Clinical imperatives for implementing regulatory science for medical devices

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European Medicines Agency
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Some definitions of regulatory science ..

US Food & Drug Administration 2010

The **science of developing new tools, standards, and approaches** to assess the safety, efficacy, quality, and performance of FDA-regulated products.

European Medicines Agency 2016

Basic and applied research that enables co-evolution of science, legislation, guidelines, and policies for benefit/risk assessment in medical product-regulatory decision-making throughout the development and life-cycle management of medical products.

Origins of regulations in the European Union

FOOD	1980s	Pulmonary hypertension and deaths from the toxic oil syndrome.	2002	Regulation (EC) 178/2002 [..] establishing the European Food Safety Authority and laying down procedures in matters of food safety.
DRUGS	1957 to 1962	Deaths and congenital malformations related to maternal ingestion of thalidomide.	1965	Directive 65/65/EEC on the approximation of provisions laid down by Law, Regulation or Administrative Action relating to proprietary medicinal products.
DEVICES	1970s	Reported malfunction of cardiac pacemakers.	**1990**	**Directive 90/385/EEC on Active Implantable Medical Devices.**
	From 1978	Deaths from fractures of Björk-Shiley convexo-concave heart valves.	**1993**	**Directive 93/42/EEC on Medical Devices.**

Fraser AG et al, European Review 2025: 1–35 / https://doi.org/10.1017/S1062798725000109

1985 European Commission White Paper:

Completing the internal market (giving target of 1992)

Annex: Directive for Electro-medical equipment planned for 1988

1985 Resolution of Council 85/C 136/01:

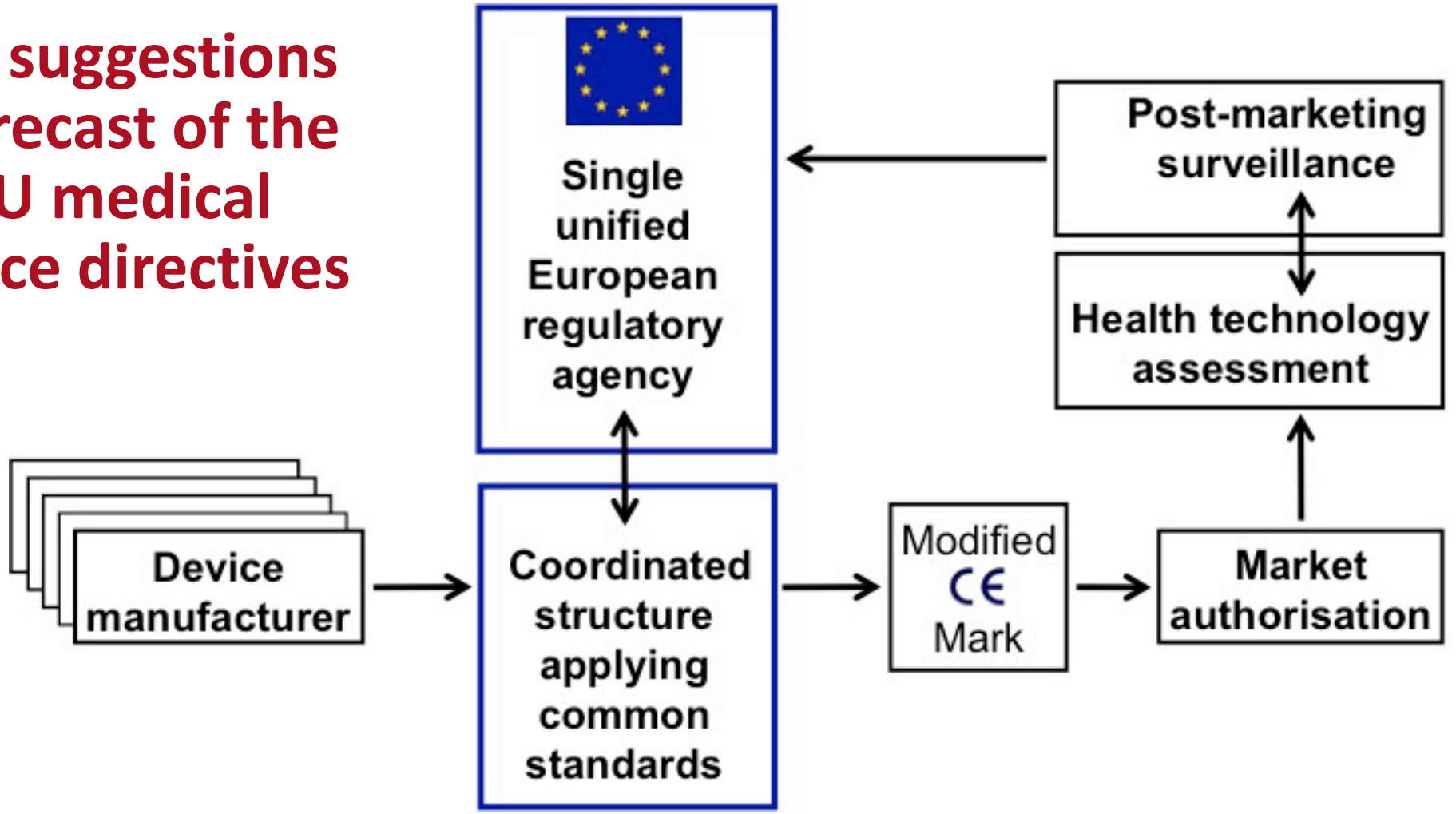
On a New Approach to Technical Harmonization and Standards

