# EU Regulation on Medical Devices 2017/745 – Novelties and implementation

**Alan G Fraser**
Chairman, ESC Regulatory Affairs Committee
Chairman, Regulatory Task Force of BioMed Alliance

*fraserag@cf.ac.uk*

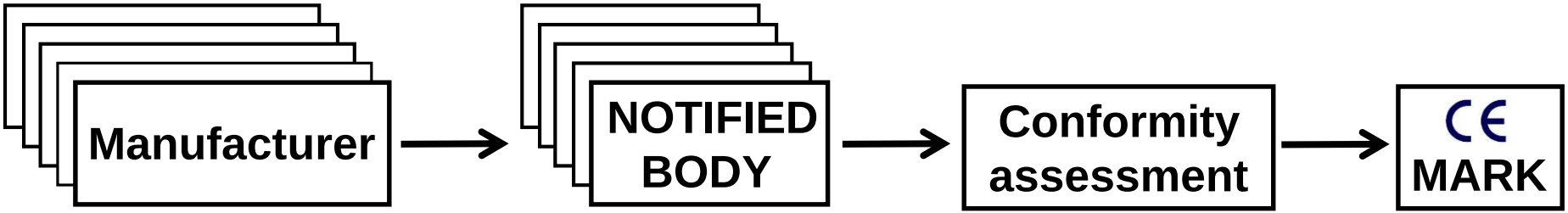
ESC
European Society of Cardiology

# A standard approach for implementing EU law

1985 Council Resolution 85/C 136/01:
On a New Approach to Technical Harmonization & 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."

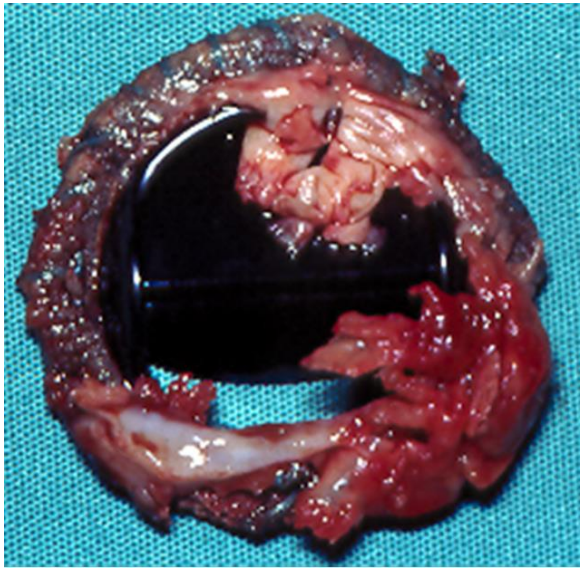
1990s **Medical Device Directives …**



# The Cardiff Embolic Risk Factor Study

## Silzone mitral /double valve replacement

ESC European Society of Cardiology



*Ionescu A et al, Heart 2003; 89: 1055-61*

Given CE mark without premarket clinical trial, as an iterative change

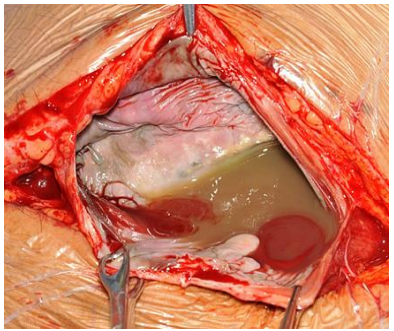
Observational study – **high rate of thrombosis of valve in mitral position (≥ 10% at 1 m)**

Randomised trial (AVERT) – **high prevalence of paraprosthetic regurgitation (9% at 2 y)**

# The need for reform – ESC Policy Paper 2011

- Clinical problems relating to failures of medical devices
- Weakness of the clinical data requirements
- Insufficient accountability of the Notified Bodies
- Lack of transparency
- Insufficient use of expert medical advice

*Fraser AG et al,*
*EHJ 2001; 32: 1673-86*



**Large head metal-on-metal hip replacement**


**Poly Implant Prothèse (PIP) breast implant**

Official Journal of the European Union

L 117

English edition

Legislation

Volume 60

5 May 2017

Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/ n (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC (1)

2020 →

Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on *in vitro* diagnostic medical devices and repealing Di EC and Commission Decision 2010/227/EU (1) .....

2022 →

http://eur-lex.europa.eu/legal-content/ENG/TXT/PDF/?uri=CELEX:32017R0745&from=EN

# What's new? What's changing?

ESC European Society of Cardiology

- Clinical evaluation
- Transparency of evidence for devices
- Expert scientific and medical advice
- Standards, common technical specifications
- Post-market surveillance and registries
- Alliance for BioMedical Research in Europe

# Article 2/1: **The new EU definition of a medical device**

Any instrument, apparatus, appliance, software, implant, reagent, material or other article, intended by the manufacturer to be used, alone or in combination, for human beings for ..

