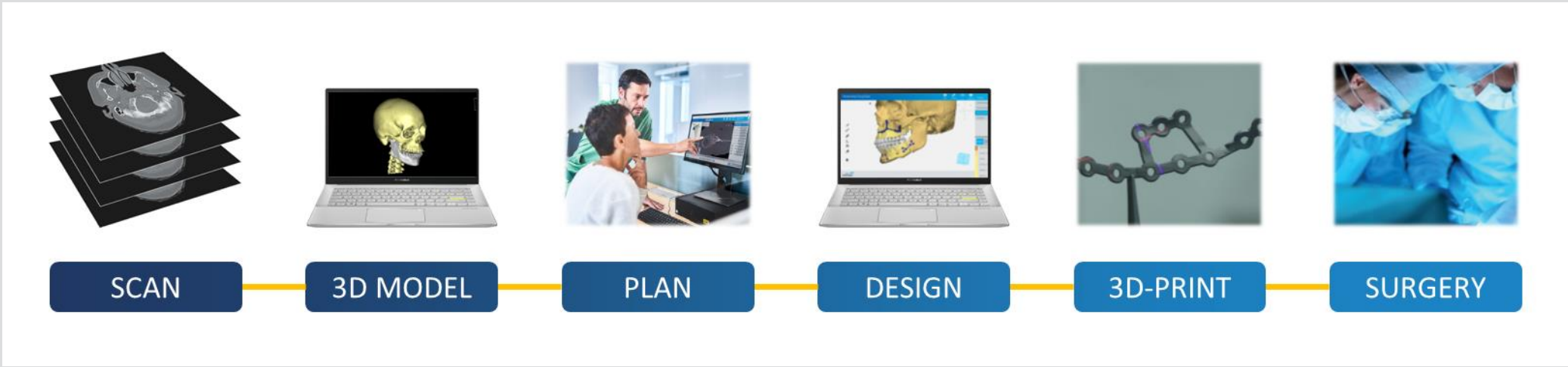
3D-printed personalized solutions



- Matched to patient's anatomy
- Complex geometry
- One-off manufacturing
- Wide range of applications
  - Anatomical models
  - Surgical instruments
  - Implants

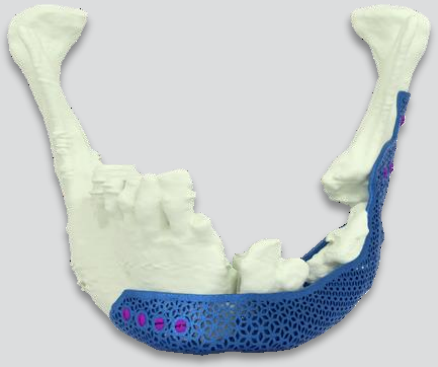
3D-planning and printing

From medical image to personalized medical device



Question 1

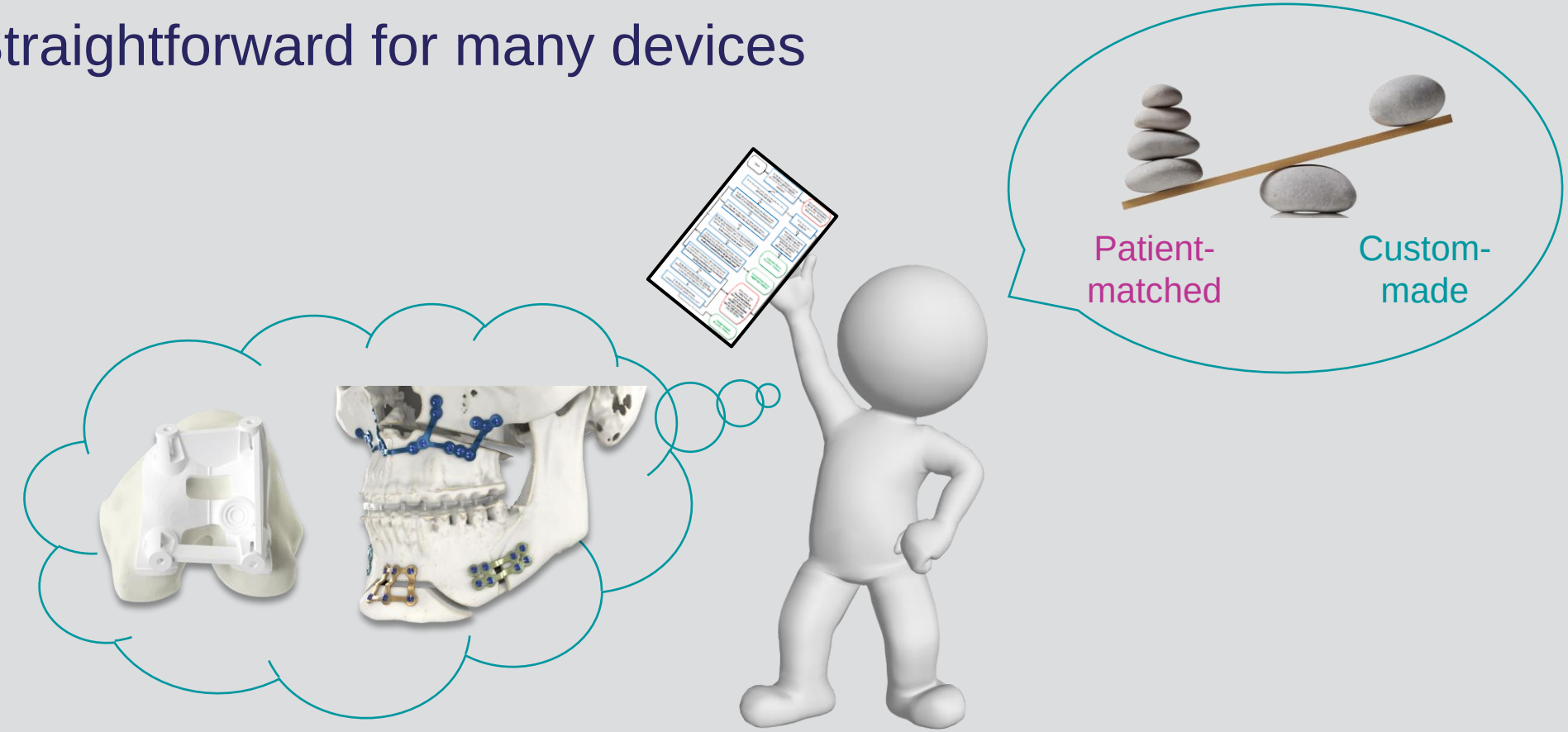
"Why do you define the device as a patient-matched device and not as custom-made?"



