Japan is Back: Recent Developments in Japan, and Implications for Asian Markets”

William Hall

14 November 2013
Key Hot Topic For Asia Pacific

“For foreign drug companies, it’s (Japan) the best market in the world right now”

Ira Wolf, Japan Representative, PhRMA

(Pharmaceutical Research and Manufacturers of America

The Economist, February 23, 2013
Some Other Hot Topics From Japan

- Good prices for innovative drugs
- Growth of generics and price reductions in long-listed drugs
- Rapidly aging society
- Genetic, aging, and cultural impacts on drug treatment practices
- Rapid improvement in review and approval times
- Government support for healthcare industry
- Disruptive technologies -- iPS stem cells, regenerative medicine, robotics, nano motors
- Disruptive impact of digital health
- Aging and bio-ethics
GDP Top 15 Countries 2012

Source: World Bank: National Accounts Data, and OECD National Accounts data files World Development Indicators 2013
GDP Comparison of Japan’s regions with some countries

Abenomics: Three Arrows

**First Arrow**
Dispel the deflation mindset
Aggressive monetary policy

**Second Arrow**
Ignite the dampened economy
Flexible fiscal policy

**Third Arrow**
Restore the confidence of companies and people, and change "expectation" into "action"
New growth strategy
"Japan Revitalization Strategy"

Revival of Japanese economy
Exit from deflation

The administration aims to achieve an average 3% nominal GDP growth and 2% real GDP growth over the next ten years. This is expected to increase the per capita nominal gross national income (GNI) by no less than 1.5 million yen in ten years.
Three Action Plans of Japan Revitalization Strategy

- **Plan for the Revitalization of Japanese Industry**
  - Strengthen industry base

- **Strategic Market Creation Plan**
  - Turn challenges into new markets

- **Strategy of Global Outreach**
  - Tap into expanding global markets
Plan for the Revitalization of Japanese Industry

1. Accelerating structural reform program (Speed up the restructuring of industries)
2. Reform the employment system and reinforce human resource capabilities
3. Promote scientific and technological innovations
4. Become the world’s leading IT society
5. Further strengthen Japan’s international competitiveness as a business hub
6. Innovate SMEs and small businesses
1. Extend the nation's healthy life expectancy

2. Realize clean and economical energy demand and supply

3. Develop next-generation safe, convenient and economical infrastructure

4. Build regional communities that use their unique local resources to appeal to the world
1. Establish strategic commercial relations and promote economic partnerships

2. Strategic initiatives to capture global markets

3. Develop funding and human resource bases that support the growth of Japan
Aging Society: Some Recent Statistics
(Keiro no Hi September 16, 2013)

25% of total population are 65+ (N=31,860,000)

70+ age totals 23,170,000 (610,000 increase in one year)

80+ age totals 9,300,000 (380,000 increase in one year)
No. of Persons Aged 100 Years in 2013

100歳以上

250% UP!

Source: 厚生労働省『敬老の日統計』
## Physician Age By Hospital Type

<table>
<thead>
<tr>
<th>Age</th>
<th>All Facilities</th>
<th>General Hospitals</th>
<th>Kaigyo(PP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under 40</td>
<td>32.3%</td>
<td>46.8%</td>
<td>6.2%</td>
</tr>
<tr>
<td>40-49</td>
<td>24.3%</td>
<td>25.6%</td>
<td>21.9%</td>
</tr>
<tr>
<td>50-59</td>
<td>22.0%</td>
<td>16.8%</td>
<td>31.5%</td>
</tr>
<tr>
<td>60+</td>
<td>21.3%</td>
<td>10.9%</td>
<td>40.4%</td>
</tr>
</tbody>
</table>

### Average Age
- All Facilities: 48.6
- General Hospitals: 43.3
- Kaigyo(PP): 58.3

Source: 厚生労働省「医師・歯科医師・薬剤師調査」（2010）
URL: http://www.mhlw.go.jp/toukei/saikin/hw/ishi/10/dl/kekka_1.pdf
Decline In Number of Pediatric Facilities OB/GYNs Facilities

Source:厚生労働省『医療施設調査・病院報告』
URL: http://www.mhlw.go.jp/toukei/list/79-1a.html
Number of Workers Supporting One Pensioner

250%
Government Gross Financial Liabilities (as % of nominal GDP)

Australia

Source: IMF, World Economic Outlook, April 2009
Gross National Medical Expenditure
Around 37 Trillion Yen (2010)

Source: 厚生労働省『平成22年度 国民医療費の概況』
URL: http://www.mhlw.go.jp/toukei/saikin/hw/k-iryohi/10/dl/kekka.pdf
Trends in Cause of Death: Three C’s

Source: 厚生労働省『平成23年人口動態統計年報(概数)の概況』
URL: http://www.mhlw.go.jp/toukei/saikin/hw/jinkou/geppo/nengai11/
Trend in Deaths in Traffic Accidents, By Age

Source: 内閣府『平成24年交通安全白書』
URL: http://www8.cao.go.jp/koutu/taisaku/h24kou_haku/pdf/zenbun/gen1_1_1_02.pdf
Fast Aging Asia
Galapagos or Convergence?