- **diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease**; ..
- investigation, replacement or modification of the anatomy or of a physiological or pathological process or state,
- providing information by .. in vitro examination of specimens ..

and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, .. but which may be assisted in its function by such means.

# New EU Regulation 2017/745 – Clinical investigation

- **Demonstration of compliance** with the general safety and performance requirements should be based on clinical data that, for **class III medical devices and implantable medical devices** should, as a general rule, be **sourced from clinical investigations** (recital 63) *[so, less equivalence]*
- '**Clinical evaluation**' means a systematic and planned process to continuously generate, collect, analyse and assess the clinical data pertaining to a device in order to verify the safety and performance, including **clinical benefits**, of the device (article 2.44)
- '**Clinical benefit**' means the **positive impact** of a device on the health of an individual, expressed in terms of meaningful, measurable, **patient-relevant clinical outcome(s)** (article 2.53)

# Evidence for medical devices is not always reported ..

ESC European Society of Cardiology

- **13,327 trials at ClinicalTrials.gov completed between 2008 and 2012 (79% drugs and 11% devices)**
- **13% reported summary results at 12 months**

  *Anderson ML et al, NEJM 2015; 372: 1031*

- **49% of studies of 177 new cardiovascular devices had been published up to 7 years after completion**

  *Chang L et al, BMJ 2015; 350: h2613*

- **92 mandated and completed post-approval studies**
- **No clinical results published for 49%**

  *Quesada O et al, JAMA Internal Medicine 2016: 176: 1221*

# Freedom of information in the European Union

## Regulation EC 1049/2001 on public access to documents

- Wider access should be granted to documents in cases where the institutions are acting in their legislative capacity, including under delegated powers .. **documents should be made directly accessible to the greatest possible extent**.
- .. **all agencies** established by the institutions should apply the principles laid down in this Regulation
- In principle, **all documents** of the institutions should be accessible to the public.

**Applies to the EMA but not to Notified Bodies**

*http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex:32001R1049*

ESC
European Society of Cardiology

# The need for transparency of clinical evidence for medical devices in Europe

*Alan G Fraser, Eric G Butchart, Piotr Szymański, Enrico G Caiani, Scott Crosby, Peter Kearney, Frans Van de Werf*

- No difference between drugs and devices
- Summary of Safety and Clinical Performance .. **"SSCP"**
- Evidence from preclinical studies should be available
- Access to advice and decisions by notified bodies
- Clinical evaluation assessment report should be available
- Draft SSCP guidance – public consultation > November 2018

*Lancet 2018; 392: 521-30*

# Summary of safety and clinical performance (SSCP)

ESC European Society of Cardiology

- Intended purpose, target populations, indications, contraindications
- Residual risks and undesirable effects, warnings and precautions
- Summary of clinical data from conducted investigations of the device
- An overall summary of the clinical performance and safety
- Ongoing or planned post-market clinical follow-up
- Possible diagnostic or therapeutic alternatives
- Clinical data obtained from the post-market surveillance plan
- Analysis of clinical data from medical device registries

*Draft guidance, from task force of the Clinical Investigation and Evaluation Committee, EU Commission, v 4: for public consultation, November 2018*

# Unresolved questions .. Expert panels

ESC European Society of Cardiology

**Recital 56**

For class III implantable devices and class IIb active devices intended to administer and/or remove a medicinal product, notified bodies **should, except in certain cases, be obliged** to request expert panels to scrutinise their clinical evaluation assessment report.

**Recital 57**

For class III devices and for certain class IIb devices, **a manufacturer should be able to consult voluntarily** an expert panel, prior to that manufacturer's clinical evaluation and/or investigation, on its clinical development strategy and on proposals for clinical investigations.

**Article 55**

**In the case of divergent views** between the notified body and the expert panels, a full justification shall also be included.

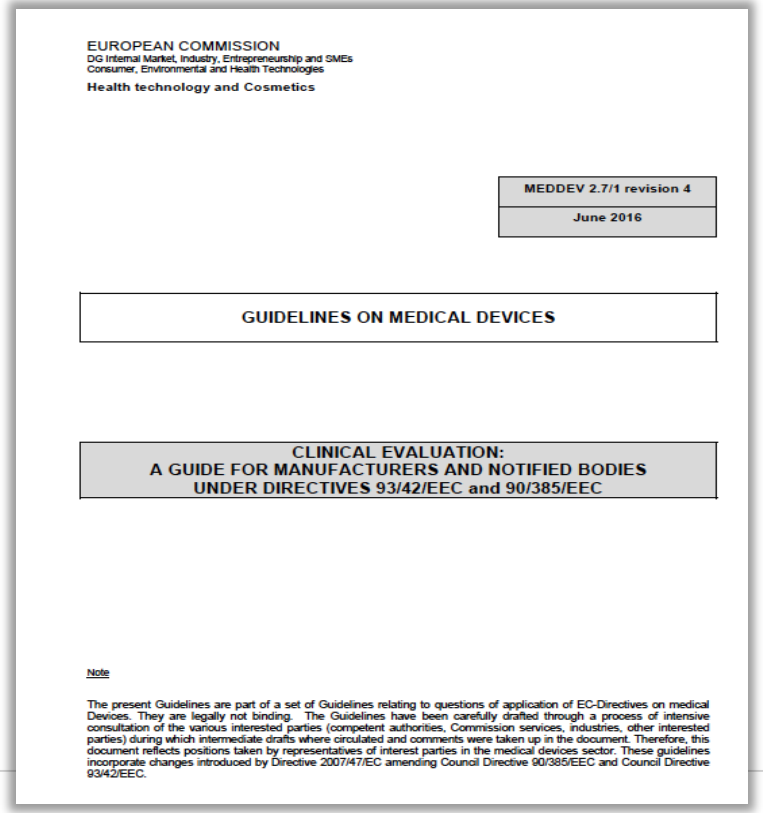
# *Wide range of expertise within panels*

