MEDICAL PUBLICATIONS FOR BETTER PATIENT CARE:
INTEGRITY, INNOVATION, AND IMPACT

20-21 January, 2015
etc.venues, St. Paul’s - 200 Aldersgate London, UK
Medical publications for devices and diagnostics

Alice Choi
Global Head, Complete Medical Communications, Macclesfield, UK
Chair of the Board of Trustees for ISMPP
Medical Devices And The European Health Care System

How to regulate diversity and constant changing complexity?

Joachim Wilke, PhD.
Director Regulatory Affairs & Policy Europe, Medtronic
Disclaimers and Conflicts of Interest

Joachim Wilke is an employee of Medtronic

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Core Technologies that Highlight our Innovation

- Targeted Drug and Biologics Delivery
- Electrical Stimulation
- Surgical Navigation and Imaging
- Implantable Mechanical Devices
- Powered and Advanced Energy Instruments
- Remote Patient and Device Management

Image copyright Medtronic
Medical Devices in Human Lifetime

Image EucoMed
Slide courtesy of GMTA presentation – IMRDF 4th meeting, Nov 2013
Diversity of Medical Devices

Class III – AIMD
50,000

Class IIb
100,000

Class IIa
150,000

Class I
200,000

Image EucoMed
Slide courtesy of GMTA presentation – IMRDF 4th meeting, Nov 2013
Constant Improvements To Benefit Patients

Similarities for the case of pace-makers and prosthetic legs:
Major increases in functionality and comfort of use

Slide courtesy of GMTA presentation – IMRDF 4th meeting, Nov 2013
EU Medical Devices Are Currently Regulated by Three Directives

- Directive 90/385/EEC Active Implantable Medical Devices
- Directive 93/42/EEC Medical Devices
- Directive 98/79/EC In vitro Diagnostic Medical Devices
The Principles of the Current EU Medical Device Regulation

Pre – market

• Risk Classification of Medical Devices
• Risk Assessment and Mitigation
• Meeting Essential Requirements/Technical Standards
• Meeting Quality System Standards
• Pre-clinical lab/animal testing
• Clinical Evaluation/Clinical Investigation
• **CE Certification By Notified Bodies**

Post - market

• Post - market Clinical Follow-Up
• Post - market Surveillance
• Post - market Notified Body Auditing
• Vigilance Reporting to Competent Authorities
• Post - market Competent Authority Supervision
• **Periodic – Recertification**
The Principles of the Current EU Medical Device Regulation

EU REGULATORY FRAMEWORK FOR MEDICAL DEVICES

Left figure provided by EucoMed, Right figure provided by BVMed
Time To Market

Medical Devices get access to the EU market
2–3 years faster than in the US

Stanford University, Dr. J. Makower, Nov 2010
FDA Impact on U.S. Medical Technology Innovation
US Survey of 200 Medtech companies
# Review Time NB vs. FDA

<table>
<thead>
<tr>
<th>Product</th>
<th>Time CE-Mark</th>
<th>Time FDA Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endeavor (DES)</td>
<td>8 months</td>
<td>14 months</td>
</tr>
<tr>
<td>EnRhythm DR IPG</td>
<td>5 months</td>
<td>13 months</td>
</tr>
<tr>
<td>Viva XT CRT-ICD</td>
<td>3 months</td>
<td>6 months</td>
</tr>
<tr>
<td>Attain CRT LV Lead</td>
<td>5 months</td>
<td>17 months</td>
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</table>

Notified Body review time about 50 – 70% shorter
Example TAVR* Medtronic CoreValve®

http://media.corporate-ir.net/media_files/IROL/25/251324/videos/CoreValve-Final-Animation-7-1-14-preview.mp4

<table>
<thead>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CoreValve (TAVR)</td>
<td>Yes 126 pts single arm</td>
<td>Yes</td>
<td>Yes 800 pts (RCT) TAVR vs. Surgery</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Clinical data related delay to market access! Review times of NBs and FDA (no panel) were comparable (< 6 mos.) CoreValve was approved in the EU 2007 and in the US 2014

*transcatheter aortic valve replacement
“There is frustration among the U.S. investigators (researchers) and U.S. care providers around delayed access to certain interventions that appear to be a winner,” said Dr. Patrick O’Gara, a cardiologist with Brigham and Women’s Hospital in Boston...

