International Regulatory Harmonization and Medical Technology Innovation

Some personal thoughts

Tokyo University
Tokyo, 13 April 2012

M. Gropp; Medtronic, Inc., Minneapolis, USA
Overview

• Overview of medical technology lifecycle and innovation

• What is regulatory harmonization?

• Is there a business case for international regulatory harmonization?
  • Conceptual models

• Brief overview of Global Harmonization Task Force (GHTF) and other international medical device regulatory harmonization initiatives

• Personal views
Background trends

- Worldwide population continues to grow
- Infant mortality continues to decrease
- Life expectancy increases
- Aging populations
- Shift of burden of disease from communicable to non-communicable conditions
- Growing policy focus on healthy aging
- Reduction in poverty, but not evenly distributed
Background trends

- Challenges of fiscal sustainability of current social models
- Changing models of health care delivery
- Growing public access to information on health
- Growing public awareness of medical technology
- Rapid expansion of access to enabling technologies such as mobile telephones and Internet
- Growing pressure to make “appropriate and affordable” medical technologies more widely available and accessible
Thesis

• Access to safe and effective health care technologies of high quality is an important contributor to economic and social progress in countries at all stages of development
Thesis

• Enlightened, appropriate, judiciously applied regulation of health care products is a public good
  • Protection and promotion of public health
  • Good governance
  • Expectation of citizens
  • Public confidence in products
  • Essential in protecting and advancing public health, promoting innovation, and facilitating international trade
**Thesis**

- Regulation and regulatory practice are determinants of successful life sciences innovation
  - Regulators are on the life sciences “critical path”
  - The efficiency and effectiveness of a regulatory authority in fulfilling its public health mandate is therefore critical to achievement of desired life sciences outcomes
  - Importance of international regulatory harmonization and use of international standards in contributing to life sciences innovation
Thesis

• Growing public discussion about needs in less developed countries for “available, accessible, appropriate, and affordable” medical technologies.

• There is a concomitant need for appropriate and affordable regulation
Regulatory harmonization

Simple in concept …

“The establishment, recognition and application of common standards and regulatory measures”

(World Trade Organization)

… more difficult in execution
Definitions – GHTF

“The objective of the Global Harmonization Task Force (GHTF) is to encourage convergence at the global level in the evolution of regulatory systems for medical devices in order to facilitate trade while preserving the right of participating members to address the protection of public health by those regulatory means considered the most suitable. ... 

Source: Global Harmonization Task Force (GHTF); The GHTF Regulatory Model; GHTF/AHWG-GRM/N1R13:2011; April 2011
Definitions – GHTF

... The purpose of such guidance is to provide a regulatory framework that would help eliminate differences between jurisdictions, decrease the cost of gaining regulatory compliance, allow patients, users, and others earlier access to new technologies and treatments and maintain a safe and effective level of healthcare over time through efficient post-market surveillance.”

Source: Global Harmonization Task Force (GHTF); The GHTF Regulatory Model; GHTF/AHWG-GRM/N1R13:2011; April 2011
Definitions – IMDRF

Regulatory convergence: “… a voluntary process whereby the regulatory requirements and approaches across regions become more similar or aligned over time as a result of the adoption of the same technical documents, standards and scientific principles (harmonization) and similar regulatory practices and procedures.

The process of convergence represents an important form of regulatory cooperation which in turn makes possible additional, enhanced forms of cooperation and collaboration between regulatory authorities.”

Source: IAPEC Life Sciences Innovation Forum; International Medical Device Regulators Forum (IMDRF); Terms of Reference, March 2012
Definitions

• Regulatory harmonization: Progressive voluntary convergence in technical regulatory requirements

• Not:
  • International regulation
  • Standardization
  • Mutual recognition
  • ‘Approved once, accepted everywhere’
  • Verbatim adoption of same text in laws, regulation, and guidance
Medical technology innovation cycle

Breakthrough innovation

Incremental innovation

Short product life cycles (~18-24 months)
Medical device technology life cycle

Source: United States Food and Drug Administration, Center for Devices and Radiological Health; Strategic Plan 2001
Medical device technology life cycle

- Concept
- Product Realisation
- Placing on the Market
- Product Use
- End of Product Life
- Destruction, disposal, manufacture, use of parts

Feedback into new design or manufacturing corrections or improvements based on market experience.

Design inputs leading to new concept or newer version.

Source: Global Harmonization Task Force: The GHTF Regulatory Model: GHTF/AHWG-GRM/N1R13:2011 [modified] Medtech_Reg_Harmonisation_and_Innovation_Tokyo_Univ_13Apr12_Gropp.ppt; All rights reserved
Medical device technology life cycle

Regulatory pre- and post-market controls
What drives the medical device technology life cycle?
What drives the medical device technology life cycle?