ESC
European Society of Cardiology

- Basic scientists / engineers / informatics ..
- Clinical specialists – in practice and research
- Across relevant ages and disciplines
- Other healthcare professionals
- Users / patients
- Biostatisticians and experts in medical ethics

# EC Guidance Documents on Clinical Evaluation

EAPCI
European Association of Percutaneous Cardiovascular Interventions



EUROPEAN COMMISSION
DG Internal Market, Industry, Entrepreneurship and SMEs
Consumer, Environmental and Health Technologies
Health technology and Cosmetics

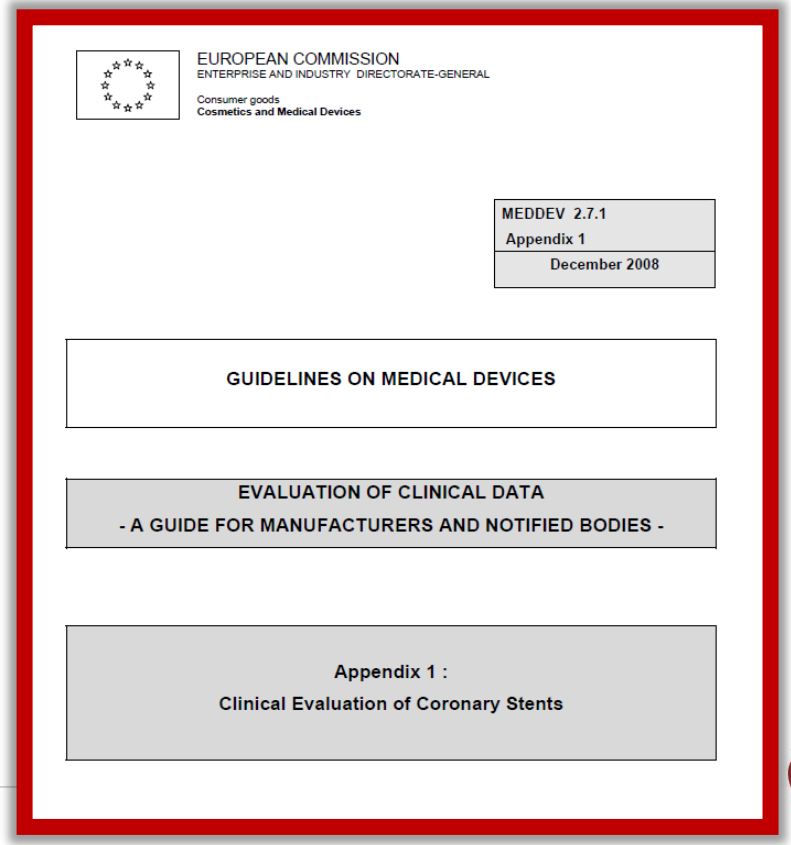
MEDDEV 2.7/1 revision 4
June 2016

GUIDELINES ON MEDICAL DEVICES

CLINICAL EVALUATION:
A GUIDE FOR MANUFACTURERS AND NOTIFIED BODIES
UNDER DIRECTIVES 93/42/EEC and 90/385/EEC

Note

The present Guidelines are part of a set of Guidelines relating to questions of application of EC-Directives on medical Devices. They are legally not binding. The Guidelines have been carefully drafted through a process of intensive consultation of the various interested parties (competent authorities, Commission services, industries, other interested parties) during which intermediate drafts where circulated and comments were taken up in the document. Therefore, this document reflects positions taken by representatives of interest parties in the medical devices sector. These guidelines incorporate changes introduced by Directive 2007/47/EC amending Council Directive 90/385/EEC and Council Directive 93/42/EEC.