- Comparison of Drug Treatment Practices in the USA and Big EU5 Countries versus Japan
Differences are known to exist between the US/EU5 versus Japan

- Historically, drug treatment practices in the US and big EU5 countries are believed to have been relatively similar, and often different from Japan.

- Anecdotal comments explaining differences in Japanese treatment practices compared to those in the US and EU5 countries are numerous and include:
  - Different medical specialties treating
  - Different approaches to diagnosis
  - Lag time in drug approval
  - Difficult to recruit and expensive clinical trials
  - Different marketing companies in Japan versus EU/US
  - Genetic differences
  - Overall differences in disease prevalence
  - Cultural differences
  - Higher proportion of older patients/aging population
  - etc.
Three key themes identified to provide context to treatment comparisons

- Numerous differences exist across — and even within — regions. The causes of these differences are usually intertwined and often difficult to extract from each other.

- We have identified 3 key themes and provided examples of how behavior differs across regions within each theme.

- **Genetics, Lifestyle and Environment**
  - Disease prevalence
  - Drug metabolism
  - Histological and gene mutation differences
  - Physical traits

- **Administrative**
  - Clinical trials, approvals and domestic development
  - Lag time to drug approval

- **Culture and Demographics**
  - Aging population
  - Focus on side effect mitigation vs. efficacy
  - Screening
Illustrating differences in treatment practices, using patient chart audit data

• This presentation will focus on illustrating differences in treatment practices utilizing data from Ipsos Healthcare’s Therapy Monitors.

• Additionally, it will touch on reasons behind differences, highlighting trends towards convergent or divergent behavior.

**What?**
Syndicated patient chart review studies that track usage of treatments across 20+ key disease areas, 200,000+ patients and 4,000 physicians

**Where?**
35 markets worldwide; including US, big EU5 (France, Germany, Italy, Spain, UK) and Japan

**How?**
Representative panels of treating physicians completing forms directly from reviewing patients’ charts, providing breadth and depth of data
Genetics, Lifestyle and Environment

- Disease prevalence
- Drug metabolism
- Histological and gene mutation differences
- Physical traits
Variability is known to exist in disease prevalence across regions, often due to environmental factors

- In oncology, the overall proportion of patients with different tumor types differs by region. One often cited example is the greater proportion of gastric tumors among cancer patients in Japan — which is four times that of the EU5.
- Drug treated prevalence is used here as a proxy for prevalence.
Ethnicity can impact prescribing patterns where there is varying efficacy of drugs among ethnic groups

- S-1 is approved only in Japan, where it is a dominant treatment. It has not been proven to be effective at the same dose level outside of Japan. There are suggestions that differing metabolism may be a factor.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Japan (n=628)</th>
<th>EU5 (n=361)</th>
<th>US (n=163)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-1</td>
<td>82%</td>
<td>43%</td>
<td>45%</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>51%</td>
<td>42%</td>
<td>39%</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>11%</td>
<td>40%</td>
<td>32%</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>8%</td>
<td>31%</td>
<td>26%</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>6%</td>
<td>16%</td>
<td>26%</td>
</tr>
<tr>
<td>Fluorouracil</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cisplatin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Docetaxel</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Differences in histology within specific tumor types lead to regional differences in treatment practices, e.g. biomarker testing.

- Greater Japanese prevalence of adenocarcinoma in NSCLC, with highest EGFR mutation testing rates and highest proportion of identified EGFRm+ tumors.

% of Stage IIIb/IV Non-Small Cell Lung Cancer that is…

- Adenocarcinoma
- Tested for EGFR mutation
- Positive for EGFR mutation

Japan (n=1721):
- 79% Adenocarcinoma
- 81% Tested for EGFR mutation
- 31% Positive for EGFR mutation

US (n=4958):
- 67% Adenocarcinoma
- 56% Tested for EGFR mutation
- 12% Positive for EGFR mutation
Cultural

- Age and ageing population
- Focus on side effect mitigation vs. efficacy
- Screening
Cultural differences lead to variety in prescribing by impacting primary focus of treatment

Cultural diversity is evident in the treatment of numerous diseases. Overall, American medicine tends to be aggressive, with the primary focus on the effectiveness of treatment and a fairly high tolerance of side effects.