Define category

Definitions for personalized devices (IMDRF/PMD WG/N49 FINAL:2018)

↳ Straightforward for many devices



Define category

Definitions for personalized devices (IMDRF/PMD WG/N49 FINAL:2018)

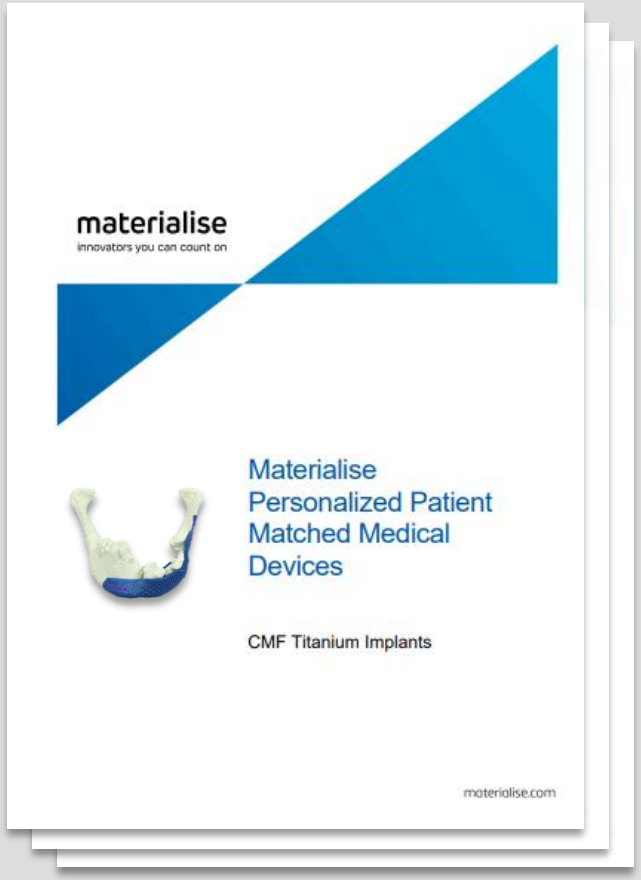
↳ Still ambiguous for many others…

Define category

Personalized device category decision document

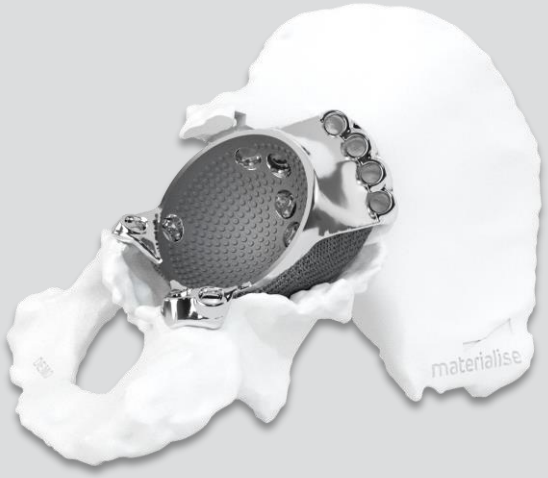
- Patient-matched
- Adaptable
- Custom-made