Unmet clinical need

Idea

Financial capital

any form of asset capable of being employed in the production of more assets of value
What drives the medical device technology life cycle?

Unmet clinical need

Idea

Financial capital

Intellectual capital

Image source: Google Images: Reiki Capital, Inc. (http://intellectualcapital.ca)
What drives the medical device technology life cycle?

Unmet clinical need

Idea

Intellectual capital

Financial capital

ITAMI Hiroyuki
Graduate School of Management of Science and Technology, Tokyo University of Science
What drives the medical device technology life cycle?

Unmet clinical need

Idea

Intellectual capital

Financial capital

Source: Asia-Pacific Intellectual Capital Centre; www.apicc.asia

Image source: Google Images: Reiki Capital, Inc. (http://intellectualcapital.ca)

Image source: Google Images: CapB Infotek; http://www.capbinfoтек.com)
What drives the medical device technology life cycle?

- Unmet clinical need
- Idea
- Financial capital
- Intellectual capital
- Value
What drives the medical device technology life cycle?

Unmet clinical need

Idea

Intellectual capital

Financial capital

?
What drives the medical device technology life cycle?

Unmet clinical need

Idea

Financial capital

Intellectual capital

Return on investment
What drives the medical device technology life cycle?

Unmet clinical need

Idea

Intellectual capital

Financial capital

Return on investment

Risks and costs
- Risks (incl. regulatory risk)
- Transparency
- Predictability

Clinical adoption

Commercial success

Government policies
- Favorable investment ‘ecosystem’
- Least unfavorable burdens
What drives the medical device technology life cycle?

Unmet clinical need

Idea

Intellectual capital

Financial capital

Return on investment

Concept

Product realization

Placing on the market

Product use

End of product life
What drives the medical device technology life cycle?

- Unmet clinical need
- Idea
- Intellectual capital
- Financial capital
- Return on investment

CONCEPT ➔ PRODUCT REALIZATION ➔ PLACING ON THE MARKET ➔ PRODUCT USE ➔ END OF PRODUCT LIFE
Medical device technology life cycle

Source: United States Food and Drug Administration, Center for Devices and Radiological Health; Strategic Plan 2001
Medtech_Reg_Harmonisation_and_Innovation_Tokyo_Univ_13Apr12_Gropp.ppt; All rights reserved
Consider … Unmet clinical needs

- USA, Japan, Germany, France, and Italy account for 13% of world population and 76% of global medical technology use

- The five most populous countries in the world – China, India, Indonesia, Brazil, and Pakistan – account for nearly 50% of world population, but only 4-5% of medical device use in 2009

- In three key developing markets – China, India, and Brazil – the 2004-2009 compound annual growth rate in medical technology use were 18.8%, 17.8%, and 12.3% respectively

Source: US Department of Commerce; National Export Initiative; 2011
## Investment in medical technology R&D

### Table 2: Research and development expenditures of leading medical device manufacturers, as a percentage of company revenue for 2008

<table>
<thead>
<tr>
<th>Company</th>
<th>Currency</th>
<th>Revenue (billions)</th>
<th>R&amp;D investment (billions)</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boston Scientific</td>
<td>US$</td>
<td>8.4</td>
<td>1</td>
<td>11.9</td>
</tr>
<tr>
<td>Medtronic</td>
<td>US$</td>
<td>13.5</td>
<td>1.3</td>
<td>9.4</td>
</tr>
<tr>
<td>Abbott</td>
<td>US$</td>
<td>29.5</td>
<td>2.7</td>
<td>9.2</td>
</tr>
<tr>
<td>Siemens Healthcare</td>
<td>€</td>
<td>11.2</td>
<td>1</td>
<td>9.0</td>
</tr>
<tr>
<td>Philips Healthcare</td>
<td>€</td>
<td>7.6</td>
<td>0.6</td>
<td>8.4</td>
</tr>
<tr>
<td>Johnson &amp; Johnson (Medical Devices and Diagnostics)</td>
<td>US$</td>
<td>23.1</td>
<td>1.9</td>
<td>8.0</td>
</tr>
<tr>
<td>Baxter</td>
<td>€</td>
<td>12.3</td>
<td>0.9</td>
<td>7.1</td>
</tr>
<tr>
<td>GE Healthcare</td>
<td>US$</td>
<td>17.3</td>
<td>1</td>
<td>5.8</td>
</tr>
<tr>
<td>Becton, Dickinson and Company</td>
<td>US$</td>
<td>7.1</td>
<td>0.4</td>
<td>5.6</td>
</tr>
<tr>
<td>Stryker</td>
<td>US$</td>
<td>6.7</td>
<td>0.4</td>
<td>5.5</td>
</tr>
<tr>
<td>Zimmer</td>
<td>US$</td>
<td>4.1</td>
<td>0.2</td>
<td>4.7</td>
</tr>
<tr>
<td>Covidien</td>
<td>US$</td>
<td>9.9</td>
<td>0.3</td>
<td>3.4</td>
</tr>
<tr>
<td>Cardinal Health</td>
<td>US$</td>
<td>4.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: No data from Japan-based manufacturers