In contrast, in Japan, a drug’s safety profile tends to play a larger role than seen typically in the US.

In Europe, treatment generally reflects a mid-position between the US and Japan.

It will be interesting to see whether cultural diversity across regions becomes more convergent, or divergent, over time.
Age has a visible influence on prescribing; older patients less tolerant of aggressive therapy

- The average age of HCV patients in Japan is considerably older than seen in the US/EU5. Japanese guidelines for HCV management recommends dual rather than triple therapy for patients over age 65.

### Mean Age

**Triple Regimen Share**

**Among Genotype 1 HCV Patients**

- **Japan**: Mean age 63 years, 62% ≥ 61 years
- **EU5**: Mean age 49 years, 18% ≥ 61 years
- **US**: Mean age 50 years, 20% ≥ 61 years

Base: All genotype 1 patients currently on treatment; Japan (n=204), EU5 (n=551), US (n=391)
Baseline screening in cancer leads to a very different profile of patients across regions

- A recent ACCJ study shows almost half of Japanese undergo an annual health check. Chest x-rays during this consultation contribute to earlier diagnosis of lung cancer, isolating stronger, fitter patients.

**All current NSCLC – Stage of Diagnosis (MAT Q2 2013)**

- Japan: 43% Stage I-IIIA, 57% Stage IIIB - IV
- EU5: 26% Stage I-IIIA, 74% Stage IIIB - IV
- US: 25% Stage I-IIIA, 75% Stage IIIB - IV

**ECOG Performance Score (MAT Q2 2013)**

- Japan (2528): 50% 0, 41% 1, 9% 2+
- EU5 (5142): 18% 0, 64% 1, 19% 2+
- US (5791): 24% 0, 59% 1, 17% 2+
Galapagos or Convergence?
Japan: moving towards both convergence and divergence

Divergence
away from other regions, embracing targeted and functional treatment practices

Convergence
towards global consistency, encouraging innovation and availability of new products

Genetic, Lifestyle and Environment factors
Cultural differences
Administrative issues
1. Extend the nation’s healthy life expectancy
2. Realize clean and economical energy demand and supply
3. Develop next-generation safe, convenient and economical infrastructure
4. Build regional communities that use their unique local resources to appeal to the world

Strategic Market Creation Plan
Japan Revitalization Strategy - JAPAN is BACK -
(Cabinet Decision on June 14, 2013)

Extended national “Healthy life expectancy”

<Future vision of the society>
The society where people can receive necessary healthcare services at the most advanced level in the world

Foster the industry specialized in extended healthy life, by developing innovative pharmaceuticals, medical devices and regenerative medicines first in the world, and by introducing these products to the market through speedy review process.

Measures

- Strengthen PMDA organization both in size and in quality
  While maintaining a keen attention to post marketing product quality and safety, further reduction of review time (achieve “0” review lag ) and improved quality will be pursued.

- Establish control tower function (Japanese version of NIH)
  Build systems where integrated research management, bridge between research and clinical practice, and world-class, high-quality clinical research/trial will be securely carried out.
Japan’s commitment to improve administration results in a rapid reduction in lag time and increase in drug approvals

Source: PMDA ACCJ Presentation Sept 2013 – Tatsuya Kondo, M.D., Ph.D.
Japan now well ahead of other regions for Standard Review Time for new drug approval

Source: PMDA ACCJ Presentation Sept 2013 – Tatsuya Kondo, M.D., Ph.D.

Japan’s Performance on NDA Review

Japan authority have achieved the target on review, 12 months for standard review and 9 months for priority review as median, in the mid-term plan of PMD for 2008 – 2013. Now it has the world’s highest performance.

Source: PMDA ACCJ Presentation Sept 2013 – Dr Kondo
1. An average derived from Thompson Reuters IDRAC database.
Promotion Program for Practical Use of Innovative Pharmaceuticals, Medical Devices, and Regenerative Medicines (MHLW 2012 budget program)

- Support establishment of regulatory science-based evaluation methodologies for safety and efficacy of products, at academia who are engaged in the research of most advanced technologies.
- Develop regulatory science experts by exchanging personnel between academia and PMDA, National Institute of Health Sciences (NIHS).

Human resource development by personnel exchange

Dispatch reviewers

Accept researchers

Learn innovative technologies
- Accelerated, higher quality review

Research results

Develop regulatory science experts
- Promote proper R&D

Early development of standards and/or guidelines, etc.