Cfr. classification statement

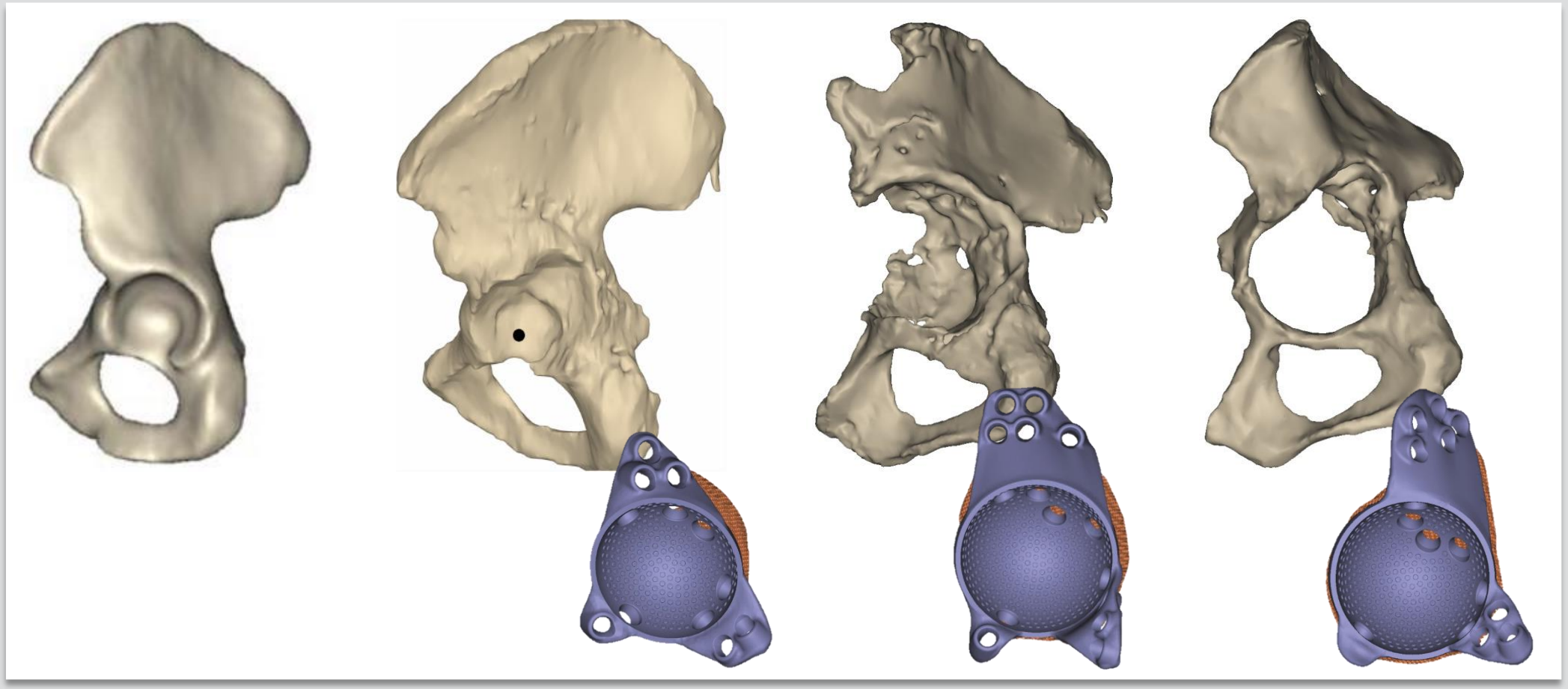


Question 2

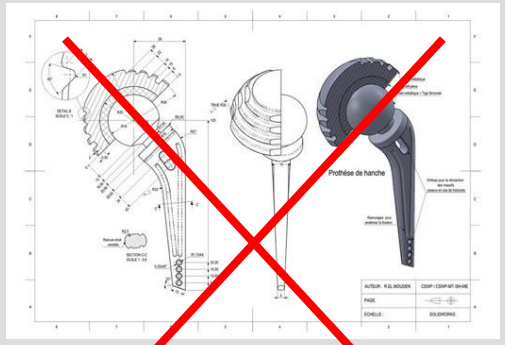
"Where is the technical drawing of your device?"