"National bodies authorized to issue marks or certificates of conformity shall be notified by each Member State to the Commission and to the other Member States."

1993 Norbert Anselmann, Principal Administrator, European Commission DG III:

"The Medical Device Directives follow the "New Approach", a methodology to be applied to the harmonization of industrial products. The EC legislation is confined to the setting up of ***Essential Requirements*** which are ***drafted in rather abstract terms***. The technical expression of these requirements is ensured by European standards, the application of which is ***at the discretion of manufacturers***."

ESC suggestions for recast of the EU medical device directives



Fraser AG et al,
Eur Heart J. 2011; 32: 1673–86

Policy conference, 28th January 2011
Clinical evaluation of cardiovascular devices

European regulatory capacity and expertise

Communication from the Commission to the Council and the European Parliament on medical devices / COM/2003/0386 final

"scarce human and financial resources at the level of public administration"

Impact assessment on the revision of the regulatory framework for medical devices. European Commission, Brussels, 26.9.2012 / SWD(2012) 273 final

The major costs for the EU budget generated by the preferred policy options are linked to the effective management of the future regulatory framework, and in particular to human resource requirements (35 to 50 FTE depending on the option eventually chosen), to the development and management of the IT infrastructure (e.g. Eudamed, ca. EUR 2mio/year) and to meetings between national experts (ca. EUR 1.4mio/year).

Team NB Annual Sector Survey 2025 / 41 members, FTE for MDR & IVDR

3,358 internal employees for conformity assessment & 741 external contractors

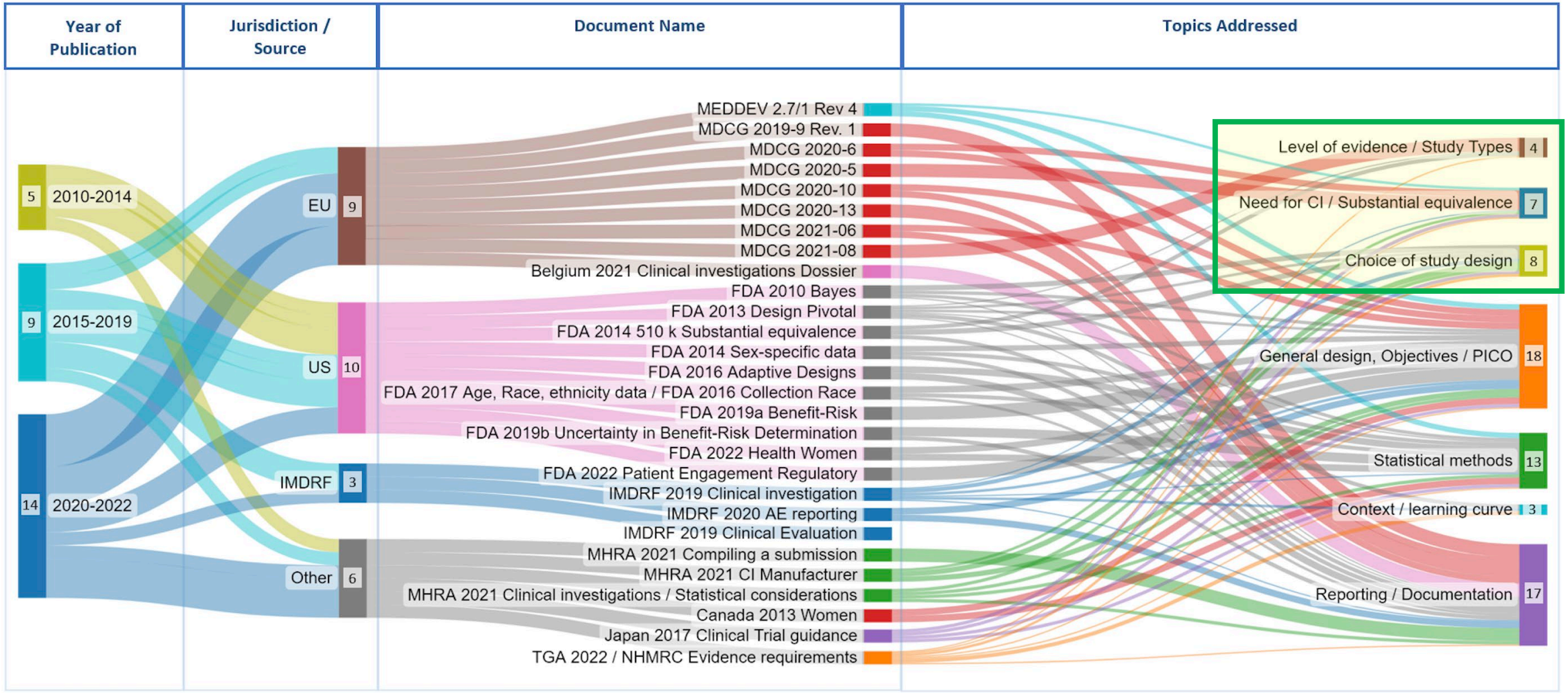
https://www.biomedeurope.org/wp-content/uploads/2025/03/BioMed-Recommendations-MDR-IVDR-2025-1.pdf

