CLINICAL TRIALS **TRANSFORMATION** INITIATIVE

European Perspective

Angeles Alonso Garcia

European Medicines Agency-SAWP
ESC-European Affairs Committee
CVRC St George´s. University of London

Disclaimer

- ***The views expressed in this presentation are the personal views of the speakers and may not be understood or quoted as being made on behalf of or reflecting the position of the MHRA, EMA or one of its committees or working parties.***

EMA scope

- *Coord Centralised Procedure for registration*
- *Scientific advice (product)*
- *Guidelines*
- *Orphan Drug Designation*
- *Paediatric Investigation Plans*
- *Information to patients & transparency*
- *Arbitration/referrals*
- *Coord EU pharmacovigilance*
- *Coord inspections (GXP)*

Regulation 726/2004

but not:

- Research & Development
- Analytical control, reference
- Inspections
- Clinical Trials Authorisation
- Ethics Committee
- Patents
- Pricing & Reimbursement
- Advertisement & Promotion
- Medical Devices, diagnostics (except combination products)

Authorisation procedure in devices according to risk-EU

	RISK	DEVICES	EVALUATION
Class I	Low	Stethoscope, cooling jackets	Little, essential requirements (sterility)
Class IIa	Medium	Monitoring BP, MRI, US, PET	**Conformity Assessment Procedure:**
Class IIb		X-ray machines	**Notified Bodies (NB)**
Class III	High	Invasive or implantable: coronary stents, prosthetic heart valves, pacemakers, implantable defibrillators, resynchronization therapy	**Conformity Assessment Procedure:** **Notified Bodies (NB)**

Conformity assessement-EU

- When equivalent to another device with data:

  1. Revision of Scientific literature available

  2. Critical evaluation of CT investigations that have address residual safety concerns

- Class III devices.

  Some human clinical investigations

  (but not compulsory RCT)

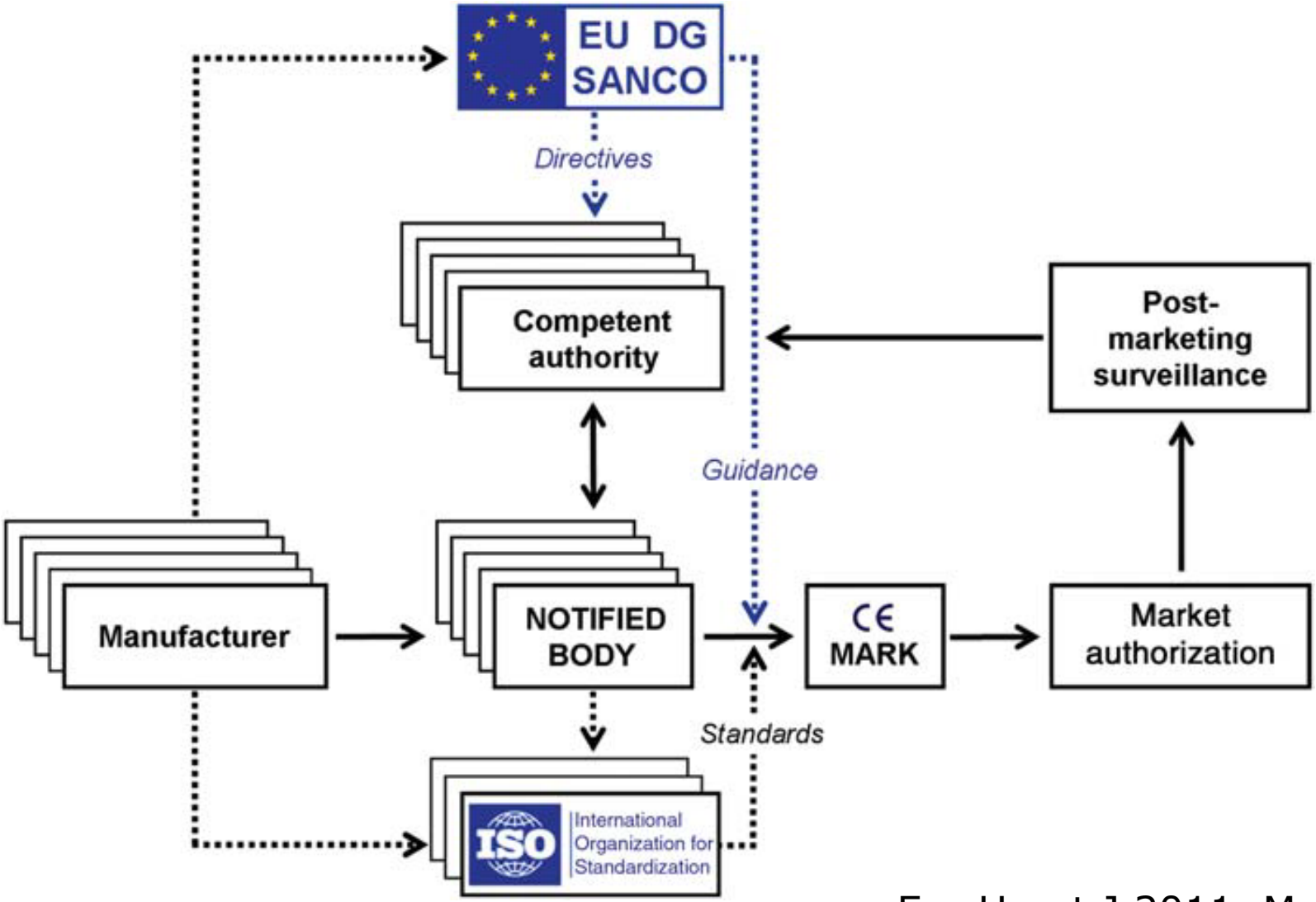
NOTIFIED BODIES (NB)

