Global Evidence and Reimbursement Strategies

Stephen Hull

September 2011
Presentation Overview

• The Outlook for Global Device Launches
• Company Reimbursement Structures
• Snapshot of Evidence Requirements
  – CE Marking
  – EU Evidence Requirements
  – Pricing and Payment
  – Japan’s Reimbursement Framework and Approach to Evidence
  – Brazil’s SUS Requirements
  – China’s Regional Reimbursement Structure
The US company dilemma: How to plan a global evidence dossier that is NOT US-centric?

• Internationally, reimbursement-related strategy and coordination is most needed around evidence and price

• Traditional approach: Efforts aimed mostly at the US market, driven mostly by regulatory requirements
  – EU-conducted studies often designed more to support FDA regulatory submissions than adoption in Europe itself
  – Overwhelming emphasis on single-arm studies
  – Comparative evidence often limited to non-inferiority studies

• Because regulatory demands for proven, clinical superiority have been low, most device companies are unprepared for such demands in reimbursement
Overview of Major Markets


Source: OECD, 2011
Overall, Europe has kept pace with Asia in terms of annual growth

Average Combined Annual Growth in Net Sales, 7 Leading US Medical Device Manufacturers, By Geographic Region, 2006 - 2009

<table>
<thead>
<tr>
<th>Region</th>
<th>2006-2009 Average Combined Growth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asia Pacific</td>
<td>11.9%</td>
</tr>
<tr>
<td>Europe</td>
<td>10.6%</td>
</tr>
<tr>
<td>ROW</td>
<td>7.3%</td>
</tr>
<tr>
<td>USA</td>
<td>5.2%</td>
</tr>
</tbody>
</table>

Combined company net sales figure data depicted in this graph: Medtronic, Boston Scientific*, Edwards Lifesciences, Zimmer, CR Bard, St. Jude Medical, Covidien.

Most launches follow a similar sequence, driven mostly by regulatory requirements, and market potential.

Map of Common Market Launch Sequencing:

1 Initial Markets
2 Second Tier Mkts
3 Third Tier Mkts
4 Fourth Tier Mkts
5 Late Adopting Mkts
How to divide the world?

<table>
<thead>
<tr>
<th>Regulatory Requirements</th>
<th>Evidence Benchmark Countries</th>
<th>Price Benchmark Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EU</td>
<td>EU-5</td>
</tr>
<tr>
<td></td>
<td>USA</td>
<td>USA</td>
</tr>
<tr>
<td></td>
<td>Japan</td>
<td>Australia</td>
</tr>
<tr>
<td></td>
<td>UK (NICE)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Germany (IQWIK)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>France (HAS)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>USA (Mult.)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nordics (Mult.)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Australia (PLAC)</td>
<td></td>
</tr>
</tbody>
</table>
An all-too common process…

**Product Commercialization Time Line**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 0</td>
<td>Year 1</td>
<td>Year 1-2</td>
<td>Year 2</td>
<td>Year 3</td>
<td>Year 4</td>
<td>Year 5??</td>
<td></td>
</tr>
<tr>
<td><strong>Market Focus:</strong></td>
<td><strong>USA</strong></td>
<td><strong>USA</strong></td>
<td><strong>EU/USA</strong></td>
<td><strong>USA</strong></td>
<td><strong>USA/EU</strong></td>
<td><strong>EU</strong></td>
<td><strong>Rest of World</strong></td>
</tr>
</tbody>
</table>

- Many companies consider OUS reimbursement at/near their launch in Europe
- The overall value proposition, economic value story, and price must then be “shoe horned” into diverse markets, in a very short time frame
There are several models of global reimbursement coordination.
Larger Companies may have a more centralized reimbursement function.

Central Corporate Reimbursement Structure

- Division Level Reimbursement Manager
  - Marketing Team
  - Clinical Trials Group
  - Regulatory Affairs

- Corporate-Level Reimbursement VP
  - US Reimbursement Mgr (Medicare)
  - US Reimbursement Mgr (Private)
  - Health Economist
  - Field Support/Modeling

- Country Level Reimbursement Manager
  - OUS Sales and Marketing
  - Downstream Marketing
Small companies typically rely on distributor resources and may need to directly manage reimbursement.