EUROPEAN COMMISSION
ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL
Consumer goods
Cosmetics and Medical Devices

MEDDEV 2.7.1
Appendix 1
December 2008

GUIDELINES ON MEDICAL DEVICES

EVALUATION OF CLINICAL DATA
- A GUIDE FOR MANUFACTURERS AND NOTIFIED BODIES -

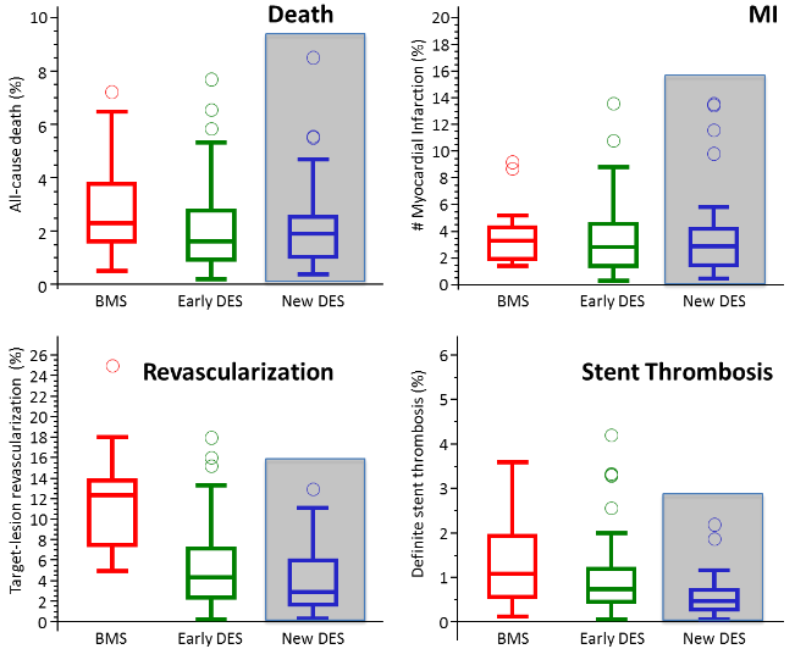
Appendix 1 :
Clinical Evaluation of Coronary Stents

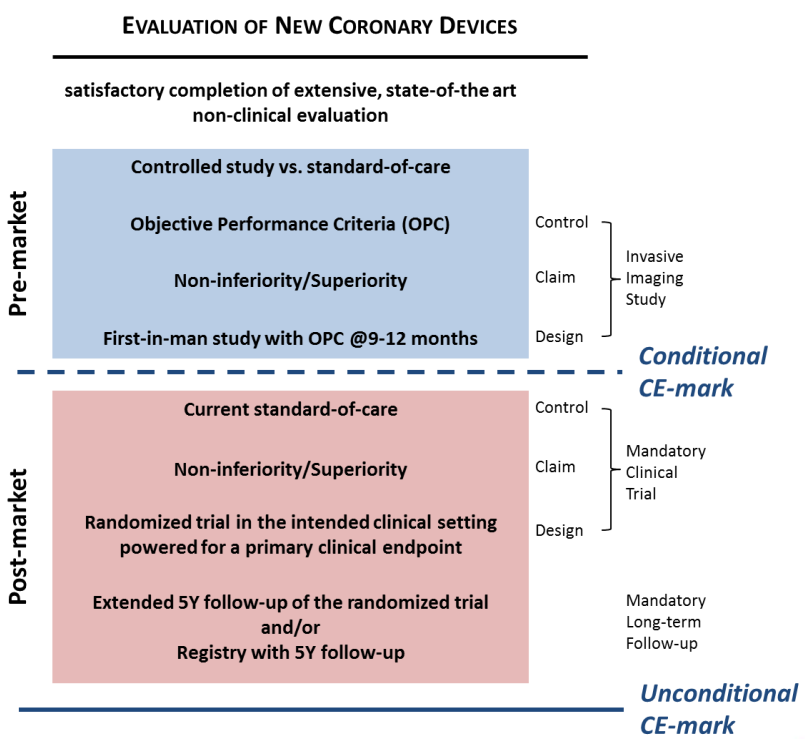
ESC

# ESC-EAPCI Task Force on Coronary Stents

EAPCI
European Association of Percutaneous Cardiovascular Interventions

## Systematic review of 158 RCTs




Pilot for future interaction with regulators

ESC

Byrne R et al, ESC-EAPCI Stent Task Force | *Eur Heart J* 2015

# ISO/TC 150/SC 2 **Cardiovascular implants and extracorporeal systems**

Ajit Yoganathan (Atlanta) / Ulrich Steinseifer (Aachen)

**ISO 5840-1: 2015**

Cardiovascular implants — Cardiac valve prostheses — Part 1: General requirements

**ISO 5840-2: 2015**

Cardiovascular implants — Cardiac valve prostheses — Part 2: Surgically implanted heart valve substitutes

**ISO 5840-3: in revision, publication anticipated in 2019**

Cardiovascular implants — Cardiac valve prostheses —Part 3: Heart valve substitutes implanted by transcatheter techniques

**ISO 5910: new international standard, final draft, undergoing approval**

Cardiovascular implants and extracorporeal systems – Cardiac valve repair devices

# Common technical specifications – device-specific guidance

- **Current EU reliance on standards from ISO & IEC / CEN & CENELEC :**
  - ✧ Preponderance of members are manufacturers
  - ✧ Need to involve more independent experts
  - ✧ More stakeholder engagement, new financial model ?
- **Regulatory convergence through IMDRF ?**
- **Development of EU documents .. such as MEDDEV 2.7.1 /4**

IMDRF
International Medical Device Regulators Forum

ISO
International Organization for Standardization

IEC

# Requirements for post-market surveillance

ESC European Society of Cardiology

- **Recitals 32 and 74:**

  ".. all manufacturers should have a .. system in place .. systematically and actively gathering information from post-market experience .."