Average ≈ 7.3%

---

Source: World Health Organization, *Landscape analysis of barriers to developing or adapting technologies for global health purposes*: 2010

Medtech_Reg_Harmonisation_and_Innovation_Tokyo_Univ_13Apr12_Gropp.ppt; All rights reserved
### Investment in medical technology R&D

**Table 2: Research and development expenditures of leading medical device manufacturers, as a percentage of company revenue for 2008**

<table>
<thead>
<tr>
<th>Company</th>
<th>Currency</th>
<th>Revenue (billions)</th>
<th>R&amp;D investment (billions)</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boston Scientific</td>
<td>US$</td>
<td>8.4</td>
<td>1</td>
<td>11.9</td>
</tr>
<tr>
<td>Medtronic</td>
<td>US$</td>
<td>13.5</td>
<td>1.3</td>
<td>9.4</td>
</tr>
<tr>
<td>Abbott</td>
<td>US$</td>
<td>29.5</td>
<td>2.7</td>
<td>9.2</td>
</tr>
<tr>
<td>Siemens Healthcare</td>
<td>€</td>
<td>11.2</td>
<td>1</td>
<td>9.0</td>
</tr>
<tr>
<td>Philips Healthcare</td>
<td>€</td>
<td>7.6</td>
<td>0.6</td>
<td>8.4</td>
</tr>
<tr>
<td>Johnson &amp; Johnson (Medical Devices and Diagnostics)</td>
<td>US$</td>
<td>23.1</td>
<td>1.9</td>
<td>8.0</td>
</tr>
<tr>
<td>Baxter</td>
<td>€</td>
<td>12.3</td>
<td>0.9</td>
<td>7.1</td>
</tr>
<tr>
<td>GE Healthcare</td>
<td>US$</td>
<td>17.3</td>
<td>1</td>
<td>5.8</td>
</tr>
<tr>
<td>Becton, Dickinson and Company</td>
<td>US$</td>
<td>7.1</td>
<td>0.4</td>
<td>5.6</td>
</tr>
<tr>
<td>Stryker</td>
<td>US$</td>
<td>6.7</td>
<td>0.4</td>
<td>5.5</td>
</tr>
<tr>
<td>Zimmer</td>
<td>US$</td>
<td>4.1</td>
<td>0.2</td>
<td>4.7</td>
</tr>
<tr>
<td>Covidien</td>
<td>US$</td>
<td>9.9</td>
<td>0.3</td>
<td>3.4</td>
</tr>
<tr>
<td>Cardinal Health</td>
<td>US$</td>
<td>4.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Note:** No data from Japan-based manufacturers

Total ≈ US$11.7 bn  
≈ ¥ 958 bn

---

*Source: Publicly available company annual reports, 2008 (8-21).*
Unmet clinical and public health needs

“The Global Forum for Health Research estimated that US$160.3 billion was spent globally on health research and development in 2005.

Of the 97% spent by high-income countries, most was used to generate products, processes, and services for their own health care markets.

The remaining 3% was spent by low- and middle-income countries. …

Source: Landscape analysis: of barriers to developing or adapting technologies for global health purposes; Global Initiative on Health Technologies; Department of Essential Health Technologies; World Health Organization, Geneva; 2010
Global access to medical technologies

“... there is a clear focus on developing high technology solutions for high income countries and subsequently a lack of innovative solutions for low- and middle income countries.”

Source: Landscape analysis: of barriers to developing or adapting technologies for global health purposes; Global Initiative on Health Technologies; Department of Essential Health Technologies; World Health Organization, Geneva; 2010
Global access to medical technologies

“There are many steps along the path to successfully devising and achieving an agenda to improve global access to appropriate medical devices, and the main components involved are the crucial 4 As –

Availability, Accessibility, Appropriateness, and Affordability”

Source: Medical devices: Managing the mismatch: An outcome of the Priority Medical Devices Project; World Health Organization, Geneva; 2010
Global access to medical technologies

Frugal healing

Inexpensive Asian innovation will transform the market for medical devices

Source: The Economist; 22 January 2011
Where will new medical technology come from?