**Small Company Reimbursement Structure**

- Clinical Trials Group
- Marketing Team
- Regulatory Affairs
- Corporate Reimbursement Director
- OUS Distributors
## Key Steps in Global Evidence Planning

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>UNDERSTAND</td>
<td>Product Objectives and Their Implications</td>
</tr>
<tr>
<td>DESIGN</td>
<td>Evidence plan to meet markets selected <em>not vice versa</em></td>
</tr>
<tr>
<td>ASSESS</td>
<td>Timing required for reimbursement into marketing, sales strategies</td>
</tr>
<tr>
<td>INTEGRATE</td>
<td>Timing required for reimbursement into market launch plan, sales strategies</td>
</tr>
<tr>
<td>REASSESS</td>
<td>Product positioning and strategies in light of a fully integrated launch plan</td>
</tr>
<tr>
<td>COLLABORATE</td>
<td>Work closely with your OUS marketing, regulatory and sales teams</td>
</tr>
</tbody>
</table>
Europe's CE marking process focuses mostly on safety, non-inferiority

• Medical device directive (93/42/EEC)

• 27 of the EU member states have regulatory Competent Authorities

• 73 independent Notified Bodies perform actual dossier reviews (mandatory for Class III)
  – Expertise and experience is highly variable
  – Enforcement is highly variable

• Many have criticized the framework, particularly for high-risk devices

➡️ Evidence needed for CE marking is often insufficient to support reimbursement in EU countries
European reimbursement-related evidence requirements are becoming a global standard

<table>
<thead>
<tr>
<th>Country</th>
<th>Current Evidence Standard</th>
<th>International Impact of HTA Decisions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany (IQWiG)</td>
<td>Clinical utility/comparative effectiveness; NEW: drug cost effectiveness</td>
<td>• Often followed by Austria, Switzerland and Nordic Countries</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Most stringent clinical evidence standards</td>
</tr>
<tr>
<td>France (HAS)</td>
<td>Clinical utility, comparative effectiveness</td>
<td>• Ltd focus on clinical utility; model is being examined by some countries to control costs</td>
</tr>
<tr>
<td>UK (NICE)</td>
<td>Comprehensive reviews, including cost effectiveness</td>
<td>• Most transparent and studied international HTA body</td>
</tr>
<tr>
<td>Spain</td>
<td>Variable (7 regional HTA agencies)</td>
<td>• Benchmark leader for cost effectiveness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• A leading market for early adoption</td>
</tr>
</tbody>
</table>
EU HTA bodies apply various methods of rating evidence quality

France HAS, ASA I and II
Dossier Reviews, 2005 - 2007

<table>
<thead>
<tr>
<th>Year</th>
<th>ASA I</th>
<th>ASR I</th>
<th>ASA II</th>
<th>ASR II</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>1</td>
<td>0</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>2007</td>
<td>7</td>
<td>0</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>2006</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>2005</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td><strong>8</strong></td>
<td><strong>0</strong></td>
<td><strong>32</strong></td>
<td><strong>6</strong></td>
</tr>
</tbody>
</table>

Numbers of HAS Dossier Reviews with Each Rating

Jean-Michel Dubernard, President CNEDiMTS

- The French HAS rates dossiers on a scale of I to V (I=Highest Evidence Level)
- ASA is a rating applied based on clinical trial evidence; ASR reflects evidence of “real world” experience, often based on postmarket studies
Required post-market studies may become the norm for high risk devices

French HAS-Requested Post-Inscription Studies (2004-2010, N=170)

- In France, post-Inscription studies are now requested for most major innovations
- Product can not be reimbursed until the protocol is approved and implemented
- Study protocol review/acceptance takes >1 year in addition to the 2-3 year original dossier review of the HAS
Coverage Benchmark Example:
Endoscopy Pill Camera in France

• Description: Non-invasive alternative to conventional endoscopic and radiological procedures to help diagnose disorders of the small intestine
• European CE Mark, small intestine: May 2001
• US FDA Approval: August 2001, small intestine, adjunctive use; approved for diagnostic use July 2003
• Initial European Reimbursement: Portugal, Sweden, Denmark, Switzerland by Jan. 2004
• USA: CPT Code/Procedure Reimbursement, Jan. 2004
• 2006: CE Mark indications added for colon
• French reimbursement implemented under the LPPR for small intestine: Late 2008

➤ Issue in France: Lack of professional society/Sickness Fund agreement on procedure coding and payment
NICE Guidance in the UK

- Historically: NICE has not been a gatekeeper for medical device coverage
- NICE issues seven different types of guidance
- Technology appraisals have had the greatest impact, but are rarely applied to medical devices