One top researcher at the meeting (ACC) called the United States "a Third World country" when it comes to availability of cutting-edge heart devices...

Asked at the ACC meeting if he found the situation frustrating, Dr. Gary Mintz, chief medical officer of the Cardiovascular Research Foundation in New York, shot back: "You mean because Algeria had TAVR before the U.S.?"
EU Medical Devices Are Currently Regulated by Three Directives

Why change?

- Original European legislation was drafted over 20 years ago.
- Number of EU member states has more than doubled.
- Different application of the medical devices directives across the EU.
- Closing gaps for non-EU regulated device types.

http://www.mhra.gov.uk/Howweregulate/Devices/Legislation/NewLegislationonMedicalDevices/
Revision of current EU Medical Devices Regulation

- Directive 90/385/EEC Active Implantable Medical Devices
- Directive 93/42/EEC Medical Devices
- Directive 98/79/EC In vitro Diagnostic Medical Devices

http://www.mhra.gov.uk/Howweregulate/Devices/Legislation/NewLegislationonMedicalDevices/
Scandals Shattered the EU Medical Device Regulatory Environment

PIP implants scandal: women march on Harley Street to demand replacements

Protesters were among the 40,000 UK women to have received implants from the now-closed French company

Press Association
theguardian.com, Saturday 14 January 2012 18.38 GMT

Protesters march down Harley Street to call for private clinics to replace PIP breast implants without charge. Photograph: Yui Mok/PA

http://www.theguardian.com/world/2012/jan/14/pip-implants-scandal-march-replacements

The EU Medical Device Regulation
The Fundamental Regulatory Questions

Notified Body Certification ↔ Competent Authority Approval
System Governance ↔ Cost Constraints
Clinical Data Demand ↔ Time to Market
Increasing Transparency ↔ Improving Traceability
CA Approval vs. NB Certification

Boston Consulting Group (BCG) report, Jan. 2011
EU Medical Device Approval Safety Assessment
A comparative analysis of MD recalls 2005-2009

Results:

• “Absolute” serious product recalls rate similar in EU and US

• Recalls relate to the same issues in EU and US
  
  Post-market issues (manufacturing): 54% recalls EU, 55% US
  
  Pre-market issues (design): 46% recalls EU, 45% US

• Recalls are concentrated in the same therapeutic areas in EU and US

Conclusion:
Competent Authority approval does not ensure patient safety
### Design-Linked Voluntary Medtronic Recalls EU v. US

<table>
<thead>
<tr>
<th>Product</th>
<th>Concerned products EU</th>
<th>Concerned products US</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyurethane Leads</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model: 6936, 6966 &amp; 6884</td>
<td>6936: 1,860, 6966: 286</td>
<td>6936: 14,006, 6966: 2,690, 6884: 57</td>
</tr>
<tr>
<td>Kappa pacemaker</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(submuscular implant)</td>
<td>79,645</td>
<td>142,473</td>
</tr>
<tr>
<td>Marquis ICD (Battery)</td>
<td>17,891</td>
<td>66,261</td>
</tr>
<tr>
<td>Fidelis ICD-Lead</td>
<td>53,312</td>
<td>169,075</td>
</tr>
</tbody>
</table>

**Lessons learned:**
1) No difference due to regulatory pathway
2) Many patient data required to identify and assess signals
System Governance vs. Cost

Devices Funding – Nominal and real terms 2009/10 – 2014/15

http://www.mhra.gov.uk
Comparing Medicines and Devices
How to proof clinical effectiveness?

