UNIVERSITÄTS
KLINIKUM
HEIDELBERG

Medical Device Regulation

Probleme – Perspektive

Prof. Dr. Matthias Gorenflo - Heidelberg

09 Nov 2023





UK HD

DISCLOSURE STATEMENT OF FINANCIAL INTEREST

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below

AFFILIATION/FINANCIAL RELATIONSHIP	COMPANY
• Grant/Research Support	• None
• Consulting Fees/Honoraria	• Janssen (PAH - medication)
• Major Stock Shareholder/Equity	• None
• Royalty Income	• None
• Ownership/Founder	• None
• Intellectual Property Rights	• None
• Other Financial Benefit	• None

Statement Mrs Stella KYRIAKIDES, Member of the Commission – 24.11.2022 im EU-Parlament Straßbourg:

26.10.22 Virt. Meeting Brüssel:
-AEPC (M. Gewillig)
- DGPK (M. Gorenflo)

The issues raised in the oral question include the specific situation of so—called orphan devices for small patient groups, which are part of that ongoing assessment. In the meantime, I am pleased to announce and share with Parliament today that the Medical Device Coordination Group has already set up a task force on orphan devices, and has held a workshop with clinicians and industry and other stakeholders.

So what are the concrete next steps for this file? In December, at the occasion of the Health Council, I will be providing the clear proposed solutions to all EU health ministers. My objective is to address both the very short-term issues, but also the structural issues that have appeared. My other objective is the intention to keep this Parliament fully involved in this process. Your support in averting shortages of medical devices is crucial, and I look forward to hearing your views today.

Was genau jetzt???

KRYPTISCH !!!

Auf den Gängen hört man:
- Sonderzulassungen erleichtern??

Orphan Devices - Definition

FDA:

"Designate medical devices that intend to benefit patients in treating or diagnosing a disease or condition that affects **fewer than 8,000 individuals in the U.S. per year**."

Quelle:
https://www.fda.gov/about-fda/office-clinical-policy-and-programs/office-orphan-products-development
- bezogen auf ca 332 Mio Einwohner in USA = 0,000024 (8000 / 332 000 000)

EU:

"Orphan Device" means a medical device specifically intended to benefit patients in the treatment or diagnosis of a disease or condition that has an annual incidence * of **not more than 1:37000 per year in the EU" = 0,000027**

*to be calculated on the basis of an EU population of 447 Mio

Orphan Devices - Schön, wenn man sie hat !! - EU versus USA

Table 3 Regulatory incentives and requirements to support orphan products

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

Quelle: Melvin T et al: Pediatric Cardiology https://doi.org/10.1007/s00246-022-03029-1

Orphan Devices - Zulassung kostet Geld !! - EU versus USA

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

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

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

Quelle: Melvin T et al: Pediatric Cardiology https://doi.org/10.1007/s00246-022-03029-1

Orphan Devices - Motivation diese Produkte in der EU zu entwickeln?

- **“Market Exclusivity“ – EC 141/2000**
- **Gebühren-Reduktion/-Verzicht im Rahmen der Registrierung**

https://health.ec.europa.eu/system/files/2020-08/orphan-regulation_study_final-report_en_0.pdf

Orphan Devices - Motivation diese Produkte in der EU zu entwickeln?

- **Gebühren-Reduktion für die Zulassung**

ACHTUNG:

- **Keine Unterstützung für die Entwicklung!**

Procedure or service	Fee reduction applicable to	Percentage fee reduction
Protocol assistance, initial and follow-up requests	SME sponsors for all assistance	100%
	Academia for all assistance	100%
	Sponsors for paediatric-related assistance, other than SME sponsors or academia[1]	100%
	Sponsors for non-paediatric-related assistance, other than SME sponsors or academia	75%
Pre-authorisation inspection	All sponsors	100%
Initial marketing authorisation application	SME sponsors	100%
	Non-SME sponsors	10%
Post-authorisation applications and annual fee, specified in Council Regulation (EC) No 297/95, in the first year from granting of a marketing authorisation	SME sponsors	100%
Pharmacovigilance fees, specified in Regulation (EU) 658/2014	All sponsors	n/a

Quelle: https://www.ema.europa.eu/en/documents/other/decision-executive-director-fee-reductions-designated-orphan-medicinal-products_en.pdf - abgerufen am 1.11.22

Orphan Devices - Gründe diese Produkte NICHT in der EU zu entwickeln?

