Medical Technology Innovation Scorecard

Price Waterhouse Cooper assessed 9 countries’ capacity and capability for medical technology innovation in 2011: Brazil, China, France, Germany, India, Israel, Japan, UK and US

Medical Technology Innovation Scorecard

• The medical technology innovation ecosystem, long centered in the United States, is moving offshore. Innovators are going outside the United States to seek clinical data, new-product registration, and first revenue.

• US consumers aren’t always the first to benefit from medical technology and could eventually be last. Innovators already are going first to market in Europe and, by 2020, likely will move into emerging countries next.

• The nature of innovation is changing as developing nations become the leading markets for smaller, faster, more affordable devices that enable delivery of care anywhere at lower cost.

## Global Medical Device Manufacturers by FY 12 revenue in billions

<table>
<thead>
<tr>
<th>Rank</th>
<th>Company</th>
<th>Revenue (in billions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Johnson and Johnson</td>
<td>$27.43</td>
</tr>
<tr>
<td>2.</td>
<td>GE Healthcare</td>
<td>$18.29</td>
</tr>
<tr>
<td>3.</td>
<td>Siemens Healthcare</td>
<td>$17.54</td>
</tr>
<tr>
<td>4.</td>
<td>Medtronic</td>
<td>$16.20</td>
</tr>
<tr>
<td>5.</td>
<td>Baxter International</td>
<td>$14.20</td>
</tr>
</tbody>
</table>
Comparison between the US and EU for Approval of Medical Devices

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

<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>

* FDA denotes Food and Drug Administration.

Medical Device Innovation in the US

Practical value of local networks

• Exchange of ideas – basic science, engineering, clinical, health care providers

• Guidance of product development and evaluation

• Operationalizing clinical studies

• Adoption
Changes in Mortality After Massachusetts Health Care Reform

Medical Device Reimbursement

1. Linkage with clinical adoption
2. Changing framework with Accountable Care Act and ACOs
3. Patient centered outcomes; cost effectiveness
Premarket approval (PMA) commonly includes single arm studies
510K pathway and PMA supplements for medical devices often approved without clinical testing


Criticism of Medical Device Trials Performed for Approval or Clearance

• Trials not always required for new product approval
• Frequently not randomized, small, sometimes unblinded, use surrogate endpoints
Devices are Different from Drugs

- Small changes in drug design may lead to off-target effects
- Device iterations lead to changes in local effects
What is unique about devices?

• Iterative improvement based on mechanical design
• Failure mode may be predicted by modelling, bench testing, or detected in single arm safety studies
• Short product life cycle
Range of Appropriate Trial Designs

• Objective performance criteria for single arm study comparison (surgical heart valves)
• Blinded randomized trial with valid surrogate endpoints (renal denervation)
• Open label randomized trial compared with medical therapy with mortality endpoint (percutaneous heart valves)
Prosthetic Heart Valves: Objective Performance Criteria Versus Randomized Clinical Trial
Gary L. Grunkemeier, PhD, Ruyun Jin, MD, and Albert Starr, MD (Ann Thorac Surg 2006;82:776–80)
Objective Performance Goal to Facilitate Single Arm Studies

>5000 patients with 1 year follow up in RCT

Multivariate OPC with modelling of impact of known risk factors for restenosis as empirically observed
Range of appropriate trial designs

• Bare metal stent primary failure mode is known – incomplete expansion
• Small procedural single arm studies are sufficient for approval
### Applications for a Performance Standard from Historical Data in Drug-Eluting Stents

#### New Product
- To provide comparator data to determine the ST or TLF incidence or components with certainty relative to approved products
- Applicable where clinical impact of design is likely to be isolated to 1 year safety or efficacy elements

#### Label Expansion
- **APPROVED by FDA**
  - DM
  - Long lesions, Small vessels, ISR
- **NOT YET APPROVED by FDA**
  - NSTEMI, STEMI
  - Bifurcation, LM, 3 Vessel Stenting, SVG

#### Generalizability
- Age>75, Female Sex, Underrepresented Race and Ethnicity, Low EF, CKD

#### Post-market Requirements
- To provide comparator data for broadly inclusive population representing actual practice

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*NOT YET APPROVED by FDA*
Advantages of Single Arm Studies

• Allow device iteration
• Allow label expansion
• Allow more predictable timelines
• Reduce clinical trial barriers (randomization)
• Allow timely evaluation of new therapy
• Detect adverse effects earlier
• Strengthen the clinical trials enterprise
• Strike the right balance between premarket and postmarket data collection