**Medicines**
- Systemic action
- Metabolic action
- Non-user dependent performance
- Longer term visible benefit
- Long R&D cycles

**Devices**
- Local action
- Physical action
- User dependent performance
- Immediate visible benefit
- Short (often iterative) R&D cycles
Typical Development Cycle for Medicines

Typical Development Cycle of Devices

Create
- Define Needs
- Define Customer Requirements
- Research
- Design

Production
- Product Design
- Process Design
- Product Development
- Regulatory Pathway
- Clinical Prototype
- Clinical Testing
- Design Validation
- Field Evaluations

Market
- Final Product
- Final Functional Design
- Manufacturing Plan
- Product Launch
- Go to Market

Traditional approach. Typically 3-5 year development cycle
Challenges in Designing Clinical Trials For Medical Devices

- **Devices are primarily used by healthcare professionals (or patients):** The clinical outcomes of a medical device’s safety and performance are a function of the user’s skill paired with the device-patient interaction.

- **Inability to blind the user/patient:** Medical devices are often designed differently and this can introduce bias into the assessment of the clinical performance if the clinical investigator is jointly responsible for treatment and assessment of performance.

- **Limitation in comparative trial design (e.g. an implanted device):** Comparative clinical trials may be precluded due to ethical considerations. The use of historical controls in the trial or patients as their own controls (pre- and post-surgery) may be required to evaluate outcomes.

- **Extensive clinical data collection may exceed product lifetime**
  Fully tested device design is already outdated when approved
Post Market Clinical Follow-Up Medtronic Product Surveillance Report

VEDR01 Versa DR (IPG)
The EU Medical Device Regulation
What will change?

• More stringent Notified Body Control: Designation, CA Auditing
• Increased NB auditing requirements: Unannounced Audits
• No PMA process, but some CA control for new technologies
• Up-classification of certain devices
• More demanding requirements for clinical investigations:
  – CCS concept
  – Registries
• More transparency and traceability (EUDAMED, UDI)
• Increased CA collaboration on Vigilance
The EU Medical Device Regulation

Steps

Revision – Timetable

- Greek Presidency
- Italian Presidency
- Latvian Presidency
- Luxembourg Presidency
- Dutch Presidency

Council reaches political agreement?

Jan 2014
Parliament elections

July 2014
Rapporteurs appointed

Jan 2015
New Commissioners in place

Begin trilogues?

July 2015
Conclude trilogues?

Jan 2016
Entry into force?
Example Innovation
Medtronic Micra™

- Ventricular one chamber pacemaker w/o leads
- Catheter-based implantation
- Battery Life Time 7–10 years

Movie and images Medtronic
Acknowledgements

• Steven Walker, Bioscript group for organizing the panel

• ISMPP for the invitation

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20-21 January, 2015
etc. venues, St. Paul’s - 200 Aldersgate London, UK
IN VITRO DIAGNOSTICS

Alisa Davis, PhD
Publication Lead, Roche Diagnostics International Ltd.
Disclaimers and Conflicts of Interest

• Alisa Davis is an employee of Roche Diagnostics International Ltd.
  – Any views or opinions expressed by the presenter do not necessarily reflect those of Roche Diagnostics International Ltd.
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DIAGNOSTICS AND THE PATIENT

The power of knowing
It starts with a story…

• Op-Ed by Angelina Jolie in The New York Times, May 14th, 2013:
  – “Cancer is still a word that strikes fear into people’s hearts, producing a deep sense of powerlessness. But today it is possible to find out through a blood test whether you are highly susceptible to breast and ovarian cancer, and then take action.”

Source: [http://www.nytimes.com/2013/05/14/opinion/my-medical-choice.html?_r=0](http://www.nytimes.com/2013/05/14/opinion/my-medical-choice.html?_r=0)
How do you find out?

- Video from Roche Diagnostics: Dx Video

Video copyright: F. Hoffmann-La Roche Ltd
Molecular testing

454 Sequencing’s Genome Sequence FLX system for DNA-based diagnostics

Source: https://www.genomeweb.com/regulatory-news/fda-approves-myriads-bracanalysis-cdx-use-ovarian-cancer-drug
Copyright for image: Roche Diagnostics
BRAF test, Roche Molecular Systems

Step 1 FFPET Section

(1) H&E staining & tumor content determination

Macro-dissect if <50% tumor content

Step 2 DNA Isolation

Sample Preparation Kit
Genomic DNA isolation
DNA quantification

Step 3 PCR Setup

PCR setup

Step 4 Results Interpretation

Standardized reporting
Automated analysis
cobas® 4800 v2.0
IVDs and regulatory control

Health authority requirements

Sample preparation

PCR setup

IVD compliant hardware and software

Automated analysis and standardized reporting

cobas®
cobas®
cobas®
cobas®
DNA Sample Preparation Kit
4800 BRAF V600 Mutation Test
4800 System, v2.0

IN VITRO DIAGNOSTICS AND PUBLICATIONS

The power of details
Technical data for technical journals

• Precision
• Accuracy
• LOQ
• Functional Sens.
• Method Comparison
• …..

