# Regulation on Regenerative Medicine products in India

India-Japan regulatory symposium, May 18-19, 2016


**Prof. Narinder K Mehra**
**National Professor and**
**Former Dean (Research)**
**Founder Head, Dept of Transplant Immunology & Immunogenetics**
**AIIMS, New Delhi**
**narin.mehra@gmail.com**

# Therapeutic Stem Cells
## *for Regenerative Medicine*

**BENEFITS**

- ❑ Pluri / Multi Potency
- ❑ Self Renewal
- ❑ In vitro Specific Differentiation
- ❑ Immune Privilege ?

**Limits of in vivo engraftment and Functionality**

- ❑ Immunogenicity /Allogenicity /Rejection /Autoimmunity
- ❑ Limiting factor – Time Line
- ❑ Aging leading to immuno senescence
- ❑ Safety
- ❑ Ethical and Regulatory issues

# The Immunity Factors in Regenerative Cell Therapies

- **THE IMMUNOGENETIC FACTOR** Allogenicity
  *HLA, MHC and much more …….*
- **THE IMMUNE EFFECTORS** : DIRECT VS INDIRECT
  Pathway of allo recognition
  *Cells, Mediators and Alloantibodies*
- **THE AGING FACTOR**: Immuno Senescence

**Towards an Immunologically Educated choice of Stem Cells**

# Allogeneic Stem Cells are not Immune Privileged

- **MHC Expression**
- **Immunogenicity increases upon differentiation**
- **In vivo Rejection**