Promote implementation of innovative technologies (Eliminate drug lag and device lag)
Support for Innovation Implementation via Science Board

- Universities, Laboratories, Medical Institutions
  - Leading researchers who have great achievements in research as well as profound expertise on pharmaceuticals and/or medical devices

- Cooperation with academia
  - Lead implementation of most advanced scientific technology implementation based on regulatory science
  - Human rotation every 2 years

- Science Board
  - Opinion exchange between top national researchers and PMDA reviewers on how to evaluate most advanced scientific technology

Enhancement and reinforcement of innovation implementation via Science Board is needed.
Toward Global PMDA

Approve innovative products first in the world!

Spread technology of Japanese origin world-wide
Collaborate with review organizations globally

Contribute to global healthcare

The society where people can receive necessary healthcare services at the most advanced level
Extend healthy life expectancy for Japanese citizens
<table>
<thead>
<tr>
<th>Requestor</th>
<th>Subject Name (ID)</th>
<th>Expected Generic Name</th>
<th>Expected Performance, Intended Use, Indications or Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shinichi Takeda National Institute of Neurolo­scienece</td>
<td>Tentative Morpholino nucleic acid</td>
<td>Intramuscular injection/Intravenous infusion/Injection dosage form</td>
<td>Treatment for Duchenne muscular dystrophy (DMD)</td>
</tr>
<tr>
<td>Toshio Miyata Tohoku University</td>
<td>PAI-1 inhibitor (TM5509)</td>
<td>Oral administration/Tablet</td>
<td>Improvement of hematogenic recovery of cord blood transplantation</td>
</tr>
<tr>
<td>Shinya Yamanaka Center for iPS Cell Research and Application, Kyoto University</td>
<td>iPS cell</td>
<td>Allogeneic iPS cell for clinical research</td>
<td>The purpose is to solve time and cost issues in preprocessing and to provide regenerative treatment for a wider range of refractory diseases, by establishing “iPS cell bank for regenerative treatment” stocked with cells from various transplant-suitable donors, and by having quality assured iPS cells and cells for transplant at hand.</td>
</tr>
<tr>
<td>Osamu Honmo Sapporo Medical University</td>
<td>Autologous marrow mesenchymal stem cell</td>
<td>Intra-venous infusion/Injection dosage form</td>
<td>Improvement of neurological symptom, daily movement problem or functional disorder resulted from cerebral infarction</td>
</tr>
<tr>
<td>CYBERDYNE K.K.</td>
<td>Robot Suit HAL for medical use (tentative) and physical training support device using some of the functions thereof</td>
<td>TBD</td>
<td>Wearable device for assisting patient’s movement. Several models are planned with different intended use, indications or efficacy.</td>
</tr>
</tbody>
</table>
HAL (Hybrid Assisted Limb)
Issues Being Discussed at Science Board (Special Committee)

Special Committee on Pharmaceuticals and Biologics

- With respect to the personalized medicine, for the time being;
  - How to organize biomarkers and endpoints in the clinical evaluation
    (especially for cancer, chronic inflammatory disease and rare disease)
- Non-clinical pharmacology study of anticancer drugs

Special Committee on Medical Devices

Current issues
- Policy for the development of combination products
- Scope of generic medical devices
- Registry development
Issues Being Discussed at Science Board (Special Committee)

Special Committee on Cellular and Tissue-based Products

How to secure quality and safety of cellular and tissue-based products
- Tumorigenicity (*)
- Requirements for CPC (Cell Processing Center), etc.

* The Committee has just published the report on the discussion about the evaluation of tumorigenicity of cellular products derived from iPS cells, etc.

** The report can be found at the PMDA website (http://pmda.go.jp)
Enhance International Cooperation: Toward Global PMDA

Summit of Heads Medicines Regulatory Agencies

• Being held annually with the attendance of top executives of medicines regulatory agencies of key nations. PMDA is attending regularly.

• Along with Japan, key regulators including FDA (US), EMA (EU), TGA (Australia), SFDA (China), MHRA (UK) and HAS (Singapore) are attending.