“Innovation is often defined as something that is new, creative and radically different from what has gone before. PwC defines innovation as value-creating novelty. A new idea becomes innovative only when it creates value. Are people willing to pay for it?”

Source: PwC: Medical technology innovation scorecard: The race for global leadership; 2010
What drives the medical device technology life cycle?

Unmet clinical need

Idea

Financial capital

Cost to clear/approve a medical device

- $31,000,000* on average to bring a 510(k) product from concept through clearance
  - With $24,000,000 spent on FDA-dependent/related aspects
  ≈ ¥2.532 bn

- $94,000,000* on average to bring a PMA product from concept through approval
  - With $75,000,000 spent on FDA-dependent/related aspects
  ≈ ¥7.679 bn

*Does not include reimbursement approval and sales/marketing costs.

Source: Makower, J., Meer, A.; FDA impact on US medical technology innovation (A survey of over 200 med tech companies); Nov. 2010
What drives the medical device technology life cycle?

- Unmet clinical need
- Idea
- Financial capital

Cost to clear/approve a medical device

- $31,000,000* on average to bring a 510(k) product from concept through clearance
  - With $24,000,000 spent on FDA-dependent/related aspects
  - ≈ ¥1.964 bn (≈ 77%)

- $94,000,000* on average to bring a PMA product from concept through approval
  - With $75,000,000 spent on FDA-dependent/related aspects
  - ≈ ¥7.679 bn (80%)

*Does not include reimbursement approval and sales/marketing costs.

Source: Makower, J., Meer, A., FDA impact on US medical technology innovation (A survey of over 200 med tech companies), Nov. 2010
Shifting demand for medical technology

- Where will growth come from for established medical technology suppliers?
- Can new small and medium sized enterprises afford the costs of regulatory compliance?
- What is the incremental sales revenue from each additional country?
- What are the incremental costs of compliance in each additional country?
- How do costs affect investment in R&D?
Business case – Innovators

Hypothetical example: US-based manufacturer

Incremental costs of compliance

Costs of compliance

Country/Region

USA  EU  Japan  Canada  Australia  A  B  C  D  E  F

0  10  20  30  40  50  60  70  80  90  100
Business case – Innovators

What forces would determine the shape of this curve in other markets?

Costs of compliance

Country/Region

Hypothetical example: US-based manufacturer
Regulation of medical devices

• ~ 85 countries regulate medical devices today

• More are considering regulation

• Default is often pharmaceutical regulation

• World Health Organization (WHO) increasingly asked by Member States for advice on medical device regulation, assessment, and procurement
Business case – Innovators

Hypothetical example: US-based manufacturer

Incremental costs of compliance
Business case

• How do incremental sales revenues compare to incremental costs of compliance in each new market?

• Can suppliers spread costs of compliance across more markets?
## Business case

<table>
<thead>
<tr>
<th>Incremental sales revenue</th>
<th>Incremental costs of compliance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Can regulatory harmonization help drive creation of more attractive markets for investment? … and does that help bring public health benefits to more people and more societies?

Incremental sales revenue

- High
- Low

Incremental costs of compliance

- High
- Low

Attractive investment

Possibly attractive investment

Unattractive investment
Can regulatory harmonization help drive creation of more attractive markets for investment? … and does that help bring public health benefits to more people and more societies?
Do high costs of compliance with regulatory requirements in large established markets compete for and “squeeze out” investment in innovative technologies needed in less developed countries?
Business case

- Does regulatory harmonization benefit only “rich country” suppliers?
  - ↑ Public confidence (at home and abroad)
  - ↑ Ability to enter larger markets
  - ↑ Facilitation of trade
Business case – Regulators

Incremental costs of assessing and enforcing compliance

Country/Region

Hypothetical example: US-based regulator
Business case – Regulators

Regulatory harmonization in support of public health

- Most countries cannot afford regulatory systems of complexity and expense of advanced economies
- Helps develop and disseminate regulatory knowledge and best practices
- Promotes wider sharing of expertise
- Contributes to regulatory risk assessment and management
- Recognizes global nature of supply chains
Medical device regulatory harmonization forums

Global Harmonization Task Force
• Began in 1992
• Voluntary forum
• Regulators and industry
• Five Founding Members:
  Australia, Canada, EU, Japan, USA
• Regional members
  AHWP
• Liaison with ISO, WHO
• Primary source of harmonized guidance documents
• www.ghtf.org
Medical device regulatory harmonization forums