“By addressing these priorities over the next two years, we hope to help medical device developers choose the U.S. as the country of first choice for their technologies. “

Goal: Improve the efficiency, consistency, and predictability of the IDE process

Targets:

IDE CYCLES
• By September 30, 2014, reduce the number of IDEs requiring more than two cycles to an appropriate full approval decision by 25 percent compared to FY 2013 performance.*
• By September 30, 2014, for disapproved IDEs, offer all sponsors a teleconference or in-person meeting to occur within 10 business days of the IDE decision.
• By June 30, 2015, reduce the number of IDEs requiring more than two cycles to an appropriate full approval decision by 50 percent compared to FY 2013 performance.*

TIME TO IDE APPROVAL
• By September 30, 2014, reduce the overall median time to appropriate full IDE approval by 25 percent compared to FY 2013 performance.*
• By June 30, 2015, reduce the overall median time to full appropriate IDE approval to 30 days.

* In FY 2013 (as of 12/11/2013), 45% of IDEs received a full approval decision within 2 cycles and median time to full IDE approval was 174 days.
Goal: Increase the number of early feasibility/first-in-human IDE studies submitted to FDA and conducted in the U.S.

Target:
EARLY FEASIBILITY/FIRST-IN-HUMAN IDE STUDIES
• By June 30, 2015, increase the number of early feasibility/first-in-human IDE studies submitted to each premarket Division compared to FY 2013 performance.

Dramatic variability in performance across sites

- ~45% of device studies fail to meet enrollment targets
- ~15% of sites across all studies fail to enroll a single subject; more than half under enroll
- Significant variability in contracting and IRB processes
Observational Studies

Randomized Trials

Large Simple Trials*

Dual Antiplatelet Therapy Study

March 2008 Statement of FDA Principles:

- A need for a large, pragmatic public health trial exploring the benefit of extending thienopyridine treatment beyond one year in patients treated with DES needs to be done expeditiously.

- FDA expects that the results of the study will change clinical practice and provide valuable new information in product labeling for DES.

Bram Zuckerman TCT 2008
Dual Antiplatelet Therapy Study

• Manufacturers of stents recognized that a definitive trial would necessarily be large
• The FDA request resulted in a unique public-private collaboration among 8 device and drug manufacturers
• RFP process via Advamed used to select academic trial leadership and execution
• First randomized trial in cardiology supported by multiple companies
• Largest randomized trial regarding medical devices
50% of patients continue on Dual Antiplatelet Therapy

50% of patients receive aspirin + placebo

18 mos.

12 mos.

Total 33 month patient evaluation including additional 3-month follow-up

DESn = 23,212

BMSn = 2,986

Completed enrollment

All patients on aspirin + open-label thienopyridine therapy for 12 months

1:1 Randomization at month 12

Mauri, Kereiakes et al AHJ December 2010

www.daptstudy.org www.clinicaltrials.gov – NCT00977938
Randomization completed 2012

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCRI DAPT-BMS</td>
<td>1689</td>
</tr>
<tr>
<td>HCRI DAPT-DES</td>
<td>5281</td>
</tr>
<tr>
<td>Cordis CYPRESS</td>
<td>804</td>
</tr>
<tr>
<td>Abbott Xience V USA</td>
<td>868</td>
</tr>
<tr>
<td>Boston Scientific Liberte PAS</td>
<td>2202</td>
</tr>
<tr>
<td>Medtronic EDUCATE</td>
<td>812</td>
</tr>
</tbody>
</table>

**DES n = 9,967**

**BMS n = 1,689**

Primary Endpoint Results Expected 2014
Dual Antiplatelet Therapy Study

- FDA – streamlining and active engagement in study execution

- Academia – simplified data collection, limited secondary data collection, but adjudication of key endpoint data

- Industry – cooperative interaction, willingness to support a study to advance clinical practice without competitive value

- Patients and physicians -- enthusiastic participation and enrollment
Innovative Medical Devices Require Innovative Clinical Trials

1. Application of methods to maximize efficiency and minimize bias – RCT, single arm studies, surrogate endpoints, missing data

2. Expediting enrollment and follow-up completeness – Large simple trials, risk based monitoring, registry based clinical trials

3. Improving trials infrastructure – contracting, reimbursement, IRB, site selection, patient/subject engagement

4. Consideration of patient-centered outcomes, and cost effectiveness
Medical Device Innovation in the US

- Efficiency, timeliness and reliability

Innovation pipeline
Adoption
Clinical trial and regulatory pathways
Reimbursement