Systematic reviews of published clinical investigations of high-risk medical devices – for cardiovascular interventions, orthopaedic surgery, and diabetes care

	Studies N	Subjects – devices N	Median sample size	Follow-up duration	Randomised trials	Published before CE mark date	Nothing published	Proportion females	Analyses by age
Cardiac	308	97,107	100 304	13 m	19%	9%	30%	38%	15%
Orthopaedic	151	1,814,953	139	4.6 y	9%	0%	27%	55%	5%
Diabetes	182	64,310	48	17.5 w	29%	18%	n/a	53%	25%

Siontis GC et al, European Heart Journal 2024; 45: 161–77
Lübbeke A et al, EFORT Open Reviews 2023; 8: 781–91
Bano A et al, Diabetes, Obesity & Metabolism 2024; 26: 4753–66

Recommendations on methodologies for clinical evaluation of high-risk medical devices



CORE-MD

Coordinating Research and Evidence for Medical Devices

Petra Schnell-Inderst et al, UMIT Tirol

www.core-md.eu

EU Horizon 965246

Recommended methodologies for clinical investigations of high-risk medical devices

Grant call → "provide a hierarchy of approaches" for "methods to generate clinical data"

Initial clinical studies	Early clinical studies	Confirmatory clinical studies	Long-term clinical studies
First-in-human and preliminary clinical studies: ***All experience to be publicly reported.*** • Case report(s) of first implants or other first use of a new high-risk device. • Observational studies assessing feasibility, safety, and early adverse events.	***Assessment of performance, safety, and positive benefit–risk ratio:*** ***Preliminary assessment of efficacy.*** ***Analysis of learning curves.*** • Non-randomised clinical study of intervention (e.g. single-arm, enrolling consecutive patients), using patient-relevant outcomes and/or validated surrogate end-points. • Observational study testing against objective performance criteria (OPC). • Cohort with matched controls, assessing differences against another device or current state-of-the-art.	***Further demonstration of safety.*** ***Assessment of efficacy for clinical outcomes:*** • Double-blind RCT, if feasible. • Single-blind RCT against active comparator – powered for 'superiority'. • 'Assessor-blinded' RCT with sham intervention (if no active comparator available, and a placebo effect is suspected). • Single-blinded RCT (as above) – powered for non-inferiority. • Large multicentre observational cohort, using OPC or other validated outcome measures.	***Long-term monitoring of device performance and safety, in comparison against alternatives:*** • 'Large simple' RCT such as a registry-based trial. • RCT in enriched cohorts. • Observational cohort using a registry or other real-world source of data, including all devices of the same type, and with results combined through a federated analysis, using appropriate adjustments to minimise bias.