Asian Harmonization Working Party
- Began in 1998
- Voluntary forum
- Regulators and industry
- 20 members
- Liaison with GHTF
- Developer of harmonized regional guidance documents based on GHTF
  - [www.ahwp.info](http://www.ahwp.info)
International regulatory harmonization and medical technology innovation

Medical device regulatory harmonization forums

Asia-Pacific Economic Coordination Life Sciences Innovation Forum
- Began in 2002
- Mandate from APEC Leaders
- 21 member economies
- Government, industry, academia
- \url{http://www.apec.org/apec/apec_groups/other_apec_groups/life_sciences.html}
- APEC Harmonization Center (Seoul) formed in 2009
- \url{http://www.apec-ahc.org/}
- Regulatory Harmonization Steering Committee
Medical device regulatory harmonization forums

Association of Southeast Asian Nations (ASEAN) Medical Device Product Working Group
- Formed in 2004
- Mandate from ASEAN Ministers
- 10 member economies
- Government, industry
- Working to establish ASEAN Free Trade Area
- Medical device directive to take effect in 2015 (based on GHTF guidance)

http://www.accsq-mdpwg.org/
PAHO resolution

“Resolves: …

2. To support the proposal for form an ad hoc group to promote and facilitate the medical devices harmonization processes in the Americas

3. To urge the Member States to:
   (a) develop and strengthen their programs for the regulation of medical devices;
   (b) promote and support the participation of their regulatory authorities the general meetings of the [GHTF] and those of its four study groups, while promoting the use of GHTF documents for the regulation of medical devices …”

Medical device regulatory harmonization forums

International Medical Device Regulators Forum (IMDRF)
- Formed in 2011
- Regulators from Australia, Canada, EU, Japan, USA, Brazil, China*, Russia*, and possibly India
- World Health Organization observer
- Government only (some invited industry participation in some working groups)

* currently observers, pending confirmation
Medical device regulatory harmonization forums

International Medical Device Regulators Forum (IMDRF)

• “… to strategically accelerate international medical device regulatory convergence to promote an efficient and effective regulatory model for medical devices that is responsive to emerging challenges in the sector while protecting and maximizing public health and safety”
Medical device regulatory harmonization forums

- GHTF
- AHWP
- PAHO/LAHWP
- APEC Funded Training Seminars
- ACCSQ MDWPG (ASEAN)
- APEC LSIF RHSC
- IMDRF

International regulatory harmonization and medical technology innovation
WHO guidance

“With the exception of commercial activities including advertising and sales, …, the GHTF Study Groups are involved in all aspects that have direct impact on the safety and performance of medical devices.

Therefore, recommendations from the GHTF [study groups] can provide excellent reference or guidance for countries that are establishing medical device regulation programmes.”

Source: Medical device regulations: Global overview and guiding principles; World Health Organization, Geneva; 2003
International regulatory harmonization and medical technology innovation

Conceptual qualitative overview of current national medical device regulatory systems – Trends

Harmonization (GHTF/AHWP)

High

Low

Comprehensiveness

High

Low

Hong Kong SAR

Pakistan

South Africa

India

Bangladesh

Argentina

Mexico

Colombia

Brazil

China

USA

Japan

Korea

Chinese Taipei

Saudi Arabia

EU, EFTA

Singapore

Canada

New Zealand

Notes:
• Position in clusters not necessarily significant
• Subjective assessment of many variables
• Variables not weighted
• Not all countries that regulate medical devices shown
• Some countries moving faster than others and with different paths

Notes:
Observations and conclusions

• Interconnected world → interconnected risks → interconnected responses
  • Public health
  • Finance

• Trend toward more regional/multilateral economic integration and free trade agreements
  • Requires technical harmonization
Observations and conclusions

• Growing regulator ↔ regulator cooperation and information exchange

• Harmonization forums in other health sectors

• GHTF guidance forms substantial basis for progressive harmonization of requirements
  Requirements → evidence → evaluation criteria (?) → decisions (?)

• GHTF regulatory model well-advanced, but can be further developed
Observations and conclusions

• Harmonization encourages conformity assessment bodies to invest in services offered to clients in multiple markets

• Technical barriers to trade are also barriers to patient access

• International regulatory harmonization facilitates trade

• Harmonization helps push quality and compliance up the supply chain
Observations and conclusions

• Regulatory harmonization represents a pooling and sharing of intellectual capital

• Regulatory harmonization frees resources for investment in R&D and innovation to address unmet clinical and public health needs
Questions?