<table>
<thead>
<tr>
<th>Type of Guidance</th>
<th>Number Published As of 10/2010</th>
<th>Includes CE Review?</th>
<th>Mandatory on the NHS?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interventional Procedure</td>
<td>319</td>
<td>No</td>
<td>Advisory</td>
</tr>
<tr>
<td>Clinical Guidelines</td>
<td>109</td>
<td>Yes</td>
<td>Advisory</td>
</tr>
<tr>
<td>Cancer Service Guidance</td>
<td>10</td>
<td>Yes</td>
<td>Advisory</td>
</tr>
<tr>
<td>Public Health Guidance</td>
<td>27</td>
<td>Yes</td>
<td>Advisory</td>
</tr>
<tr>
<td><strong>Technology Appraisals</strong></td>
<td><strong>199</strong></td>
<td><strong>Yes</strong></td>
<td><strong>Yes</strong></td>
</tr>
<tr>
<td>Diagnostic Technologies</td>
<td>0</td>
<td>TBD</td>
<td>Advisory</td>
</tr>
<tr>
<td>Medical Technologies Guidance</td>
<td>0</td>
<td>Yes</td>
<td>Advisory</td>
</tr>
</tbody>
</table>

Only ~16% of tech appraisals focus on medical devices!
NICE committees apply an evidence evaluation framework *in the context of each guideline*

<table>
<thead>
<tr>
<th>Evidence Level</th>
<th>Type of Evidence</th>
</tr>
</thead>
</table>
| 1++            | RCTs with *very low* risk of bias  
                | High Quality meta-analyses |
| 1+             | RCTs with *low* risk of bias  
                | Well conducted meta-analyses |
| 1-             | RCTs with *high risk* of bias  
                | Meta-analyses |
| 2++            | *High quality* systematic reviews of case-control or cohort studies with low risk of bias |
| 2+             | *Well conducted* case-control or cohort studies with low risk of bias |
| 2-             | Case-control or cohort studies with *high risk* of bias |
| 3              | Non-analytic studies (case reports, case series) |
| 4              | Expert opinion, formal consensus |

Case Study:
UK Guideline on Lower Urinary Tract Symptoms in Men

- Technology: Laser prostate ablation with shorter LOS, fewer post treatment side effects
- Relatively high price to other lasers, standard of care (TURP), but offsetting savings
- Laser therapy supported by >50 peer reviewed papers, but only 2-3 RCTs
- Most evidence rejected by the NICE Guideline Development Group
- RCT evidence by itself (on an early-generation product) proved insufficient clinical benefit
- Recommendation for use only in the context of a randomized controlled clinical trial
Key questions to address an EU evidence plan

Me-Too Technology

- What is the minimum threshold for entry of any competitor?
- Is it considered a high risk device?
- Will it substitute for products with stronger evidence profiles?
- Is coding and payment already established?
- What are the existing coverage restrictions? Are they brand-specific?

Novel Technology

- What is the risk/benefit profile of the technology?
- What is the evidence standard for similar benchmarks?
- How soon is a coverage review/HTA likely to occur?
- Will it have a positive cost-effectiveness profile in each target market?
- What are the evidence requirements of each key stakeholder?
To understand pricing, companies need to assess the currencies of healthcare...
Cost offsets of innovations are typically far lower in Europe than in the USA

<table>
<thead>
<tr>
<th>Technology</th>
<th>Procedure Codes</th>
<th>DRG</th>
<th>Tariff €</th>
<th>2009 Cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric Bypass</td>
<td>5-445.**</td>
<td>K04A</td>
<td>7,759</td>
<td>5,014 (65.4%)</td>
</tr>
<tr>
<td>Gastric Sleeve</td>
<td>5-434.5*</td>
<td>K04A</td>
<td>7,759</td>
<td>1,537 (20.0%)</td>
</tr>
<tr>
<td>Gastric Banding</td>
<td>5-448.c*</td>
<td>K04B</td>
<td>5,767</td>
<td>983 (12.8%)</td>
</tr>
<tr>
<td>Bilio-Pancreatic Diversion</td>
<td>5-434.3* / 4*</td>
<td>K04A</td>
<td>7,759</td>
<td>112 (1.5%)</td>
</tr>
<tr>
<td>Vertical Gastroplasty</td>
<td>5-448.a*</td>
<td>K04A</td>
<td>7,759</td>
<td>25 (0.3%)</td>
</tr>
</tbody>
</table>