- **Article 83:**

  Data gathered .. shall in particular be used

  (a) to update benefit-risk determination and improve risk management
  (b) to update the design and manufacturing information ..
  (c) to update the clinical evaluation ..
  (d) to update the summary of safety and clinical performance ..
  (e) to identify need for preventive .. or field safety corrective action

**EU Medical Device Regulation 2017/745**

# Requirements for post-market surveillance

ESC European Society of Cardiology

- **Annex III:**

The post-market surveillance plan shall address the collection and utilization of available information, in particular:

- information concerning serious incidents
- data on any undesirable side-effects
- information from trend reporting
- relevant specialist databases and/or registers
- information .. provided by users

“ Post-market clinical follow-up (PMCF) shall be .. a continuous process that updates the clinical evaluation .. and shall be addressed in the manufacturer's post-market surveillance plan.”

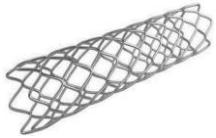
**EU Medical Device Regulation 2017/745**

# SWEDEHEART

- The Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (**SWEDEHEART**) was launched 2009 after merging of the:

  - National registry of acute cardiac care (**RIKS-HIA**)
  - Swedish coronary angiography and angioplasty registry (**SCAAR**)
  - National registry of secondary prevention (**SEPHIA**)
  - Swedish heart surgery registry

    - The registry enrolls **80,000** cases each year:
      - **30,000 with ACS**
      - **40,000 undergoing coronary angiography/PCI**
      - **7,000 undergoing heart surgery**



Restenosis in all stents implanted >1000 times in Sweden, 2007 - January 23th 2018.