- Any independent commercial organization designated to assess if manufactured product conform with requirements of EU directive.
  - 2271 NDs in Jan 2011 (registered)
  - 74 approved to evaluate medical devices
- Designated, monitored & audited by the competent authorities of the ME in which they are based.
- Supported in part by the fees paid by device companies.

NOTIFIED BODIES (NB): Duties

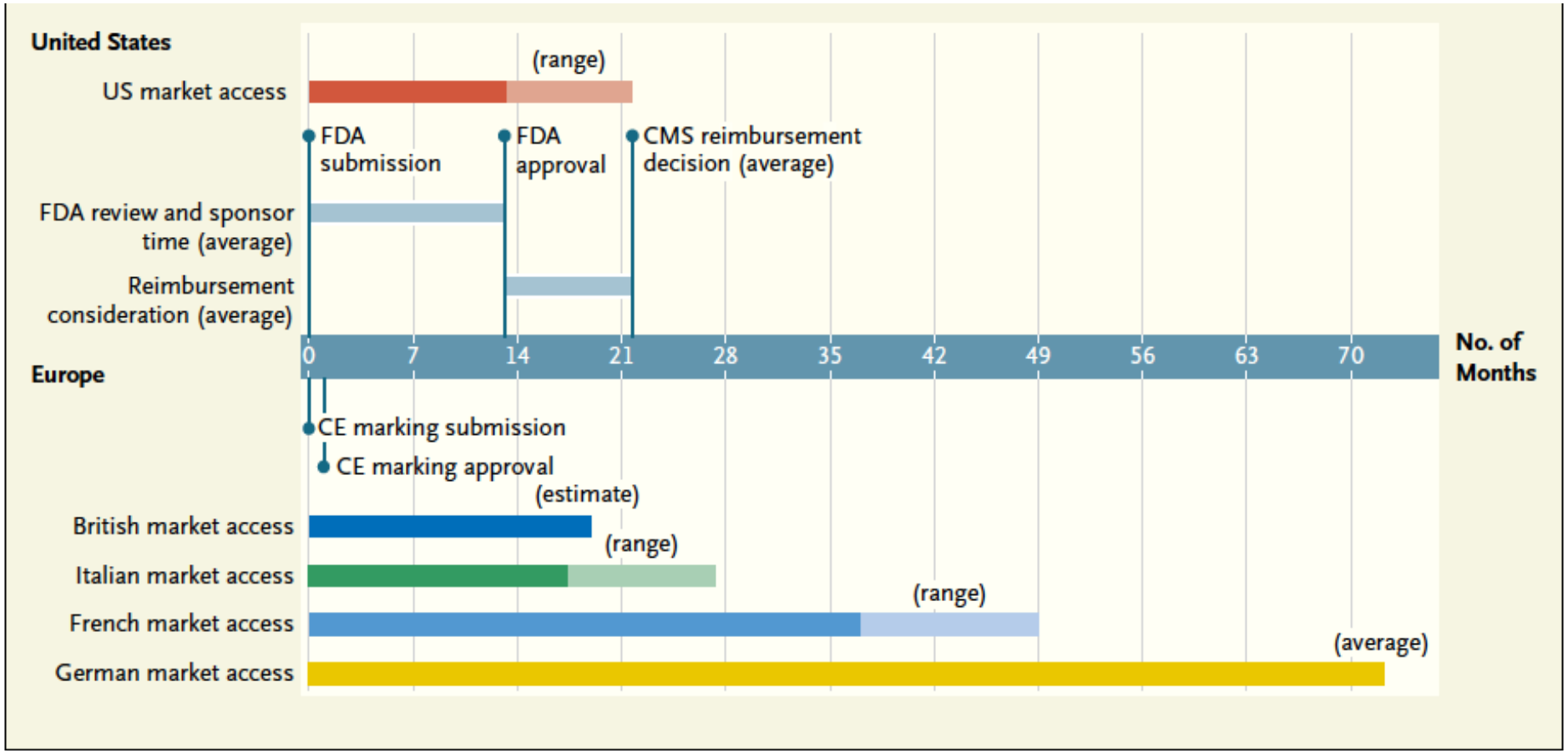
- Review the technical dossier. Assess the manufacturer. May visit the manufacturer.
- Evaluate evidence : Quality, animal, clinical.
  - "the device works as intended may be sufficient"
- May conduct direct testing, especially if it is an active medical device.
- Certificate: CE mark: the device can be marketed throughout the EU (max 5y before renewal).