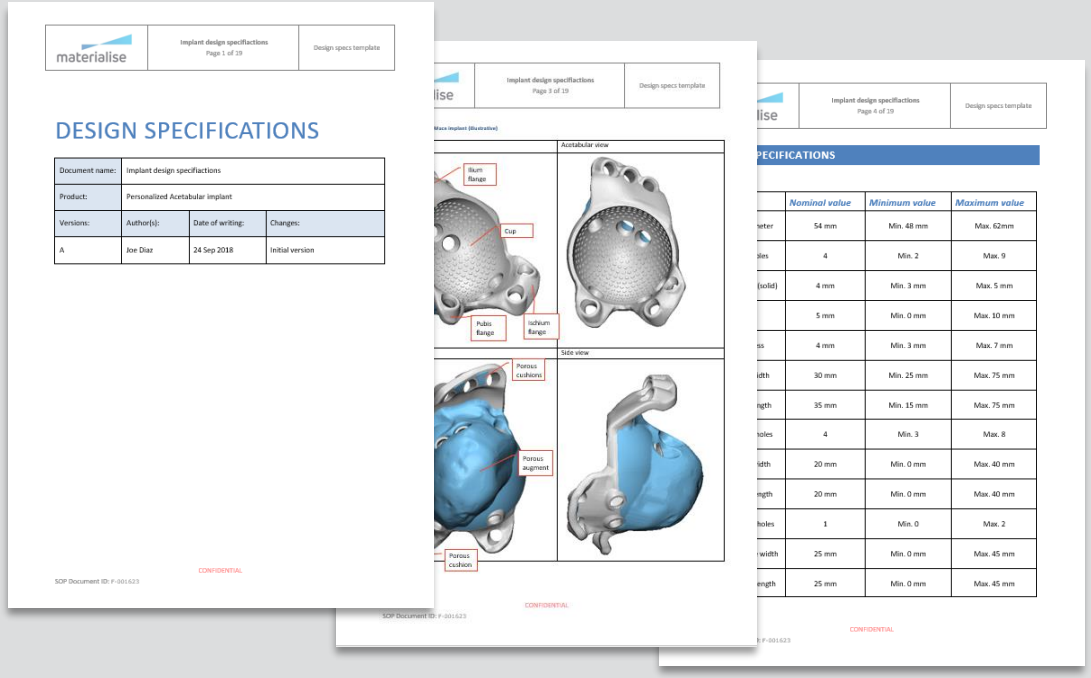
Patient variation

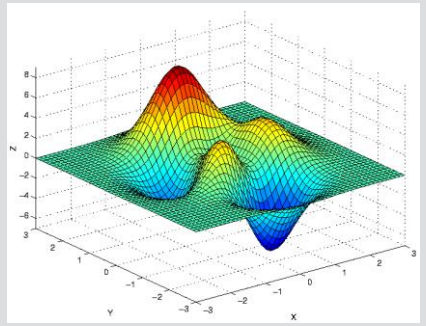


Design parameters



Size 42, 46, 50…



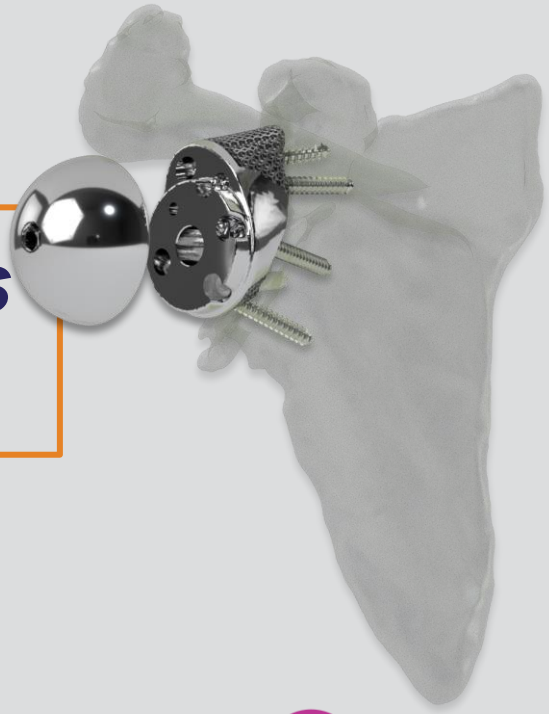


Implant design

- Specific to needs of one patient
- Within design envelope for patient-matched devices
- Including design characteristics for custom-made devices

Question 3

"Provide additional clinical evidence for this indication & patient-population?"



Clinical evidence

- Essential aspect of design validation
- Challenging for many personalized medical devices
  - Niche applications
  - New manufacturing technologies
  - Limited comparable devices
- Potential to assess benefit-risk profile through
  - Single-arm clinical investigation
  - Comparison with standard of care or natural clinical course
  - Post-market clinical follow-up

IMDRF/PMD WG/N74 FINAL: 2023

Final considerations

- Clear guidance & definitions
- Safeguard safety and effectiveness
- Harmonized regulations
- Common understanding
- Predictable regulatory path
- Patient need ~ Regulatory burden

THANK YOU / QUESTIONS

Jan Demol

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Medical Device Production Systems

Dr. Matthias Neumann European Commission DG HERA

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OVERVIEW

Introduction

What is a MDPS ?

IMDRF N74 Regulatory consideration for MDPS

Next steps

Why special considerations for MDPS?