Cumulative rate of restenosis

10%
5%
0%

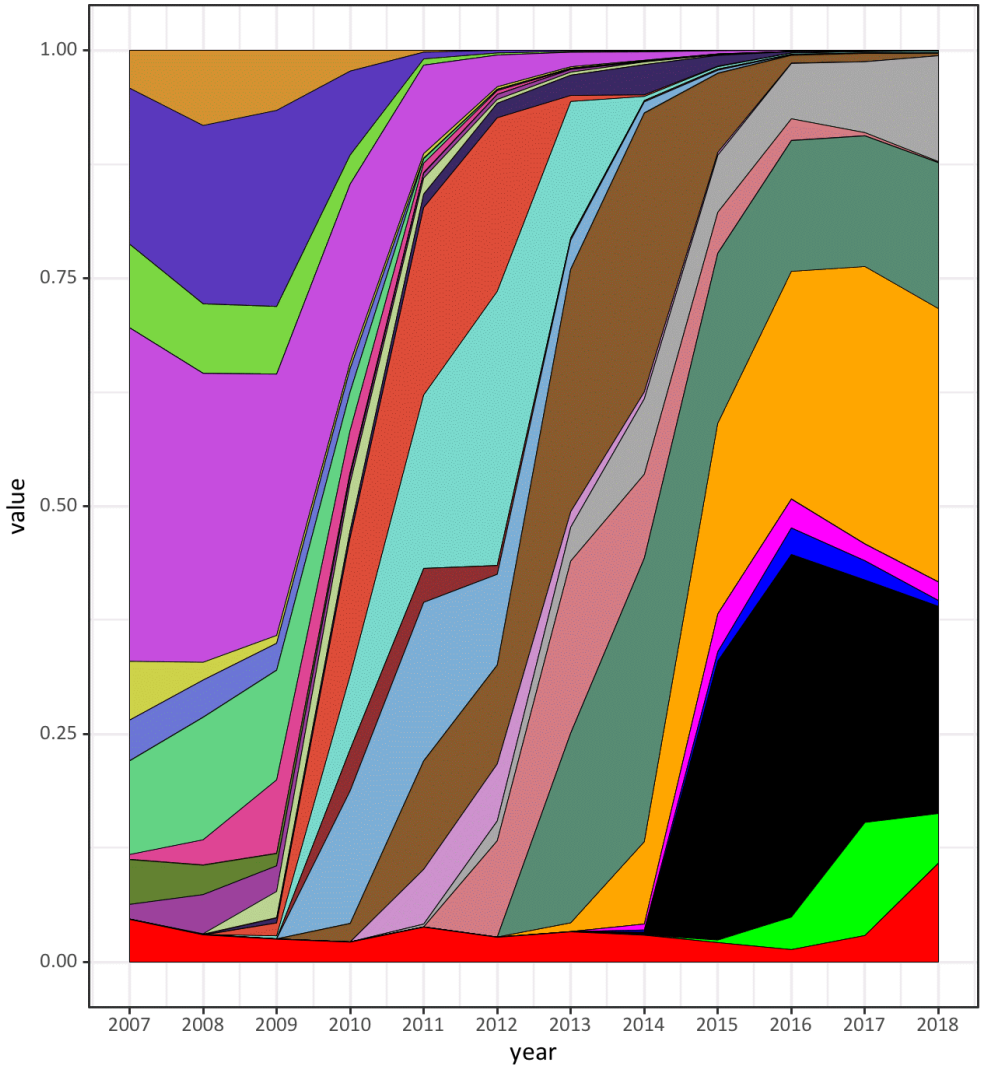
0 1 2 3 4 5 6 7 8 9 10 11

Time (years)

- Cypher
- Driver
- Multilink Vision
- Liberté
- Coroflex Blue
- Endeavor
- Taxus Liberté
- Xience V/Promus
- Chrono
- Titan2
- Endeavor Resolute
- BioMatrix
- Xience Prime
- Promus Element
- Multilink8
- Integrity
- Resolute Integrity
- Omega
- Orsiro
- Xience Xpedition
- Promus Premier
- Synergy
- Ultimaster
- Biofreedom
- Onyx
- Xience ProX
- Other stents

© SCAAR, courtesy of David Erlinge

# Stent use over time



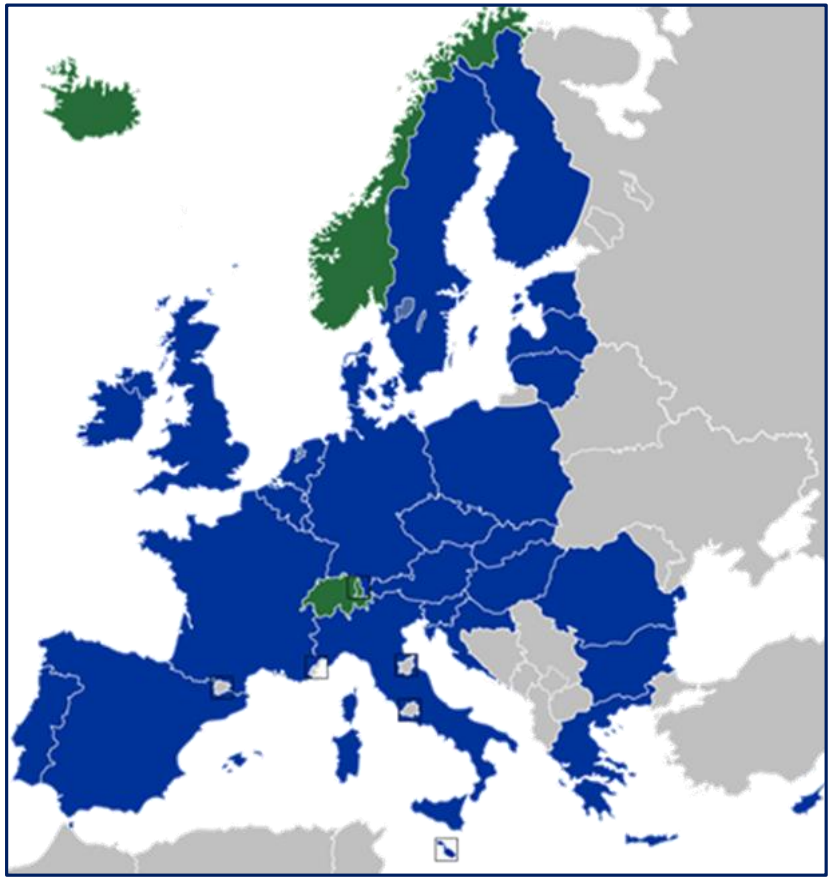

Stent

- Cypher
- Driver
- Multilink Vision
- Liberté
- Coroflex Blue
- Endeavor
- Taxus Liberté
- Multilink8
- Integrity
- Resolute Integrity
- Omega
- Orsiro
- Xience Xpedition
- Promus Premier

**2016/679** **General data protection regulation**

Recital 33 It is often not possible to fully identify the purpose of personal data processing for scientific research purposes at the time of data collection. Therefore, data **subjects should be allowed to give their consent to certain areas of scientific research** when in keeping with recognised ethical standards for scientific research.

Recital 157 By coupling information from registries, researchers can obtain new knowledge of great value with regard to widespread medical conditions such as cardiovascular disease ..
In order to facilitate scientific research, **personal data can be processed for scientific research purposes**, **subject to appropriate conditions and safeguards set out in Union or Member State law**.