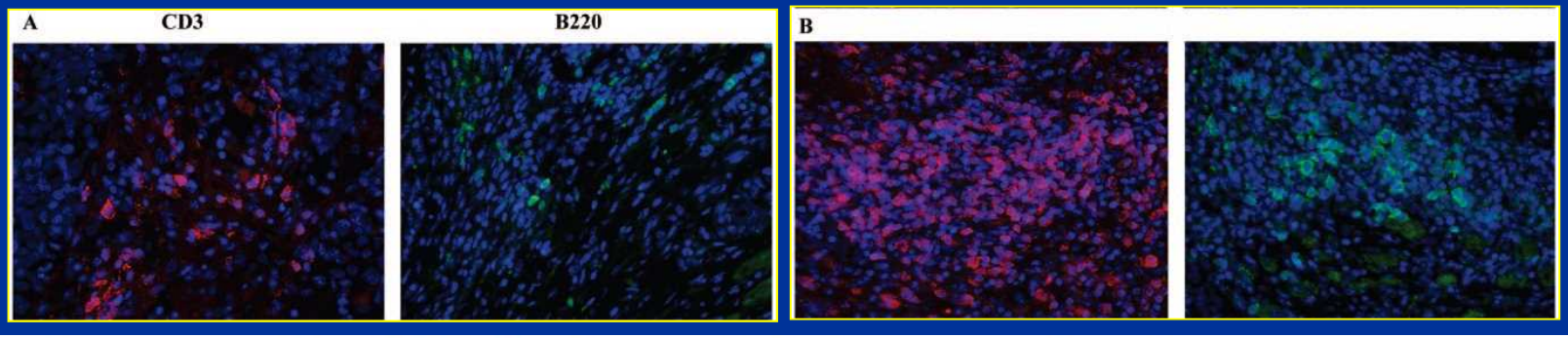
Several support papers

# Embryonic Stem Cell Immunogenicity Increases Upon Differentiation After Transplantation Into Ischemic Myocardium

Swijnenburg *et al., 2005, Circulation, 112[suppl I]:I-166–I-172*

**Graft infiltration of immune cells after transplantation of in vivo differentiated ESCs**

**T-cells**




**Cellular Composition of Graft Infiltrates Over Time After Intramyocardial ESC Injection**

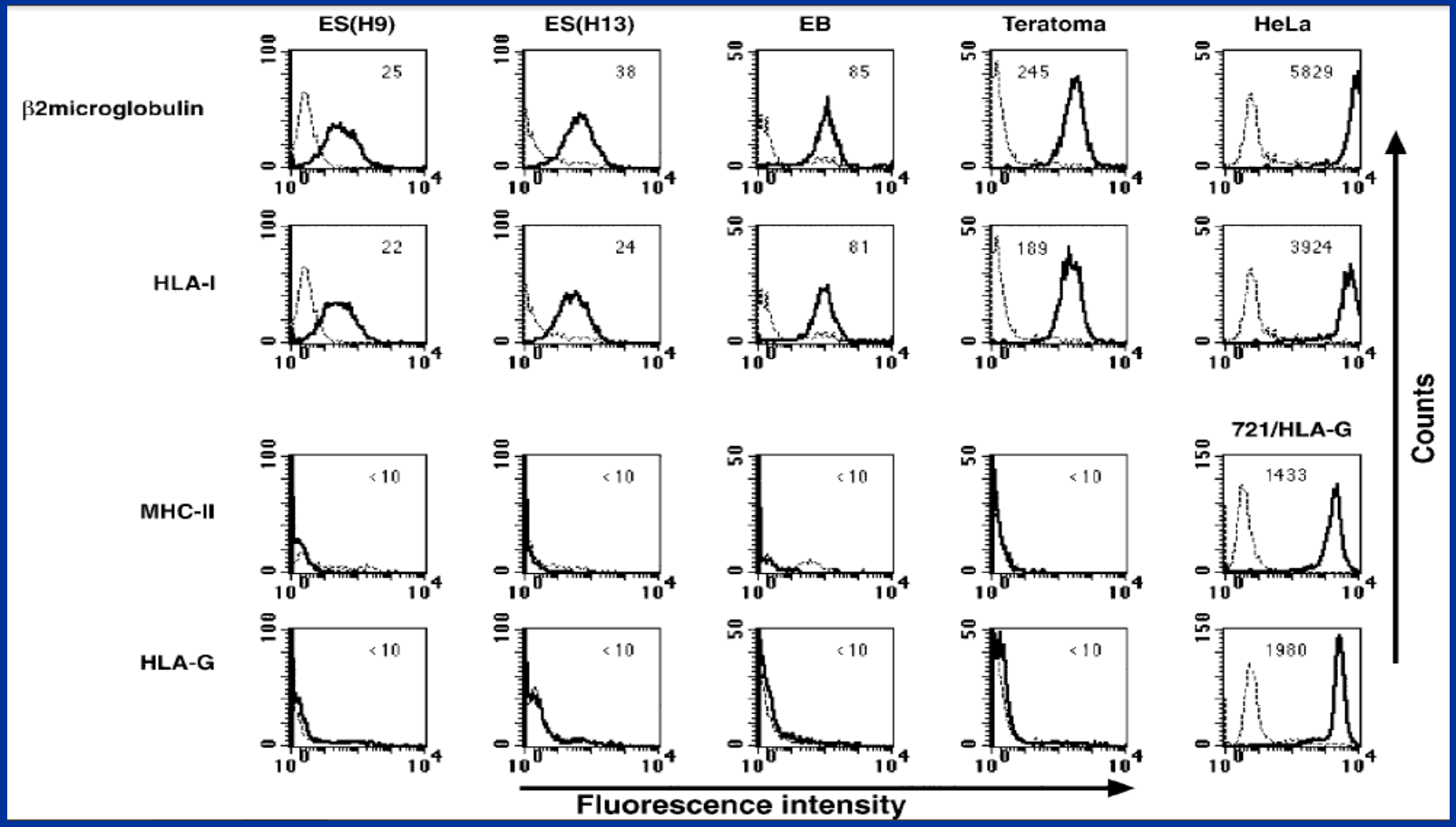
| | 1 Week* | | | 2 Weeks* | | | 4 Weeks* | | | 8 Weeks* | | | 2 Weeks After HTX† | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Sham | Syn | Allo | Sham | Syn | Allo | Sham | Syn | Allo | Sham | Syn | Allo | Sham | Allo |
| CD3 | +/− | + | + | +/− | + | ++ | +/− | + | +++ | +/− | + | +++ | +/− | +++ |
| CD4 | +/− | + | + | +/− | + | ++ | +/− | + | +++ | +/− | +/− | +++ | +/− | +++ |
| CD8 | +/− | +/− | +/− | +/− | +/− | ++ | +/− | +/− | +++ | +/− | +/− | +++ | +/− | ++ |
| B220 | +/− | + | + | +/− | + | ++ | +/− | + | ++ | − | +/− | + | +/− | +++ |
| CD11c | +/− | +/− | +/− | − | +/− | + | − | + | ++ | − | +/− | ++ | − | + |
| Mac-1 | ++ | ++ | ++ | ++ | +++ | +++ | + | ++ | +++ | + | ++ | +++ | ++ | +++ |
| Gr-1 | + | + | + | + | + | ++ | + | + | +++ | + | + | ++ | + | +++ |