- **Zeitdauer der Bearbeitung durch EU – Admin: 18 – 24 Monate! versus 30 Tage in USA und 47 Tage Kanada**

  Quelle: Melvin T et al: Pediatric Cardiology https://doi.org/10.1007/s00246-022-03029-1

- **EU fördert Forschung für Seltene Erkrankungen (orphan disease) – nicht spezifisch für orphan *devices*!**

  https://health.ec.europa.eu/system/files/2020-08/orphan-regulation_study_final-report_en_0.pdf
  Abgerufen am 1.11.2022

Also: Hohe Entwicklungskosten – lange Dauer bis Verfügbarkeit auf dem Markt

MDR Probleme - was können wir tun als Anwender?

- **Nicht Jammern – sondern punkten!! - ganz konkrete Daten über Relation MDR-Implementierung und Nicht-Verfügbarkeit**

Ungutes Beispiel:

- **Rashkind Katheter Fa Medtronic – Rückruf und Prod.-Stop – 11.03.20**
- Medtronic Recalls Rashkind Balloon Septostomy Catheters for Quality Issues | FDA

Nicht als Argument zu verwenden, dass MDR hieran ursächlich Firmenpolitik ??

WAS NICHT ZU BEWEISEN IST - WIRD POLITISCH GEGEN EINEN VERWENDET:

Patientensicherheit statt Industrieinteresse bei Hochrisiko-Medizinprodukten - GKV-Spitzenverband

URGENT MEDICAL DEVICE RECALL

Rashkind Balloon Septostomy Catheters

Product Number – Name	Product Description	Lot Identification
007160	5F Rashkind Balloon Catheter Single Lumen	Refer to Table 1
007161	4F Rashkind Balloon Catheter Single Lumen	
008764	6F Rashkind Recessed Balloon Catheter	

September 2020

Dear Risk Managers or Healthcare Professional

In August 2020, Medtronic initiated a Urgent Medical Device Recall for a subset of Rashkind Balloon Septostomy Catheters (Product 008764 lots GFDY1136 and GFDV2179) to associated accounts. After completing the risk assessment, it has been determined that the scope of this recall be expanded to include all model and lot numbers listed in Table 1.

Through August 31, 2020, Medtronic has received nine (9) complaints involving balloon integrity and subsequent failure that involved one patient death and one patient material embolization. Material rupture / balloon failure during procedure can result in material embolization, balloon leak, balloon burst, inversion or stretching resulting in balloon failure, or surgical intervention. As a result of these complaints and the potential for serious injury, Medtronic is initiating a product recall of Rashkind Balloon Catheters lots per Table 1.

Customer Instructions:

Medtronic records indicate that your facility has received one or more of the affected Rashkind Balloons Catheters. As a result, Medtronic requests that you immediately take the following actions:

- Identify and quarantine all unused Rashkind Balloon Catheters as listed in the table below
- Return all unused affected product in your inventory to Medtronic. Contact Medtronic Customer Service at 1-888-283-7868 to initiate a product return. Your local Medtronic Representative can assist you in the return of this product.
- Please complete the enclosed Customer Confirmation Form and email to RS.CFQFCA@medtronic.com.
- Please forward this notice to all those who need to be aware within your organization.

There are no actions required for patients where the Rashkind Balloon Catheter was used during a procedure. These patients should continue to be monitored in accordance with your medical facility's standard care protocols.

Medtronic will notify all applicable regulatory agencies about this matter.