ESC
European Society of Cardiology

## Opportunities

Safer & more effective devices

Evidence-based choices

Engagement for experts

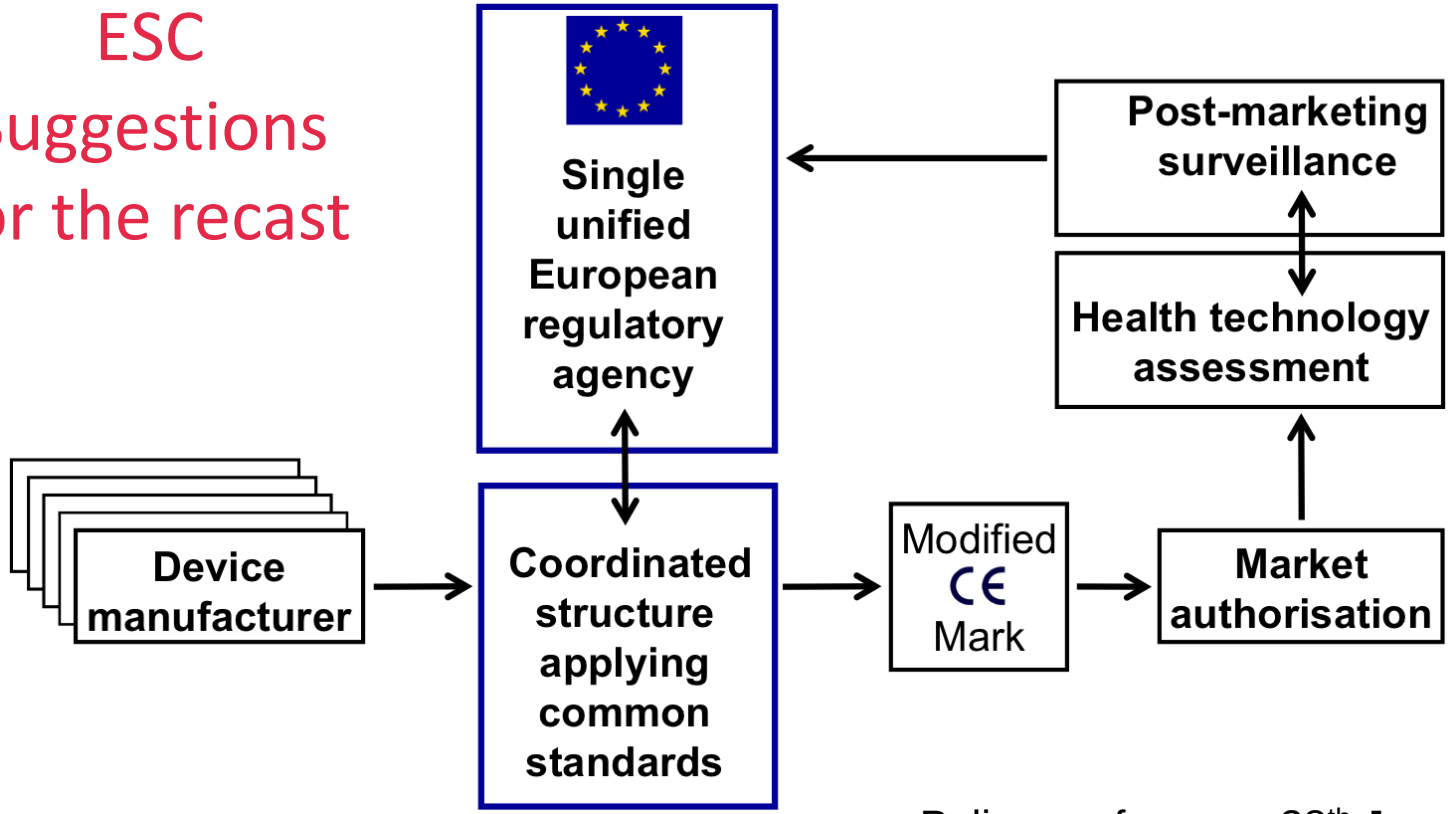
## Challenges

Regulatory capacity

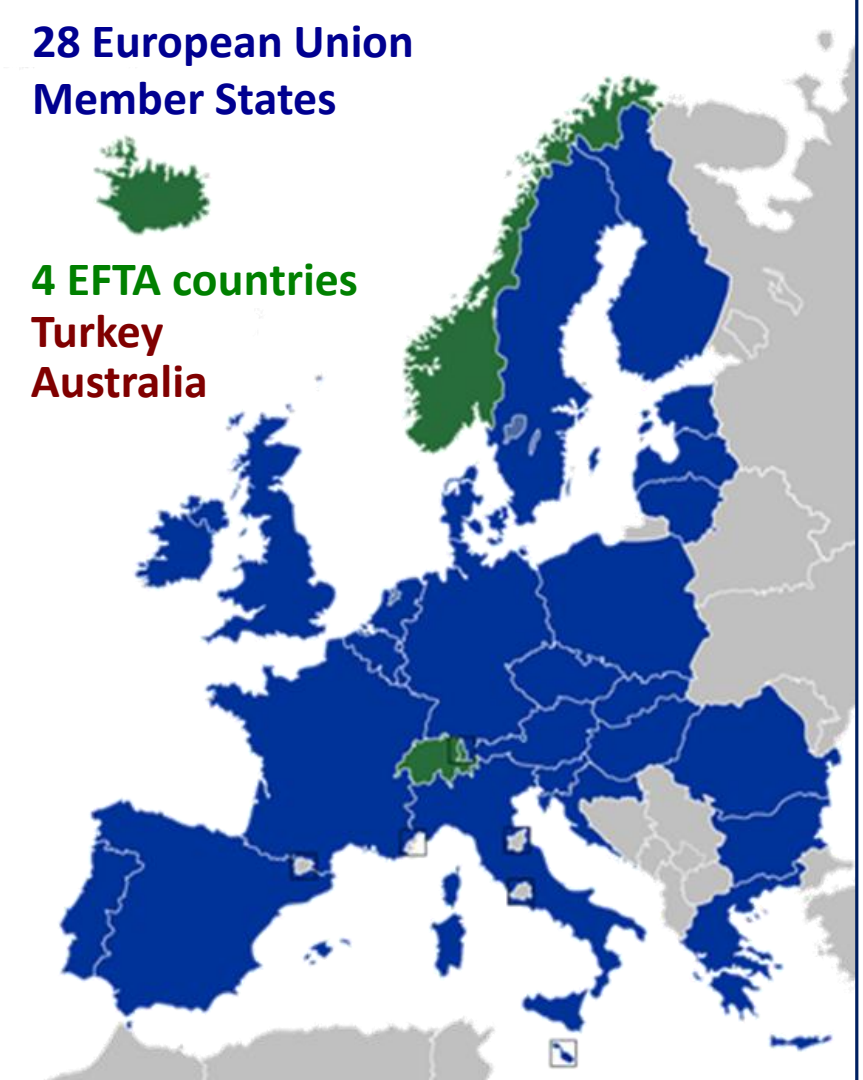
Full transparency

Changing medical practice

# ESC Suggestions for the recast




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




# Priorities for implementation

- **Major logistic challenges, no EU agency**
- **CAMD roadmap and task forces (>38)**
- **Transition periods 3 – 5 – 7 years**
- Implementing acts, delegated DG Grow
  - minimum essential **= 14**
  - total envisaged by regulations **≈ 80**
- Development of **EUDAMED** database
- Implementation of **UDI**
- [Re-] Designation of all Notified Bodies
- In vitro diagnostics – 80% evaluated..

Live plenary session Strasbourg **25-10-18**

## Oral question - Implementation of the Medical devices and In-vitro diagnostic medical devices Regulations

17:02/17:21 - 25-10-2018


“ We need the Regulations to be implemented in full and on time .. you do need to give us more detail ..”

“ We are on track .. work is advancing and progressing .. EU citizens will receive the most reliable and the most innovative medical devices in the world .. we are putting a lot of human resources on this file ”

# CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

| CDRH Scientific & Technical Staff (January 2017 Estimates) | |
|---|---|
| **Positions** | **Staff Count** |
| **Total** | **1,184** |
| Medical, Hospital, Dental, and Public Health Group | 424 |