- Point-of-Care (PoC) production of patient-matched/personalized medical devices is becoming important
- Regulatory requirements on medical devices exist, but the regulatory status of machines/equipment used to produce medical devices (in particular at the PoC) is often not clear.
- N74 is offering the possibility that such equipment can be placed on the market as a medical device.

Medical Device Production System (MDPS)

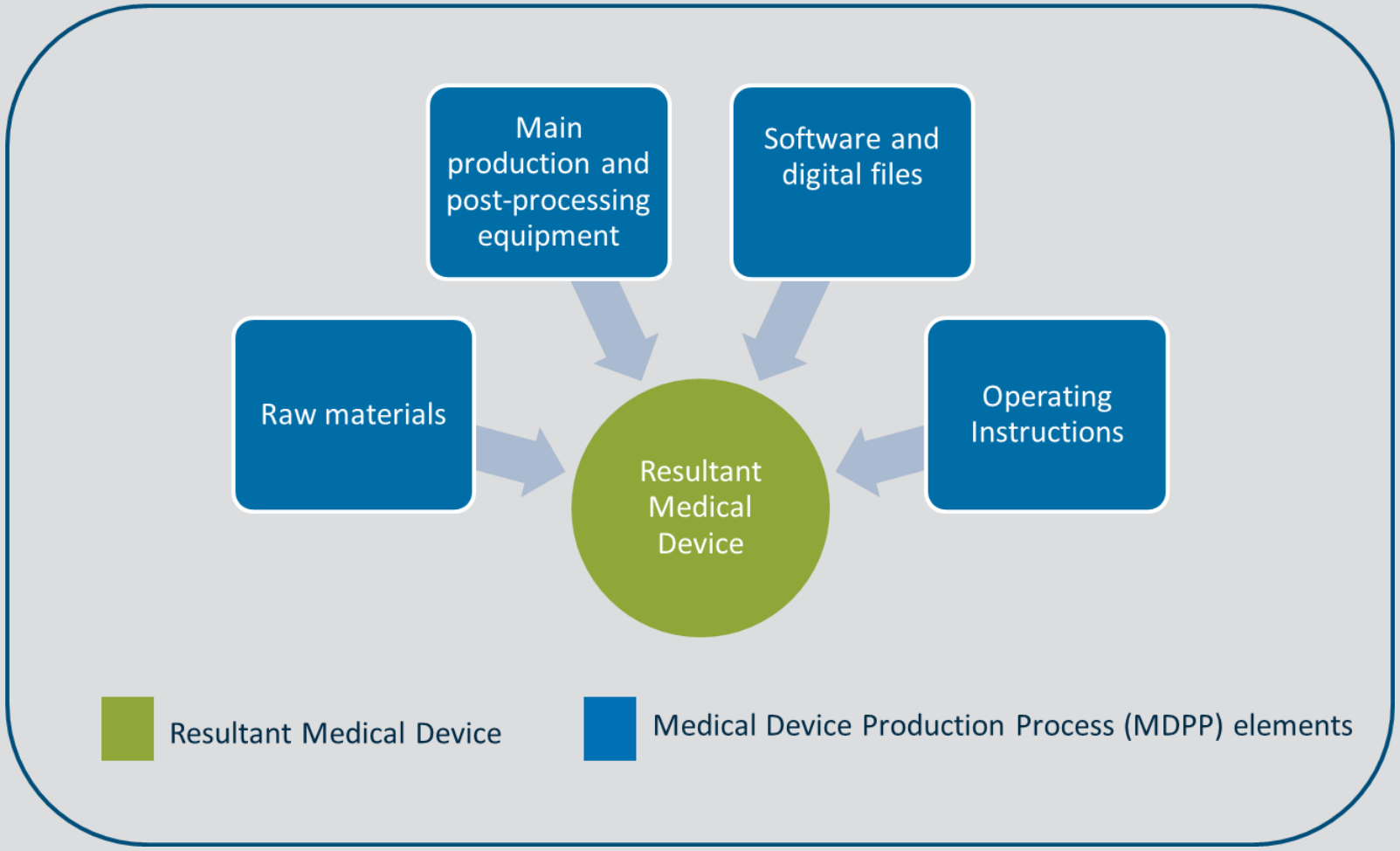
- **is a collection of the raw materials, software* and digital files, and main production and post-processing (if applicable) equipment intended to be used by a healthcare provider, or healthcare facility, to produce a specific type of medical device at the point of care, for treating their patients**
- A MDPS includes the medical device it is intended to produce and the intended use for the device validated in accordance with safety and performance requirements in the relevant regulatory jurisdiction.
- The MDPS may require the use of ancillary equipment, human factors considerations, technical capability requirements, or other specified input and design limit controls;

*Software used as part of production rather than software that meets the definition of a medical device in its own right.