- New entrant technologies will need to compete with Gastric Bypass in terms of cost and outcomes
- Patient preference and convenience are not sufficient to alter German coverage guidelines
Companies also must assess local price competition

Medived (India), Stellar
Single Chamber Pacemaker
India Price: ~$2,000

Medtronic EnRythm
Dual Chamber with Managed Ventricular Pacing
Approx India Price: ~$10,000
Other global markets are not necessarily “easier” in terms of evidence requirements

- **Brazil** is a leading high growth market
- Device sales are believed to have grown 50% over the past 4 years.
- Brazil device production is second largest among emerging markets, behind China.
- Public reimbursement covers 80% of the population, but accounts for only 32% of device consumption.
- Has an extensive sector of private insurers, managed care organizations
Typical Technology Adoption Pathways in Brazil

**Providers: Initial Demand**
- State and Municipal Hospitals
- Federal Hospitals
- Military, Veterans, etc
- HMOs
- Private Hospitals
- Private Clinics

**Review/Standards**
- Physician Society Support

**Coding and Payment**
- SUS Technology Listings (CITEC)
- CPHBM Procedure Fee Schedule (AMB)
- TUSS National Nomenclature (ANS)
- ROL Listing (ANS)

Adoption
Clinical evaluation and adoption in Brazil can require 6 years or more for novel technologies

**Private Sector Pathway**

- Ltd introduction in large, high volume private centres
- Review and approval by specialty societies
- Applications/Approval for CBHPM, TUSS procedure code + Payment
- Application to ANS for ROL
- Product listing
- Years 5 - 6: ANS listing of Product in ROL (2 year cycle)

**Public Sector Pathway**

- Introduction on a Pilot basis in major Public research hospitals
- HTA evaluation and endorsement by University Hospital
- Targeted sales among state and municipal hospitals
- Limited adoption in 10 Brazilian states
- Design and conduct of health economic study
- Years 6 - 8

- Submission of SUS dossier to CITEC;
- Clinical Review by DECIT
- Economic Review by Insurance Board
- CITEC Determination
- SUS Publication by Ministry of Health
Japan also applies unique requirements for evidence

- **Japan** is the second largest medical device market, but known for long delays due to its regulatory process.

- Reimbursement of most hospital devices is governed by the “DIMM” functional category system.

- Companies must understand the nuances of seeking a new functional category.

- Related evidence strategies often will involve Japanese studies.

- DIMM prices are capped at 1.5 times the Foreign Average Price (FAP) of four countries (USA, France, Germany, UK).
Functional Category System

- Japan has five major groupings for device reimbursement
  - A1: products that are covered within physician fees
  - A2: a supplemental physician fee is provided
    - Usually devices that are adjunctive to surgical tools or capital equipment
  - B: Separate fee provided for the medical device (DIMM)
  - C1: Novel devices with existing physician procedures
  - C2: Breakthrough devices with novel physician procedures
- Most major devices are assigned an existing “B” category
• C1 approvals have grown in recent years
• Price premiums can range from 0 to 30% for products with existing comparators (supplemental premium)
### Examples of Recent Orthopedic C1 Approvals

<table>
<thead>
<tr>
<th>Name of product</th>
<th>Description</th>
<th>Class</th>
<th>Calculation Method</th>
<th>New Price (¥)</th>
<th>Addition</th>
<th>Supplier</th>
<th>C1 rationale(new functional category)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blend-E</td>
<td>Patella</td>
<td>III</td>
<td>Equiv.</td>
<td>56,000</td>
<td>10%</td>
<td>Nakashima Medical</td>
<td>Less risk of replacement due to high resistance to abrasion</td>
</tr>
<tr>
<td>Blend-E</td>
<td>Tibial bone Insert/Polyethylene Plate</td>
<td>III</td>
<td>Equiv.</td>
<td>84,300</td>
<td>10%</td>
<td>Nakashima Medical</td>
<td>Less risk of replacement due to high resistance to abrasion</td>
</tr>
<tr>
<td>X3 Acetabular Liner</td>
<td>Acetabular Liner</td>
<td>III</td>
<td>Equiv.</td>
<td>77,500</td>
<td>10%</td>
<td>Stryker</td>
<td>Less risk of replacement due to high resistance to abrasion</td>
</tr>
</tbody>
</table>
Common Evidence Hurdles for C1 Status