Steps for approving medical devices-EU



Eur Heart J 2011, May 14

Time to access to medical devices



"Has not been the case in most Cardiolgy Devices"

N Engl J Med 2012; 367:485

AF catheter ablation

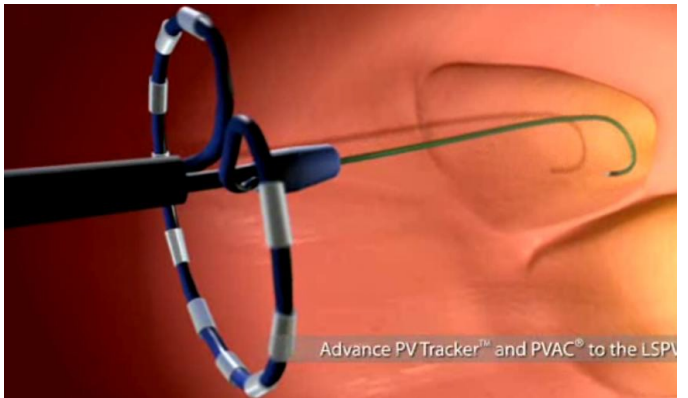
Early access before proven safety?

A catheter AF ablation was marketed in EU in 2006 on the basis of pilot data

Not approved by FDA 2011:

CT: Tailored Treatment of Permanent Atrial Fibrillation (TTOP-AF):

1. safety issues: stroke, asymptomatic emboli
2. established Tx alternatives
3. Tx target QoL rather than survival



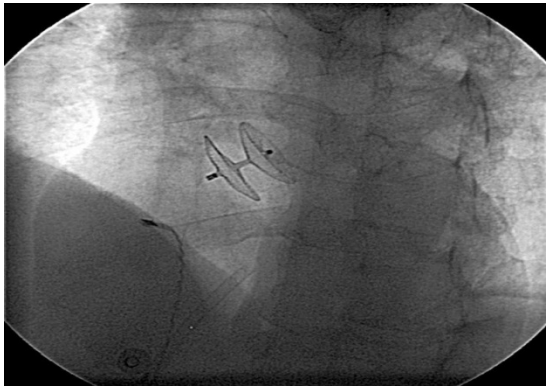
ClinicalTrials.gov Identifier: NCT00514735

Closure of patent foramen ovale

Early access before proven clinical benefit?

- At least 12 PFO closure devices received CE (**2002**)
- Risk
  - Pericadial effusion, tamponade
  - Unsuccessful deployment
  - Incomplete closure
  - Device migration, thrombosis, and AF

- Clinical Trials: MIST & CLOSURE-1:
  PFO closure no better medical Tx



Circulation 2008;117:1397
Sroke 2010;41:2872

RENAL DENERVATION FOR HTA

Early access before proven clinical benefit?