In vivo differentiated ESCs elicit an accelerated immune response as compared with undifferentiated ESCs. These data imply that clinical transplantation of allogeneic ESCs or ESC derivatives for treatment of cardiac failure might require immunosuppressive therapy

# Characterization of the expression of MHC proteins in human embryonic stem cells

*Drukker et al., 2002, PNAS, 99(15): 9864-9869*

**Expression of MHC proteins in undifferentiated and differentiated human ES cells.**




**Results demonstrate that human ES cells can express high levels of MHC-I proteins and thus may be rejected on transplantation .**

# Background Information

- India is seen as the world's low cost pharmacy as far as conventional therapies are concerned and the recent economic and epidemiological changes present a good opportunity for the Indian biotech industry to replicate this success in the **field of novel and innovative healthcare therapies** like Regenerative Medicine.

- **Regenerative Medicine addresses the root cause of the disease** and is gaining momentum world wide. Some of the stem cell based products approved globally : **Prochymal – for pediatric GVHD, Cartistem – for Osteoarthritis, TemCell - for GVHD (both adult & pediatric), Anterogen – for rectal fistula …….**

- There is high demand for **early and safe access to such innovative therapies** in treating serious and life threatening diseases by providing meaningful benefits over existing treatments.

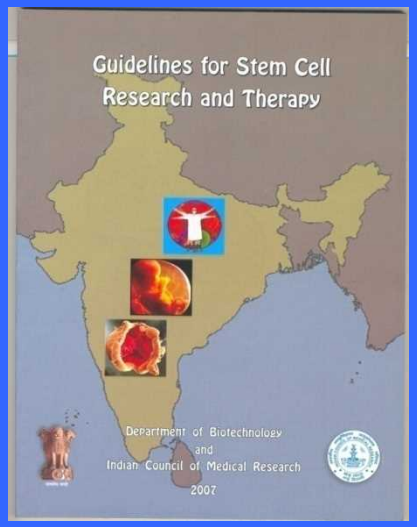
- In the absence of a strong regulation – **stem cell therapies are mushrooming without following any norms and guidelines.** Patients are becoming guinea pigs.

**Strong Regulations with fast track approval system is need of the hour…. Ensure science drives the business**

# National Guidelines : *ICMR – DBT initiative*

- Draft guidelines for Stem Cell Research & Regulation in 2002
- First prepared in 2007 by an 'expert group' constituted by the ICMR and DBT : *Guidelines for Stem Cell Research and Therapy - GSCRT 2007*
- Underwent thorough intensive public debate and consultation
- National Guidelines for Stem Cell Research - NGSCR 2013
- Further revisions are under progress

## GSCRT 2007 → NGSCR 2013 → Revision 2016






**Guidelines for stem cell research are continuously evolving**

# Current Indian FDA Guidelines

## Regenerative Medicine

The regeneration of damaged cells, tissues or organs through the use of cells, scaffolds and/or biomolecules through tissue engineering approaches

As per the ICMR-DBT guidelines, there is **no approved indication for stem cell therapy as a part of routine medical practice, other than the Hematopoietic stem cell Transplantation (HSCT/BMT).**

Accordingly all stem cell therapy other than BMT shall be treated **experimental**. It shall be conducted **only as clinical trial** after prior approval from CDSCO. All such experimental trials shall be registered with CTRI.

**Indian FDA is the nodal point for approval any marketable product – for allogeneic and autologous stem cell clinical trials**

# Categorization of Research on stem cells in India

- Permissible area of research
- Restricted area of research
- Prohibited area of research

**According to the source and nature of experiments, research on human stem cells is categorized**

# Permissible areas of research

***Any in vitro*** **studies on established pluripotent stem cell lines or those involving fetal/adult stem cells**

**In vivo studies in experimental animals (other than primates) with established cell lines (pluripotent stem cells or fetal/adult somatic stem cells)**

**Establishment of new hES cell lines from embryos left unutilized in IVF programme, or iPS cell lines.**

**Establishment of Umbilical Cord stem cell bank**

**Cells for clinical trials must be processed as per the National GTP / GMP guidelines**

**All clinical trials on stem cells shall be registered with CTRI through IC-SCR/IEC**

# Restricted areas of Research

**Creation of a human zygote** by IVF, SCNT or any other method with the specific aim of deriving a hES cell line for any purpose.