- US, European regulatory approval and acceptance
- Published, peer reviewed articles in support
- Japanese publications and/or studies
- Strong evidence of significant improvements in structure, purpose, medical effects and efficacy
1. Application for Reimbursement
2. Hearing
3. Review, Expert Review
4. Listing Decision
5. Notification
6. Public Announcement and Listing in the Functional Category System
China has a predominantly regional system of reimbursement
Overview of the Chinese Market

- Chinese device market estimated at ~$15 bn
- Estimated 15% annual growth – market forecasted to double by 2014, to $28 bn
  - ~3,000 domestic producers account for roughly 20% to 40% of consumption
- Ranks sixth globally in market size
- Largely a hospital-dominated marketplace
- China has 9,000 hospitals
- Current efforts are focused on developing rural hospital, clinic infrastructure and capacity
China’s Highly Regionalized Markets

HC expenses per capita in 2007 (US$)

- $X < 60$
- $60 \leq X < 80$
- $80 \leq X < 95$
- $X \geq 95$
In total, China has ~9,000 Hospitals

Numbers of Chinese Hospitals, By Size

- Class I (Local Hospitals)
- Class II (100-500 beds)
- Class III (>500 Beds)
Healthcare Coverage in China

• Different national insurance programs for urban and rural populations

• Distribution of provider resources is a major challenge
  – Approximately 70% of the Chinese population lives outside of the major coastal urban areas
  – Coverage of rural populations has traditionally been low

• Provincial health authorities have discretion in listing products on local lists

• Negotiation of pricing is key; listing may not be appropriate for small niche products
Agencies Involved in Reimbursement

• Ministry of Health
  – Administers rural health insurance system
  – Administers public hospitals
  – Bidding/tendering system

• Ministry of Labor and Social Security
  – Administers urban health insurance system

• Provincial Health and Pricing Bureaus
  – Review regional purchases of large capital equipment items
  – Establish reimbursement rates (ceiling prices) for devices and certain IVD tests

• The National Development and Reform Commission (NDRC): lead role in proposals related to Healthcare Reform
China is attempting to address the inequities of cash pay markets

• 2003: Shanghai, price ceiling program
  – Based on retail and import prices
  – Compromise: agreed to accept recommended retail prices

• 2005: MOH Eight City Tendering Program (Orthopedic and Cardiac)
  – Objective to lower prices 30 to 50%
  – Involved a working expert committee and an independent “tendering company”

• 2006 - Present: NDRC Pricing Proposals
  – Targeting manufacturer price, country of origin price and distributor mark-ups
  – Fixes allowable profit for existing and new products
  – Caps premium that can be charged for new products
  – Raises numerous industry concerns; not yet implemented
Key Points for Approaching the Chinese Market

• Local value proposition is always a key factor for success
• Economics, and profit potential for hospitals, should be factored in
• Distribution rights should be closely guarded and assigned on a regional basis only
• Local fee schedule reimbursement can be important – but may not be needed for all products
• International company support may be needed around price strategy and government tendering
• National and regional reference pricing proposals pose the greatest threats
Strategic Steps to Prepare for Foreign Markets

• Understand market opportunities and optimal sequencing
  – What are the payment system parameters?

• Coverage, coding and payment processes and related time lines

• “Definitional” problems:
  – Are you defining and positioning your product to follow a successful precedent?
  – Does the related procedure fit into an existing code?

• Understand the evidence needed to support premium payment and a positive HTA review (Benchmarks, HTA guidances)

• Does the economic premise of your product hold up in a foreign context?
About Hull Associates

- Proudly Serving Medical Device and Diagnostic Companies in the following OUS Markets:

<table>
<thead>
<tr>
<th>WESTERN EUROPE</th>
<th>NORTHERN AND EASTERN EUROPE</th>
<th>AMERICAs</th>
<th>ASIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>Sweden</td>
<td>Canada</td>
<td>Australia</td>
</tr>
<tr>
<td>France</td>
<td>Denmark</td>
<td>Chile</td>
<td>New Zealand</td>
</tr>
<tr>
<td>Germany</td>
<td>Norway</td>
<td>Brazil</td>
<td>China</td>
</tr>
<tr>
<td>Italy</td>
<td>Finland</td>
<td></td>
<td>Japan</td>
</tr>
<tr>
<td>Netherlands</td>
<td>Poland</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spain</td>
<td>Czech Republic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>United Kingdom</td>
<td>Russia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
THANK YOU!

100 Ledgewood Place, Suite 204, Rockland, Massachusetts 02370
EL: 001.781.982.8600
FAX: 001.781.982.8601
WEB: www.hullassociates.com
EMAIL: inquiries@hullassociates.com