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)

but not:

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

Regulation 726/2004
<table>
<thead>
<tr>
<th>RISK</th>
<th>DEVICES</th>
<th>EVALUATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Low</td>
<td>Little, essential requirements (sterility)</td>
</tr>
<tr>
<td></td>
<td>Stethoscope, cooling jackets</td>
<td></td>
</tr>
<tr>
<td>Class IIa</td>
<td>Medium</td>
<td>Conformity Assessment Procedure:</td>
</tr>
<tr>
<td></td>
<td>Monitoring BP, MRI, US, PET X-ray machines</td>
<td>Notified Bodies (NB)</td>
</tr>
<tr>
<td>Class IIb</td>
<td>High</td>
<td>Conformity Assessment Procedure:</td>
</tr>
<tr>
<td></td>
<td>Invasive or implantable: coronary stents, prosthetic heart valves, pacemakers, implantable defibrillators, resynchronization therapy</td>
<td>Notified Bodies (NB)</td>
</tr>
</tbody>
</table>
Conformity assessment-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
“Has not been the case in most Cardiology Devices”
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
Stroke 2010;41:2872
RENAL DENERVATION FOR HTA

Early access before proven clinical benefit?

CE marc 2008 based on uncontrolled investigations

SYMPPLICITY 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 enthusiasts?

Jan 2014

Pivotal SYMPPLICITY 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”

Core Valve Extrem Risk Trial TCT: Nov 2013
## Differences EU-FDA Device Approval

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

N Enlg J Med 2012; 366:848
ESC recommendations for approval & monitoring Medical Devices

Eur Heart J 2011, May 14
THANK YOU