CE marc **2008** based on uncontrolled investigations

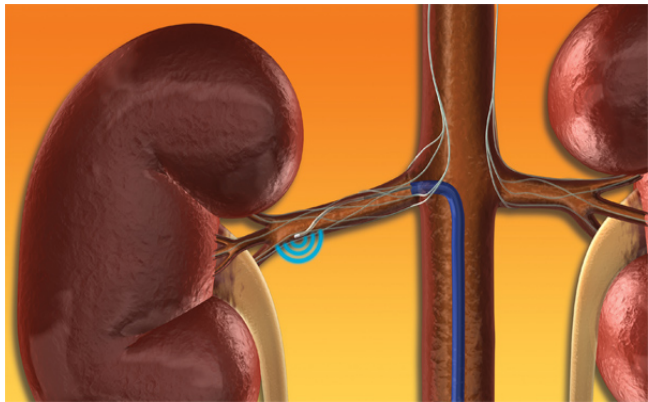
SYMPLICITY HTN-2 positive: not a sham-control arm

Not known the exact number of patients "denervated" in EU:

Medtronic Registry (2012), GREAT (Germany), other Cy,s (St Jude), not reported…..

Scientific Societies too enthusiastics?

Jan 2014
Pivotal SYMPLICITY HTN-3 trial fails to achieve 1 EP: change office sBP



Transcatheter aortic-valve implantation (TAVI)

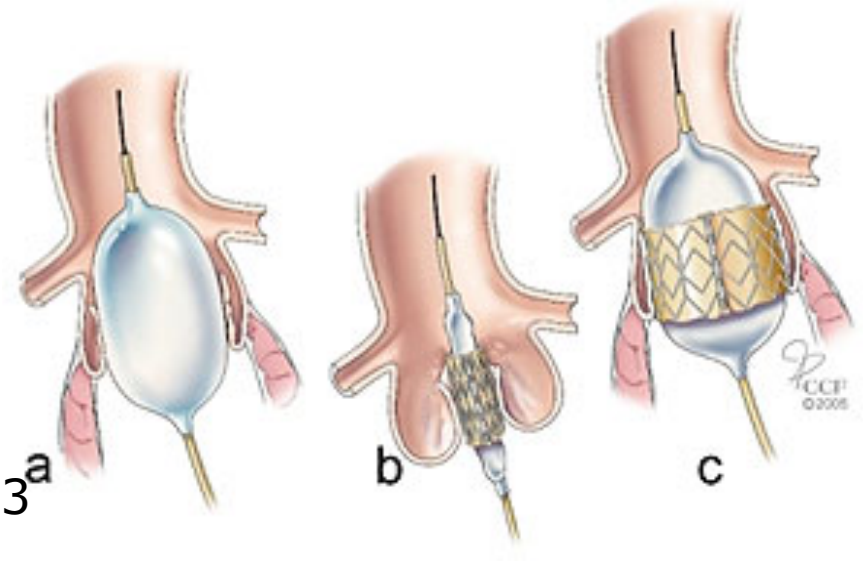
The other side of the coin?. Avoiding early access to patients?

Two devices had CE marc since **2007**

2010 TAVI was shown to reduce mortality in patients who cannot undergo surgery (Mortality and QoL). FDA approved one TAVI model late in **2011**

FDA approved January **2014** one TAVI model : lowest stroke and paravalvular leak rates seen in any study to date!

"Safety & effectiveness shown in the studies performed to meet FDA requirements"