**Clinical trials** sponsored by multinationals involving **stem cell products imported from other countries.**

Research involving **introduction of pluripotent cells into animals including primates**, at embryonic or fetal stage of development for studies on pattern of differentiation and integration of human cells into non- human animal tissues.

**Studies on chimeras** where stem cells from two or more species are mixed and introduced into animals including primates, at any stage of development, for studies on pattern of development and differentiation.

Research in which the **identity of the donors** of blastocysts, gametes, or somatic cells from which the hES cells were derived is readily ascertainable or might become known to the investigator.

# Prohibited areas of research

Any research related to human germ line genetic engineering or reproductive cloning.

Any *in-vitro* culture of intact human embryo, regardless of the method of its derivation, beyond 14 days or formation of primitive streak, whichever is earlier

Transfer of human blastocysts generated by SCNT or parthenogenesis or androgenetic techniques into a human or non-human uterus.

Any research involving implantation of human embryo into uterus after *in-vitro* manipulation, at any stage of development in humans or primates.

Animals in which any of the human stem cells have been introduced at any stage of development should not be allowed to breed.

Research involving directed non autologous donation of any stem cells to a particular individual is also prohibited.

# Approval & Monitoring Clinical Research using stem cells

Approval and monitoring of clinical trials will take into consideration the following factors but not limited to:

- ✓ **Source and type of stem cells** - somatic, embryonic, iPSC etc.
- ✓ Autologous or allogeneic application
- ✓ **Degree of manipulation** - minimal, more than minimal or major
- ✓ **Stage of research** – in vitro, in vivo, preclinical or clinical research
- ✓ Whether the proposed cell based research is intended for developing a marketable product or an academic institutional directed research for advancement of knowledge

# Design of a Clinical Trial

- ✓ **Should be planned carefully** - The investigator must fully understand and document benefits of the proposed clinical trial, understand the basic characteristics of SCs.

  *(caution: stem cells may survive indefinitely and differentiate unpredictably giving rise to teratomas once introduced in the human body).*

- ✓ Have suitable follow up periods
- ✓ Appropriate end points
- ✓ Stakeholders should be fully conversant with the current regulations
- ✓ No unproven therapy is to be offered outside of clinical trials
- ✓ Records to be kept for a minimum of 5 yrs for autologous and 10 yrs for allogeneic and ESCs

# Levels of manipulation (processing)

## Minimal manipulation

- **No major alterations in cell population and/or function**
  - Ficoll - Hypaque separation , washing, centrifugation etc;
  - all laboratory procedures not exceeding few hours,
  - carried out under strict aseptic conditions

## More than Minimal manipulation

- **Defined as alterations in cell population, but not function.**
  - e.g. T cell depletion, cancer cell depletion, CD34 enrichment and expansion, all of which is expected to result in alteration of cell function.
- All laboratory processes under strict aseptic conditions, and not exceeding a few days

## Major manipulation

- **Definite alteration in both cell population and function**
- Long term culture of cells through multiple passages leading to genomic instability or pathogenic genetic alterations or induction of genetic alteration by insertion of gene/siRNA etc

# Mechanism for Review and Regulatory Oversight

**A separate mechanism of committees has been established for review and monitoring of stem cell research and therapy.**

- ✓ **At the National level, there is the National Apex Committee for Stem Cell Research and Therapy (NAC-SCRT)**

  - meets every 3 months or as often as required
  - sub committees as per requirements

- ✓ **At the Institutional level, there is the Institutional Committee for Stem Cell Research (IC-SCR)**