• “Medical Laboratory Technology” Category of Thomson Reuters Journal Citation Reports© Science Edition (2012)
  – 32 journals
  – I.F. < 3 for 27 of 32

Source: http://thomsonreuters.com/journal-citation-reports/
Technical data for technical journals

Shipkova M. et al., Clin Biochem. 2014 Aug; 47(12):1069-77
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It continues with a possibility…
MEDICAL PUBLICATIONS FOR BETTER PATIENT CARE: INTEGRITY, INNOVATION, AND IMPACT

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etc.venues, St. Paul’s - 200 Aldersgate London, UK
Medical Publications for Devices

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Global Scientific Communications Director,
SOFRADIM/COVIDIEN, Trevoux, France
Disclaimers and Conflicts of Interest

• Patrice Becker is an employee of Sofradim/Covidien

  – Any views or opinions expressed by the presenter do not necessarily reflect those of Sofradim/Covidien
Background

- EU directive and FDA regulate medical devices, based on their risks
  - Class I
  - Class II
  - Class II a & b for EU
  - Class III
Strategic Background

• In the medical device industry, a traditional approach is to get CE mark without clinical data (coming from a clinical study). Clinical evaluation with “predicates” is the common route, even if the EU regulation has been reinforced.

• Technical and pre-clinical studies are critical to understand how a product performs.

• Clinical studies frequently performed in post-market are then supporting the clinical performance or efficacy.
Strategic Background

• The medical device industry now has to respond to increased requirements for clinical evidence:
  ➢ In obtaining market approval (especially class III)
  ➢ In addition to post-market studies to support regulatory: PMS & PMCF
  ➢ Market adoption

• Overall, with the change in the traditional customer base (HCPs) to HC administrators, it is more important than ever (mandatory) to have peer-reviewed clinical evidence to support purchasing decisions.

• Also, with the change in customer base (hospitals), comparative cost effectiveness and QoL data is more important than ever.

• Thus, it is important to tell the “story” of a medical device throughout the lifecycle of the product.
Geographical Differences in Development and Registration of MD

**US**
- **1 year**
  - Concept / Design
- **1 - 3 years**
  - Pre-clinical & engineering development

**Class 1**
- 510(k) exempt
- 1-9 months

**Class 2**
- 1-3 years
- Clinical Trial
- 510(k) Approval
- 9-36 months

**Class 3**
- PMA Approval

**EU**
- **1 year**
  - Concept / Design
- **1 - 3 years**
  - Pre-clinical & engineering development

**Class 1**
- 1 month
  - EC marking
  - Sign off declaration of conformity QMS system insurance

**Class 2a**
- 1-3 years
  - Clinical Trial

**Class 2b**
- 3/6 months
  - EC marking
  - EC Design examination
  - EC certification

**Class 3**
- Reimbursement Assignment

Pre-clinical and bench testing
Clinical efficacy and safety for new indication
Justify cost
Implantable Devices: Study Types

Study Types

• Pre-Clinical:
  Biocompatibility, functional model, new model validation

• Clinical Pre-Approval:
  Clinical efficacy or performance, safety, clinical utility, health economics

• Post-Approval:
  Clinical efficacy or performance, clinical effectiveness, clinical utility, usability, health economics
Publication Challenges

- R&D and animal data – difficult to publish
- Timing and utility of R&D publications with devices that are studied but never commercialized
- Objective evidence required on efficacy, safety, and comparison to competitors
- Early alignment of clinical/technical and health economics objectives to ensure market access
Regulatory context