Build trusty relationship among key nations at the highest level

• Execution of Confidential Agreement

• Dispatch of International Liaison Officers respectively to EU (from Nov. 2011) and US (from Feb. 2011) on long-term basis

• Discussion on-going with Health Canada and Swissmedic on possible personnel exchange

Achieve close information exchange
Strategy for Asia

- **Training seminar**
  One-week training program at PMDA intended mainly for Asian regulators

- **Acceptance of on-site trainees**
  Tailored training ranging from one week to two months, upon request of regional regulators

- **Joint Symposium**
  Joint symposium with overseas regulators. (held with Indonesia in FY2012, to be held respectively with Indonesia, Thailand and Taiwan in FY2013).
  Typically combined with bilateral meeting

- **APEC LSIF RHSC**

Through these activities, PMDA intends to lead Asian regulators by providing better understanding of PMDA, while promoting sharing of review results through proliferation of review and safety measure systems of PMDA.
About FiRM

The Forum for Innovative Regenerative Medicine (FIRM) was established on June 17, 2011 to promote the commercialization of regenerative medicine in Japan.
Future Market Expectation of Regenerative Medicine

Size of the regenerative medicine market in 2050 is approximately 25 billion USD (domestic market), 380 billion USD (global market), which promises that enormous economic effects.
Discussion is going on with the government and academia to innovate the social foundation for the Industrialization of Regenerative Medicine.
Working Groups

Our four working groups collaborate together in their activities.

1. Working Group on Regulations and Systems

Goal:
Regulations and systems related to regenerative medicine and cell therapies and to compile opinions and proposals.

Activities for Fiscal Year 2013:
Contracting of cell-processing to nonmedical institutions, early post-marketing phase vigilance and post-marketing surveillance following approval, development of a minimum consensus on safety studies, and possible uses for heterologous cell therapies.
2. Working Group on Medical Economics

Goal:
Identify issues and discuss solutions regarding pharmaco-economics aspects of regenerative medicine and cell therapies.

Activities for Fiscal Year 2013:
Pharmaco-economics studies of regenerative medicine, examination of the economic issues on contracting cell processing, and study on insurance system for regenerative medicine business.
Working Groups

3. Working Group on Supporting Industries

Goal:
Establish the value chains required to promote the spread of industries that provide products and services required for regenerative medicine.

Activities for Fiscal Year 2013:
Criteria to be required of related facilities, devices, equipment, materials, culture media, reagents, and transport.
3. Working Group on Supporting Industries

Designing value chain of regenerative medicine
...for safe, convenient and affordable RM services

- Sampling
- Receiving inspection
- Cell culturing and processing
- Quality monitoring
- Transplantation

Transportation

Machines
Facilities

Medium
Reagents

Devices
Equipment
Working Groups

4. Working Group on Standardization

Goal:
To develop Japan's standardization strategy for regenerative medicine and, based on that strategy, to propose international standards to the ISO and other standardizing organizations.

Activities for Fiscal Year 2013:
To investigate international activities on the standardization related to regenerative medicine, and, in cooperation with other working groups, examine what should be standardized and what should be included in international proposals from Japan.
Digital Health Toilet

Source: 大和ハウス ウェブサイト
みまもりほっとライン＠ZOJIRUSHI

無線通信機能を内蔵した「i-ボット」をお年寄りが使うと、その情報がインターネットを通じて、離れて暮らすご家族に。ご家族はその様子を携帯電話やパソコンでいつでもどこでも思いやりなく見守ることができます。

1. i-ボットを使う

使用状況（電源のオン、給湯、保温中）を送信。※1

2. システムセンタ

3. 最新の情報を1日2回、Eメールで受信。

※1「おでかけ」キーを押すと（外出または帰宅）を送信。
Wireless

It is a bit freaky with this wireless technology
Controlling Electric Wheelchair by Brain Waves in Real Time

Source: 独立行政法人理化学研究所 ベブサイト (2009)
Controlling Robots by Brain Waves

Source: HONGA ウェブサイト (2009)
RIBA: nursing-care robot can lift people out of bed

Source: RIKEN-TRI Collaboration Center Website (2009)
川崎重工、衛生面に優れた医薬・医療向けアーム型ロボット2機種を発売
2013国際ロボット展

介護・福祉用自立生活支援ロボットアーム RAPUDA (ライフロボティクス)
PARO (Furry White Baby Seal Robot)
Aging and Bio Ethics

Current Finance Minister and Former Prime Minister Taro Aso

- Old people in costly terminal care should be allowed to “hurry up and die” to ease the burden on an over-indebted state.
If you were to become ill with no prognosis for recovery, would you like to receive treatment that keeps you alive

NO: 94.8%

Do not want life extending treatment
81%

参照:読売世論調査
URL:http://www.yomiuri.co.jp/national/news/20131011-OYT1T01238.htm
“危機”

危機 = CRISIS

危 = danger

機 = opportunity
Nichiryoku Robotic Retrieval
Columbarium
ATM for Visitors

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