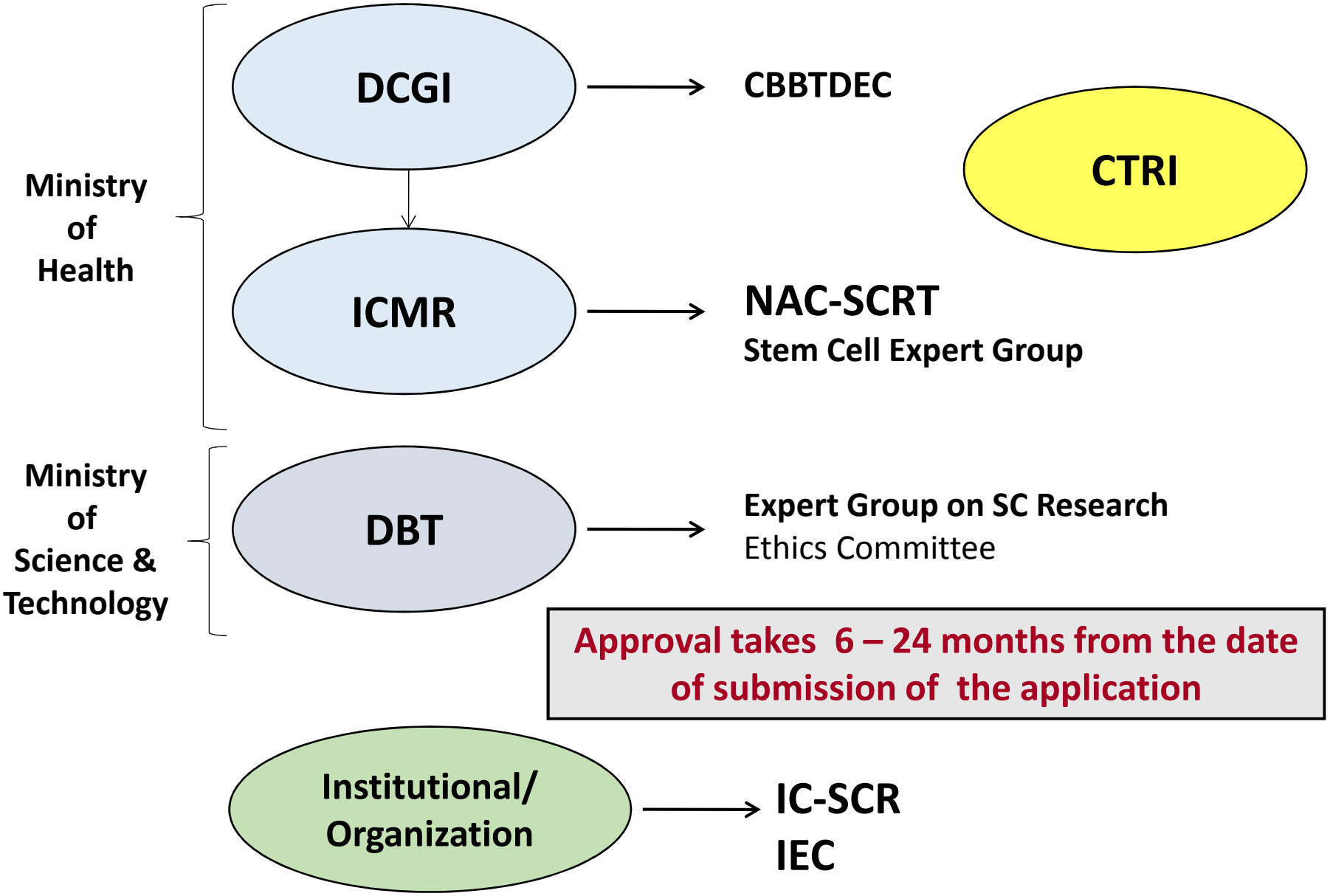
# IC-SCR

## A Multi disciplinary body at the institutional level

All research institutions conducting stem cell research are expected to set up a special review body to oversee this emerging field of research

- To be registered with the NAC-SCRT
- Provide overview to all issues related to stem cell research
- All therapy related projects must be referred to NAC-SCRT
- Review and approve the scientific merit of research protocols
- Review compliance with all relevant regulations and guidelines
- Maintain registries of hES cell research conducted at the institution and hES cell lines derived or imported by institutional investigators
- Facilitate education of investigators involved in stem cell research
- Submit annual report to NAC-SCRT