We regret any inconvenience this may cause. We are committed to patient safety and appreciate your prompt attention to this matter. If you have any questions regarding this communication, please contact your Medtronic Field Representative.

Sincerely,

Eliezer De Jesus Hernandez
Vice President, Quality
Medtronic Coronary and Structural Heart

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Denn: In Brüssel und Berlin glaubt man immer noch, dass es gar kein Problem mit der MDR gibt!

Dr. Neumann BMG 26.10.22 und 9.11.22:
„There is a Dutch Study demonstrating that there is no problem with devices for children…..“ NB: Unbekannte Studie (Nico Blom)

MDR Probleme - was können wir tun als Anwender?

- **Nicht Jammern – sondern punkten!! - ganz konkrete Daten über Relation MDR-Implementierung und Nicht-Verfügbarkeit**

Gutes Beispiel:

- **Offenlegen der Probleme seitens Fa. Pfm und AndraTec (20.11.22)**

Dear Marc,
sorry for the delayed response.

- *What devices have you already withdrawn ?*
  Probably the Exeter Snare, depending on the NB, May be the Optimus Stent bare and Covered, Depending on the NB may be all Balloons (AltoSa-XL, AltoSa-XL-Gemini, AltoSa-SFT, AltoSa-HP

- *Which devices under MDD will not be applied MDR ?*
  AltoSa T18, AltoSa-SEP (Septostomy Catheter), Pillow-Occluder, Pillar-Bifurcation stent

- *How did it affect your research ?*
  At the moment all new Projects are on hold no new development is planned, US market will be eventually targeted, EU market not targeted.

- *What costs are involved*
  - *Notified body invoices*
    Changes towards costs of over 100.000,- Euro / and nothing is guaranteed in contrary the NBs are extremely strict, they speak to lawyers themself and get told that they have to be strict in order to comply with the MDR and their local government officials!
  - *Direct costs for your company*
    Increase of regulatory cost with external consultants to more than 150.000,- Euro
  - *Indirect costs*

MDR Probleme - Lösungsansätze -Schlußfolgerungen

- **Konkrete Beispiele mit zitierfähigem autorisiertem Text seitens Med.-Produkte Hersteller an politische Vertreter!!**
- **MDR wird – leider – bleiben und bestenfalls verschlimmbessert ab März 2023**
- **Weg über Sonderzulassungen in Kooperation mit Med.-Produkte-Hersteller suchen!!!**

Konkret: BVMed will Hersteller und Anwender zusammenbringen

Daher:

- **Eine Auflistung aller Produkte die für uns wichtig sind ist weiter absolut notwendig**
- **Ob diese spezifisch “Orphan Device“ Charakter haben oder im “Off-lable Use“ eingesetzt werden ist weniger bedeutend**
- **Dies gilt – als Zielsetzung - definitiv auch für Bestandsprodukte!!**

Denn: Ziel muss es sein für die für uns relevanten Produkte den Weg der Sonderzulassung zu gehen!!

DANKE !

NQS – German Quality Assurance of Congenital Heart Disease

- **Sustained by the „Deutschen Gesellschaft für Thorax-, Herz- und Gefäßchirurgie e. V.“ and „Deutschen Gesellschaft für Pädiatrische Kardiologie“**
- **Financed by fees from participating Centres wich offer congenital cardiac surgical and interventional therapy**
- **Recording: a) acute outcome of procedures and b) long term outcome**
- **Centres contribute voluntarily – CAVE: NO complete evaluation of outcome for all procedures performed in Germany**

Example: Aortic Coarctation (Dittrich S et al. Thorac Cardiovasc Surg 2022; Dec;70(S 03):e21-e33. doi: 10.1055/s-0042-1757175. Epub 2022 Sep 29.