R&D, Pre-clinical Studies on Medical Devices

• No restriction with EU Directive or FDA

• Maximizes communication/publication capabilities
  • Bench to Bedside

• Aligns marketing, regulatory, and evidence-based medicine

• Prepares the marketplace to better understand the unmet need for the technology
Regulatory context

Clinical Studies on Medical Devices (On-Label Usage)

- No restriction with EU Directive or FDA
  (EU directive under revision and data publication obligation in discussion)

- Intermediate and final congress abstracts

  Encore company policy and congress recommendations

- Intermediate and final publication

  Journal selection
Regulatory context

Clinical Studies on Medical Devices (Off-Label Usage)


• FDA Restrictions
  “Independence and transparency”

• Be published by organization with editorial board and independent experts
• Publicly-stated policy of full disclosure of conflicts of interest or biases: Authors, Contributors, Editors…
• Peer-reviewed
• Describe consistent clinical investigations recognized by experts to evaluate the safety and effectiveness
Regulatory context

Clinical Studies on Medical Devices (Off-Label Usage)

- FDA Restrictions
  “Independence and transparence”

- Include opposite view (when available) regarding the unapproved use
- Manufacturer must make clear…with a prominently displayed and permanently affixed statement that the use described is not approved by FDA!
- Unabridged reprint
- Be distributed with the approved labeling (if distributed by the company)
- Be distributed separately from promotional information (if distributed by company)
An Evidenced Based Culture

**CLAIM**

*Why is the claim needed?*
- Customer and market insight

**EVIDENCE**

*What is needed to prove the claim?*
- Bench
- Clinical
- Pre-Clinical
- HE&R

**MESSAGE**

*What is the target and what is the format?*
- Brochures
- Peer Reviewed Publications
- White Papers
- Case Reports

**COMMUNICATE**

*How is the data effectively shared?*
- Sales Organization
- Peer to Peer
- PACE
Evidence Strategy Throughout Product Lifecycle

R&D and Pre-Clinical

Clinical

Product Adoption

Innovators

Early Adopters

Followers

Late Adopters

Pre-clinical Studies

Pilot Studies (L2)

PMA / IDE (L1)

CE-Mark (L1,2)

510K / IDE (L1,2)

Indication Expansion PMAS / IDE (L1)

Experience Papers (L5)

Multi-Center PMS (L1~3)

Investigator Initiated (L1~5)
## Scientific Communication: a Relay Race

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<thead>
<tr>
<th>Communication</th>
<th>Objective of the communication</th>
<th>Team players</th>
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<tbody>
<tr>
<td>Pre-launch</td>
<td>Identification of a clinical issue</td>
<td>Science/Technology/R&amp;D +++ HE&amp;R + Clinical +</td>
</tr>
<tr>
<td>Peri-Launch</td>
<td>Resolution of the issue: Company product</td>
<td>R&amp;D/Pre-Clinical +++ HE&amp;R + Clinical +</td>
</tr>
<tr>
<td>Post-launch</td>
<td>Clinical evidence</td>
<td>Clinical +++ HE&amp;R +++ R&amp;D/Pre-Clinical +</td>
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# Hip prosthesis

## Pre-Launch Communications 2015

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<th>Deliverable</th>
<th>Date</th>
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<th>Speaker</th>
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<td>Literature review</td>
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<td>Interest of XY in surgeries</td>
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<tr>
<td>Medico economic analysis</td>
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<td>Cost associated with post-op complications</td>
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<tr>
<td>Animal model</td>
<td>Congress 2015</td>
<td>Pilot study: performance evaluation of Z in the indication</td>
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## “Defibrillator plus”
### Peri-Launch Communications 2015/16

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<tr>
<td>Manuscript</td>
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**“Stainless steel mesh”**
Post-Launched Communications 2017

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<th>Speaker</th>
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Conclusion

• Scientific communication on medical devices is a cross-functional initiative
  • Shared commitment
  • Focus on the overall long-term strategic objectives

• Need alignment of Regulatory, R&D, Clinical, and Marketing to deliver relevant EBM

• Regulation and publication rules to be respected
  • Integrity
  • Transparency
  • Trial registration
  • ICMJE