# Various Committees/ Registry



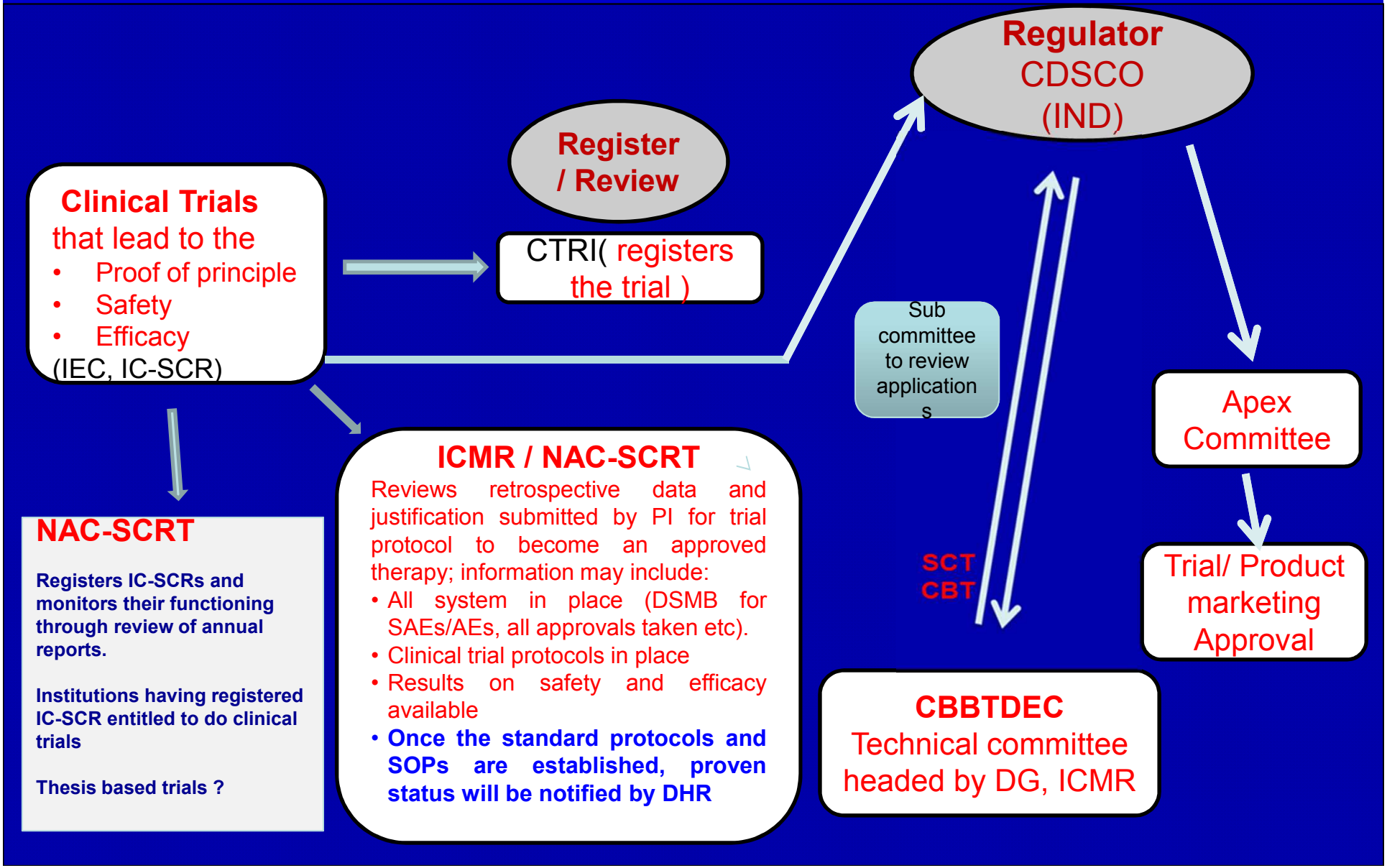
# Regulatory approvals for Clinical Trials

- All clinical trials using stem cells shall be registered with CTRI
- Currently, minimally manipulated, autologous SSCs for homologous use are approved by IC-SCR and IEC.
- However application of these cells for non homologous use to be approved by DCGI.
- Stem cells with substantial manipulation shall be approved by DCGI after obtaining clearance fro
- Allogeneic SSCs (with any degree of manipulation) or autologous SSCs with major manipulation shall be approved by DCGI after obtaining clearance from NAC-SCRT through IC-SCR and IEC
- Clinical trials with hES cells (or their derivatives) shall be approved by DCGI after obtaining clearance from NAC-SCRT through IC-SCR and IEC
- Stem cell based product already approved and marketed outside India (or for concurrent clinical trial in India) will require approval of DCGI for pre- license clinical trial.
- Any clinical trial with a product intended to be licensed and marketed shall have prior approval of DCGI through IC-SCR and IEC