Key Considerations in MDPS Design Development

1. Resultant Medical Device Design Development
2. Medical Device Production Process Design Development
3. Medical Device Production System Verification
4. Medical Device Production System Validation
5. POC Validation Activities

Medical Device Production System



Next Steps

- MDPS concept (and also the design envelope concept) is very innovative but untested
- Before implementing such concepts into national/regional regulations more experiences on the feasibility and pragmatic use necessary
- Industry is invited

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Medical Device Production Systems Applications beyond PMDs

Christophe Carrein, Velsera

25 September 2023

European Commission

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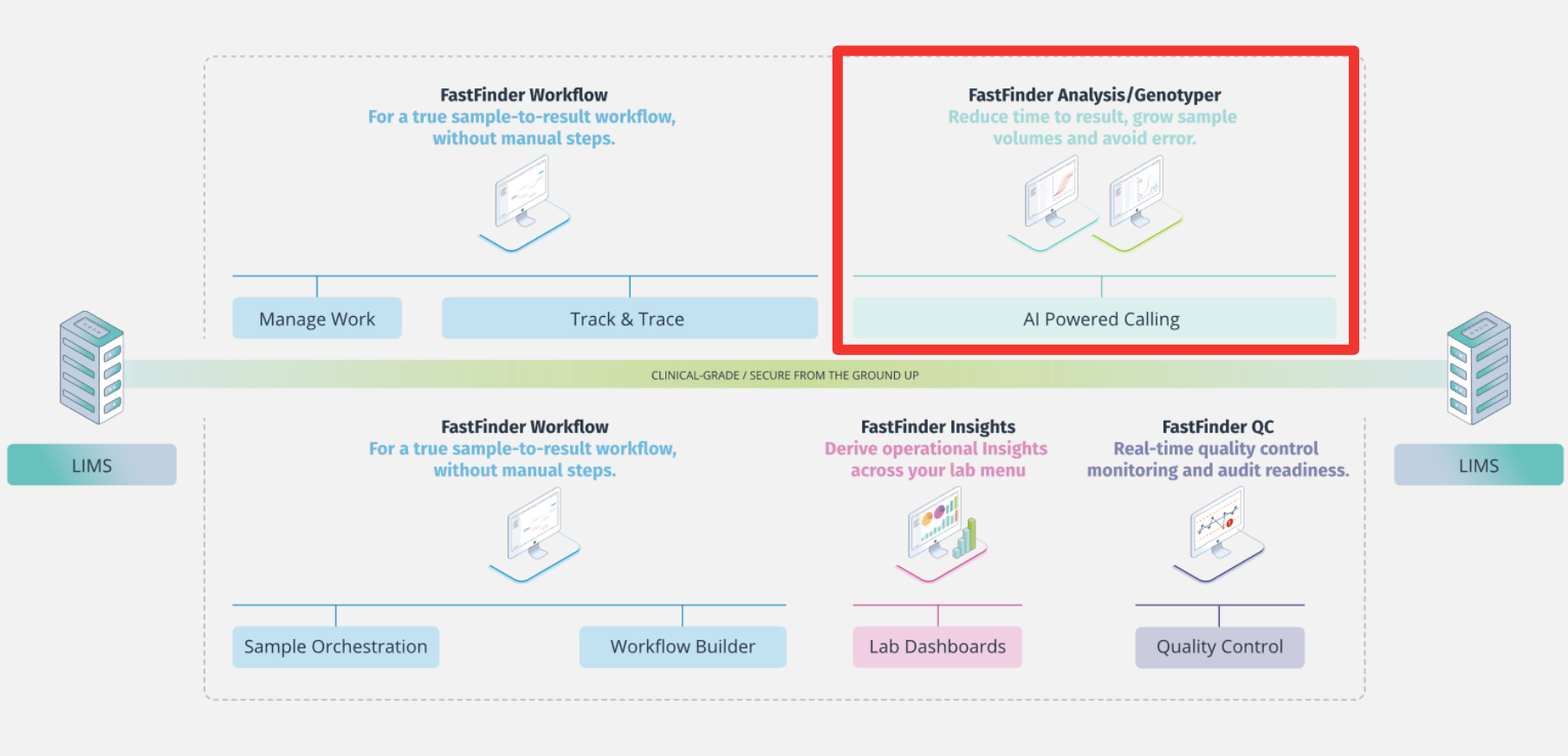
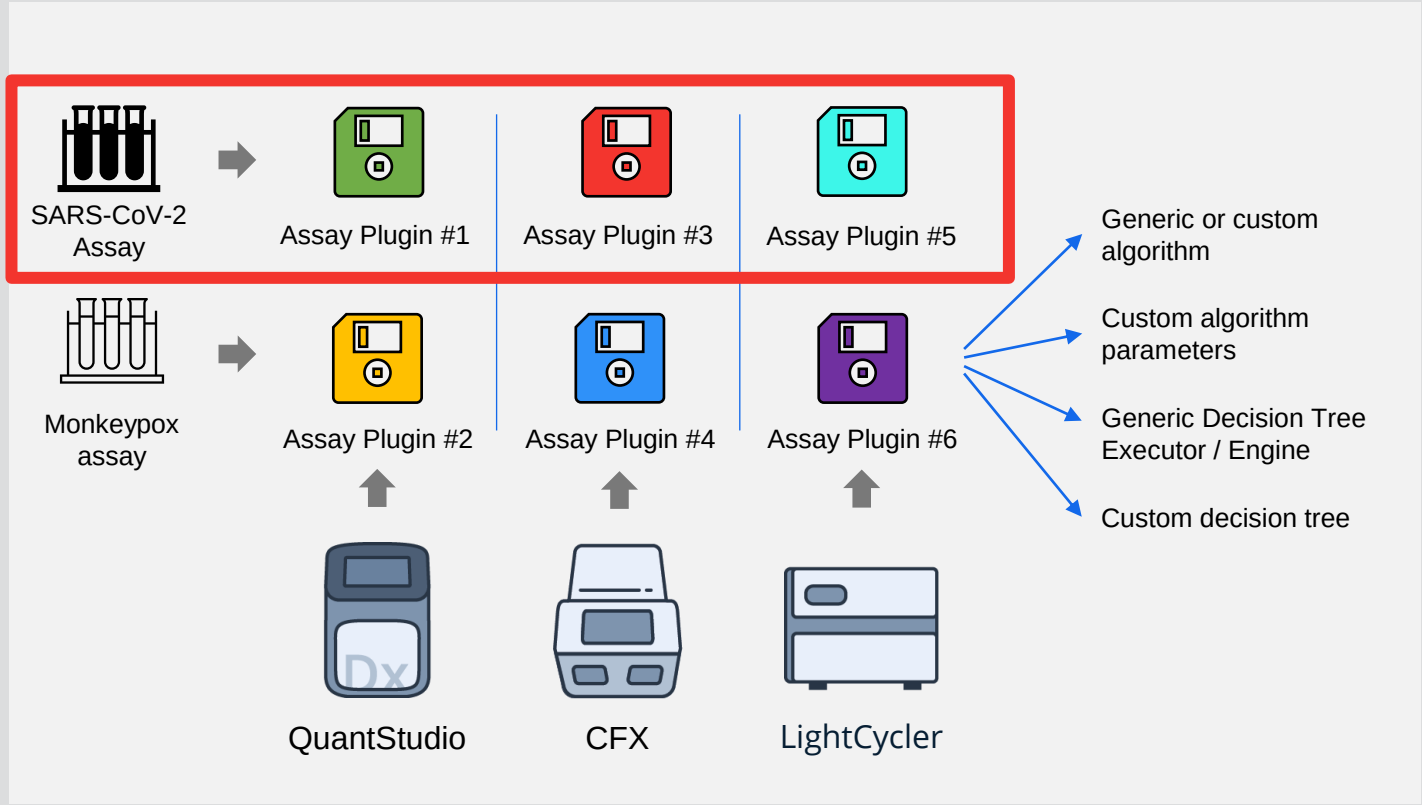
OVERVIEW