Fraser AG et al, The Lancet Regional Health Europe. 2025; 58: 101460

CORE–MD Recommendations for stages of clinical evaluation

DRUGS	Phase 1 Safety	Phase 2 Efficacy	Phase 3 Effectiveness	Phase 4 Surveillance
	Initial clinical studies	Early clinical studies	Confirmatory clinical studies	Long-term clinical studies
EU MDR	Exploratory	Confirmatory pivotal investigations		Post-market clinical follow-up
ISO 14155	Pilot	Pivotal		Post-market
FDA	Exploratory	Pivotal		Post-market
IDEAL	Idea (stage 1) Development (2a)	Exploration (Stage 2b)	Assessment (Stage 3)	Long-term study (Stage 4)

CORE-MD
Coordinating Research and Evidence for Medical Devices

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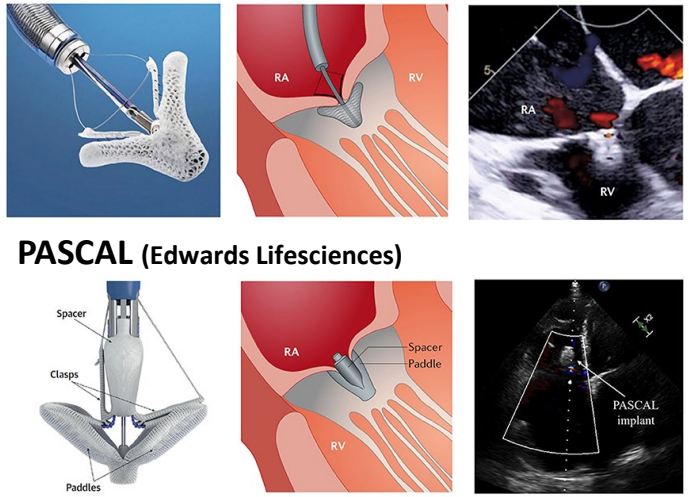
EU Horizon 965246

New percutaneous interventional devices for tricuspid valve regurgitation

Coaptation devices

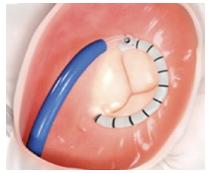
TriClip (Abbott)



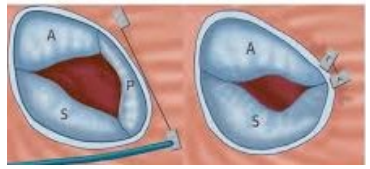
PASCAL (Edwards Lifesciences)

Annuloplasty devices

Cardioband
(Edwards Lifesciences)



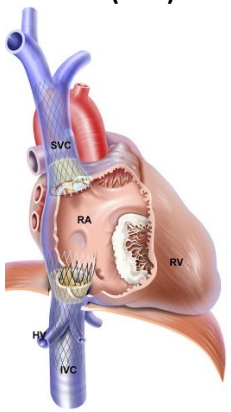
Trialign
(Mitralign)



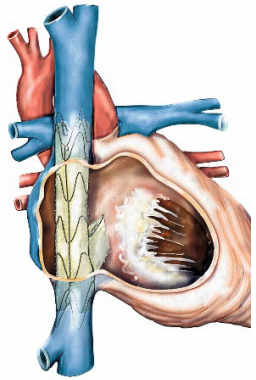
MIA-T
(Micro Interventional Devices)

Caval valve implant devices

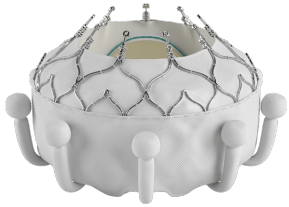
TricValve
(P&F)



Tricento
(Medira AG)

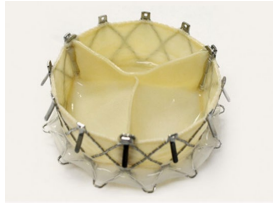


Tricuspid valve implantation



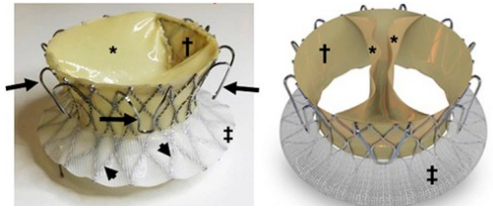
EVOQUE
(Edwards Lifesciences)

Lux-valve Plus
(Jenscare Biotechnology)



Navigate
(Navigate)

Intrepid
(Medtronic)



Trisol
(Trisol Medical)

.. Innovation

- Independent designation of status
- Full reporting of all clinical experience
- More use of conditions on certificates
- Maintain restricted use of claims of equivalence
- Device vs. device trials
- Comprehensive post-market registries

- **Predictability**
- **Flexibility**
- **Access to advice**
- **Costs of certification**

Courtesy of Stephan Windecker, Bern

- Development of legislation has been **reactive rather than proactive**
- Adopting methods from industrial sectors and for needs of manufacturers
- Criteria for performance rather than clinical effectiveness
- Protective of intellectual property, more than clinical imperatives

- Regulatory approval needs to be based on **shared scientific principles**
- Clinically qualified experts in Commission, agencies, & Expert Panels
- Collaboration, specialisation, transparency of all clinical evidence
- Need for technical specifications and open standards (instead of ISO)
- More substantial progress towards global regulatory convergence