Harmonization

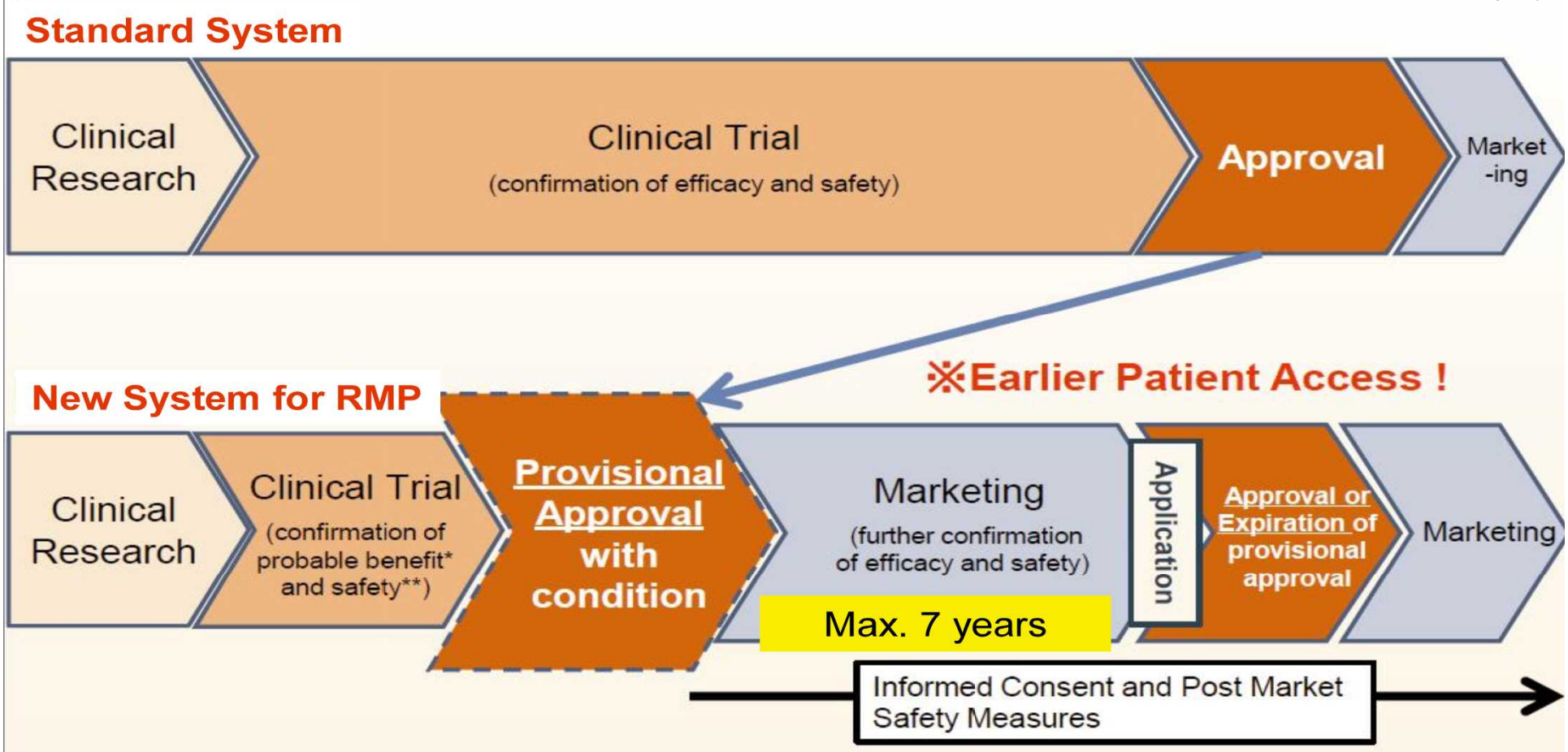
# Approval Mechanism for Clinical Trials