Use case
Description of the FastFinder Platform



- Lab automation software for PCR
- >250MM wells analyzed
- Supported covid testing programs in BE, NL, UK, FR

Use case
Description of the FastFinder Assay Plugins



- IVD software functions packaged in deployable form
- Separate lifecycle from the underlying platform
- Standardized interface with rest of the platform
- Typically cleared as part of an assay

Use case
Conclusions and key takeaway

Operating environment

- Variability between and within operating environments (labs, lab technicians and instruments);
- Rapidly evolving field (cf. urgent testing requirements for covid and monkeypox);
- Lots of analysis data and related insights available
- Routine use of lab-developed or lab-adapted tests.

Regulatory considerations

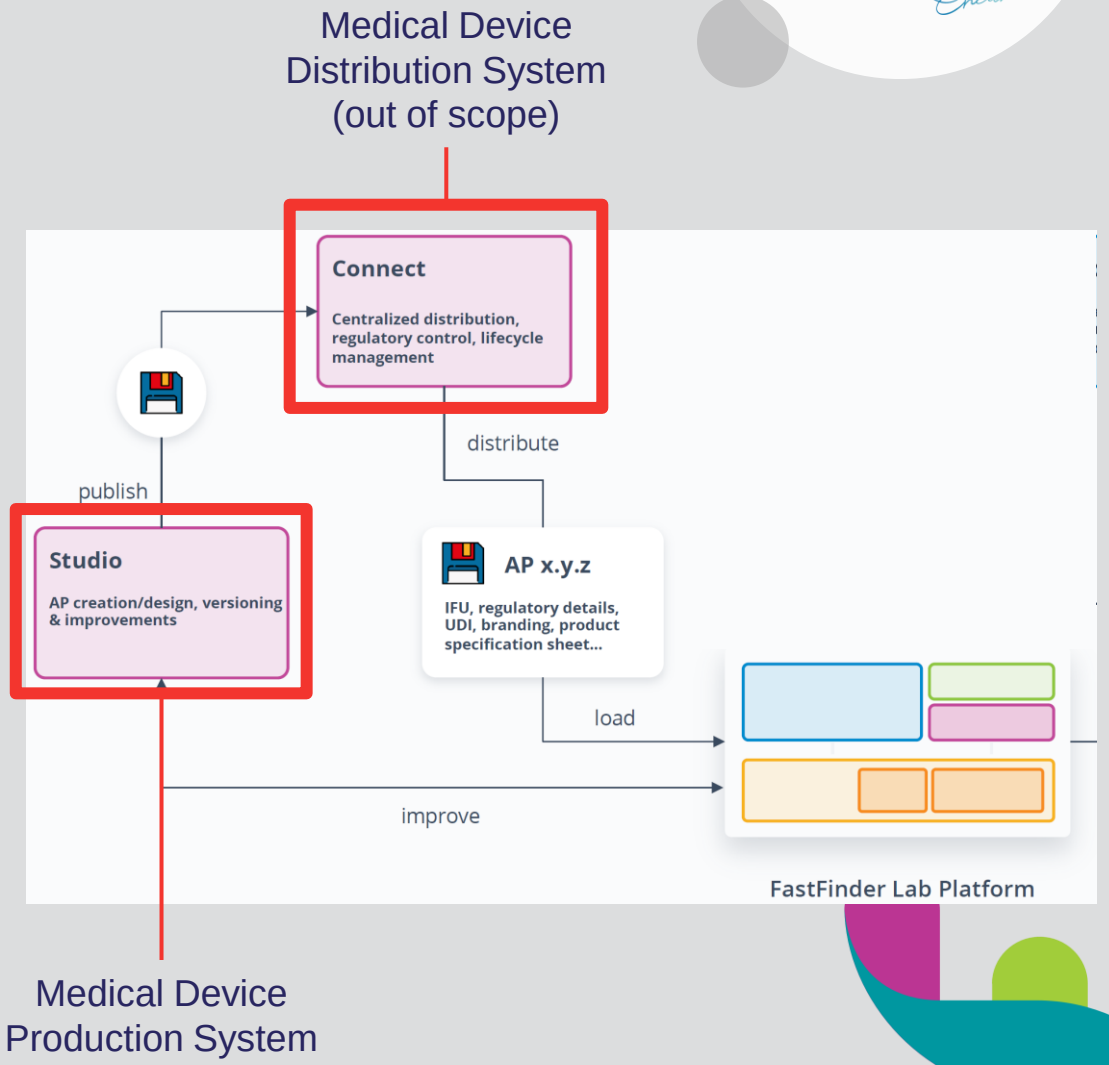
- Fixed design required for conformity assessment;
- New regulations (IVDR art. 5; VALID act) result in decreased appetite for lab-developed or -adapted tests.
- Product changes almost immediately result in changed performance characteristics;
- Highly controlled operating environment (e.g. ISO15189 or CAP/CLIA certifications)

➔ An opportunity for a better device by adapting to the environment within a design envelope

Example of the operating environment (Belgian covid context):
Van Vooren S, Grayson J, Van Ranst M, Dequeker E, Laenen L, Janssen R, Gillet L, Bureau F, Coppieters W, Devos N, et al. **Reliable and Scalable SARS-CoV-2 qPCR Testing at a High Sample Throughput: Lessons Learned from the Belgian Initiative.** *Life*. 2022; 12(2):159. https://doi.org/10.3390/life12020159

Application of MDPS concepts

- A *medical device production system (MDPS)*[1] is a collection of […] software and digital files, and main production […] equipment intended to be used by a healthcare provider, or healthcare facility, to produce a specific type of medical device at the point of care, for treating their patients.
- The design envelope may include generic components (e.g. AI) that can be considered as *Materials that are medical devices*[2]
- The assurance that the final assembled medical device will perform as intended comes from the validated (and optionally enforced) instructions provided by the manufacturer.



[1] IMDRF/PMD WG/NSSFINAL:2020
[2] GHTF/SC/N4:2012

Proposal for extension of scope

- Expand the scope of MDPS beyond production or adaptation for *individual patients*
  - ➥ Significant design variability exists due to factors other than patient anatomo-physiologic features.
  - ➥ Possible regulatory pathway for Foundation Models (AI) and SaMD / MDSW Analysis Toolboxes
- Inclusion of In-Vitro Diagnostics
  - ➥ reduce the need for lab-developed or lab-adapted test pathways

[1] IMDRF/PMD WG/NSSFINAL:2020
[2] GHTF/SC/N4:2012

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