N Engl J Med 2010;363:1597
Core Valve Extrem Risk Trial TCT: Nov 2013

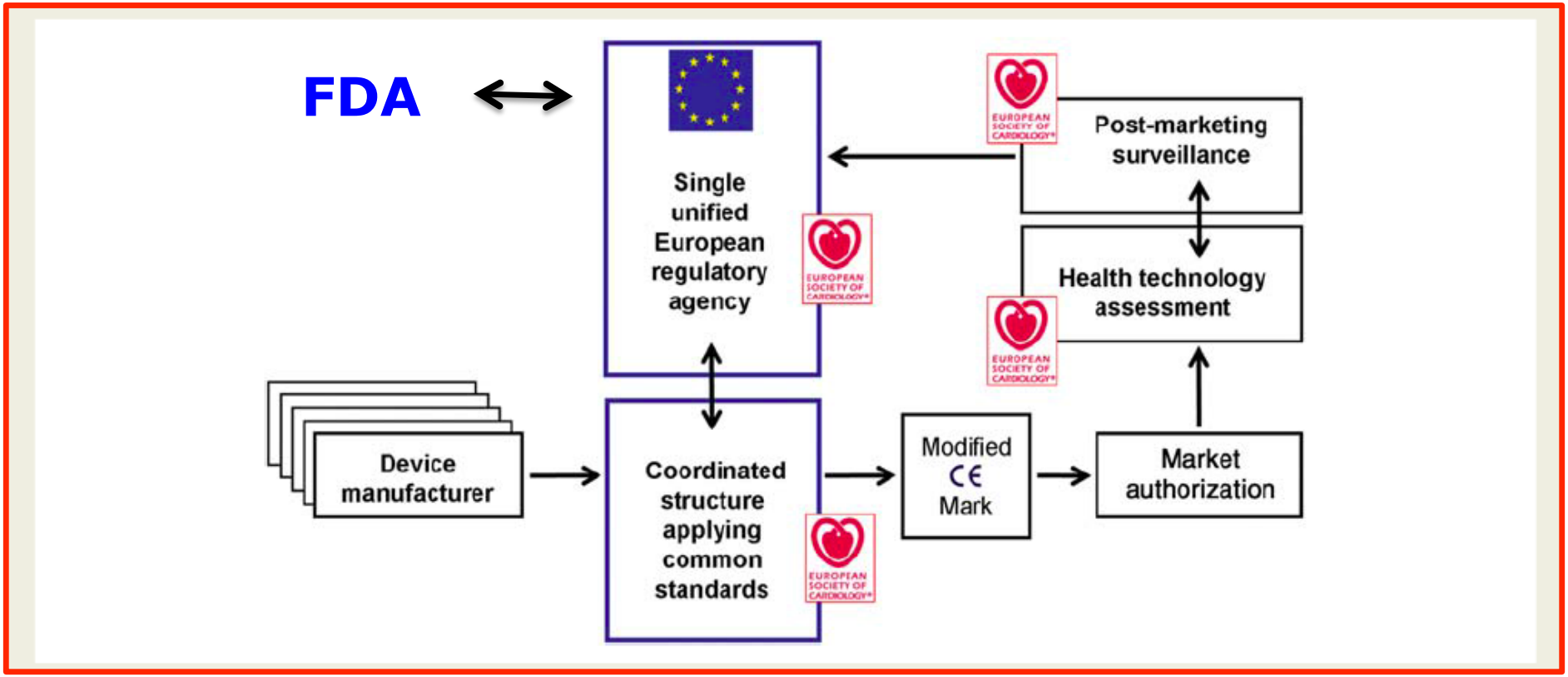
Differences EU-FDA Device Approval

Table 1. Prominent Points of Comparison between the United States and European Union for Approval of Medical Devices.*

System Feature	United States	European Union	Potential Implications
Mandate	Oversight of public health	Device safety (overseen through Competent Authorities), device approval (through Notified Bodies), and facilitation of trade	May influence dealings with industry clients, and attention paid to balance between effectiveness and risk of safety concerns
Centralization	Oversight of all device regulation by the FDA	Directives outline processes carried out by Competent Authorities and Notified Bodies	Standardization and coordination of premarketing and postmarketing evaluation are theoretically simpler and easier to enforce in the United States
Data requirements	Reasonable assurance of safety and effectiveness for approval of high-risk devices, "substantial equivalence" for 510(k) clearance	Generally performance-based analysis, requiring proof that device works as intended	E.U. assessment made by manufacturers and Notified Bodies; provides less insight into clinical end points for high-risk devices
Transparency	Proprietary limits with public reporting of premarketing review of approved devices, recalls, and adverse events	Review of Notified Bodies not made public; postmarketing data shared among Competent Authorities but not with the public	Greater public access to evidence in the United States
Funding	Combination of federal appropriations (80%) and user fees (<20%)	Funding of Competent Authorities variable among countries; Notified Bodies paid directly by sponsors	Notified Bodies may be vulnerable to conflict of interest with industry client; the FDA may be influenced by changes in federal funding and political climate
Access	Clinical premarketing testing of high-risk devices delays patient access to these devices (no differences for low- and moderate-risk devices)	E.U. patients may have access to certain high-risk devices sooner than in the United States, subject to limitations by payers	E.U. patients have faster access to certain devices, but these products are marketed with less rigorous proof of effectiveness and may have a greater chance of later-identified adverse events

N Enlg J Med 2012; 366:848

ESC recommendations for approval & monitoring Medical Devices



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THANK YOU

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