| Engineering Group | 405 |
| Biological Sciences Group | 177 |
| Physical Sciences Group | 95 |
| Mathematical Sciences Group | 75 |
| Veterinary Medical Science Group | 8 |

| | |
|---|---|
| **Medical, Hospital, Dental, and Public Health Group** | **424** |
| Consumer Safety Officer | 132 |
| Medical Officer | 117 |
| Regulatory Health | 80 |
| Public Health Advisor | 36 |
| Medical Technologist | 26 |
| Nurse Consultant | 24 |
| Optometrist | 3 |
| Dental Officer | 3 |
| Audiologist | 2 |
| Pharmacist | 1 |
| **Veterinary Medical Science Group** | |
| Veterinary Medical Officer | 8 |

***USA 326 million – EU 508 million (2016)***

BioMed Alliance

ESC European Society of Cardiology

# Priorities for engagement

- Regulatory Affairs Task Force – call for members
- **EU Call** to stakeholders for working groups of MDCG (Medical Device Coordination Group) : **OCTOBER 2018**
- Advisory meeting at Joint Research Centre, early 2019
- **EU Call** for individual scientific experts : **SPRING 2019**
- Responses to public consultation on contents of Summary of Safety and Clinical Performance

*https://www.biomedeurope.org/*

# Research, regulatory and clinical decision-making: the importance of scientific integrity

ESC European Society of Cardiology

## ***Regulatory integrity***

- Over-reliance of small, short trials
- Over-reliance on trials with surrogate markers
- Misapplication of expedited pathways
- Inadequate post-market requirements
- Insufficient regulatory oversight
- Insufficient regulatory enforcement

*Wallach JD et al, J Clin Epidemiol 2018; 93: 88-93*