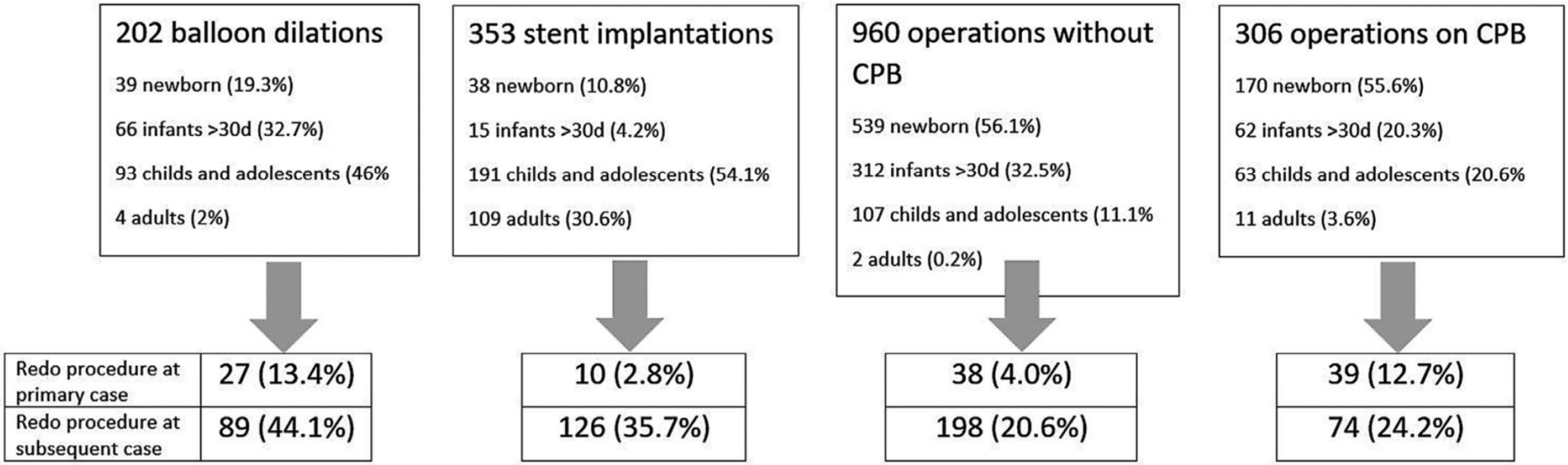
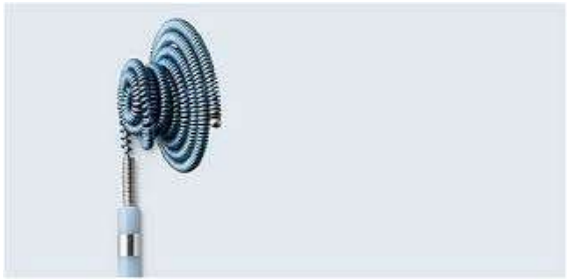


Fig. 8 Nine years' follow-up observation in patients with native coarctation of the aorta. Subsequent procedures during the primary case occurred in 13.4% after balloon dilations and in 12.7% after cardiopulmonary bypass (CPB) operations. After discharge from primary care, redo cases with follow-up procedures were frequent in all treatment arms but more frequent after primary interventional treatment (44.1% and 35.7%

Issue: MDR – Data for evaluation of medical products/devices

What can NQS (German Quality Assurance of Congenital Heart Disease) contribute?
What can the National Register for Patients with Congenital Heart Defects (NRAHF) contribute?

- **NQS data allows for publication of follow-up results**
  Example: Outcome after percutaneous duct occlusion



Important: Your need to know what is important BEFORE you collect data!
Therefore: Focus on relevant topics for data collection: survival etc.

- **Even better: Both NQS and NRAHF – data allow to define study groups for specific clinical studies (eg surveillance studies)**
  (question of financing and stewardship!)

How do other European countries proceed ?

Austria:

RIS

Bundesrecht konsolidiert

Kurztitel

Einrichtung eines Registers zur Qualitätssicherung in der Kinderkardiologie

Kundmachungsorgan

BGBl. II Nr. 434/2008

From:
https://www.ris.bka.gv.at/Dokumente/Bundesnormen/NOR40102834/NOR40102834.pdf