## leading to product / process development



# New Approval System for Commercialization of Regenerative Medicine Products

PMDA of Japan = Pharmaceutical and Medical devices agency



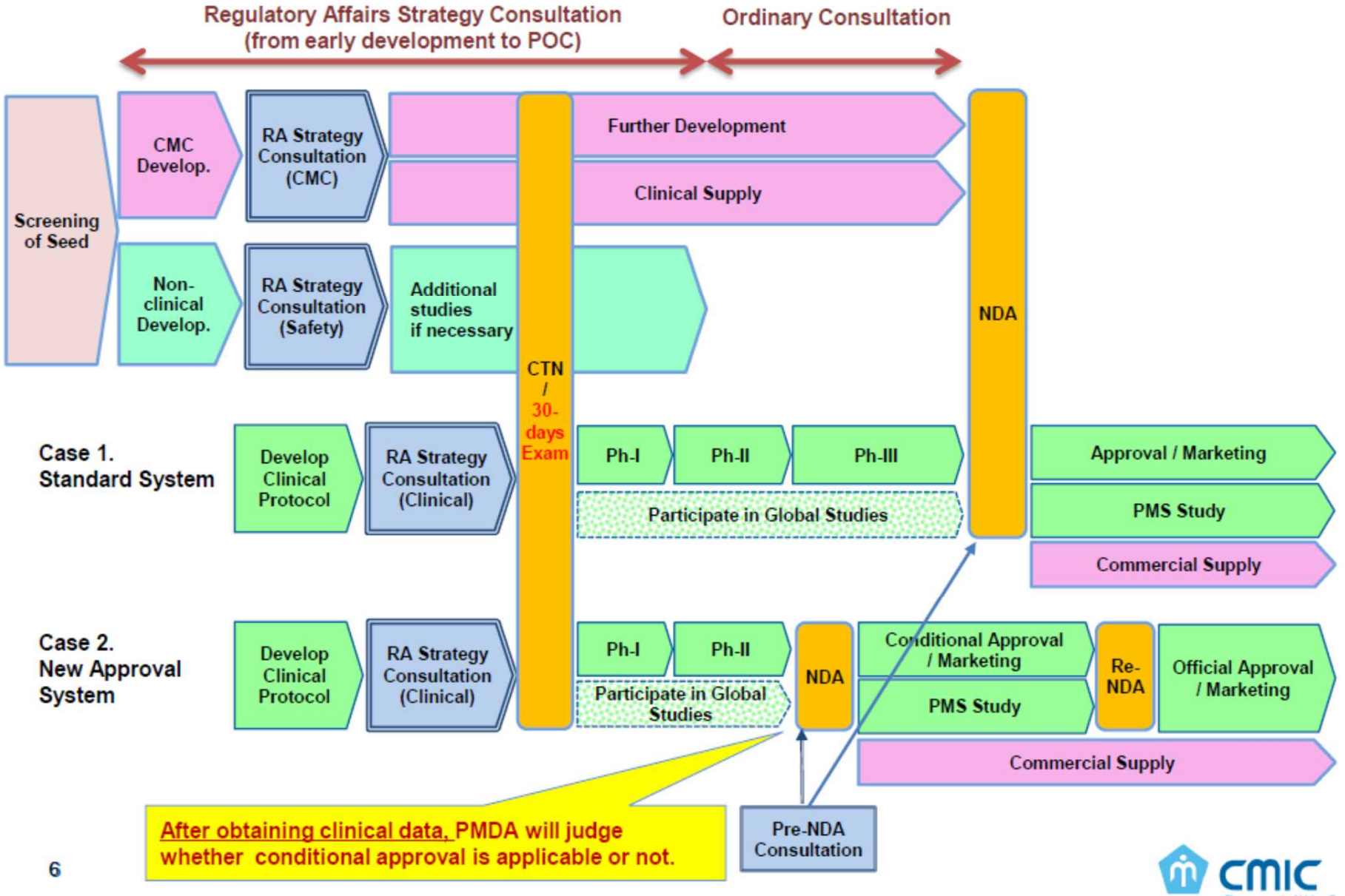

* Probable benefit: Confirmation of efficacy with small patient population.
** Safety: Earlier detection and evaluation of adverse events.

from PMDA presentation, modified



**PMDA Japan has revised Pharmaceutical Affairs Law for Regenerative Medicinal Products:**
***providing conditional approval***

# Fast track approval process in Japan



# REGROW ACT introduced in Senate of the United States

To amend the Federal Food, Drug, and Cosmetic Act with respect to cellular therapies.
IN THE SENATE OF THE UNITED STATES
**March 16, 2016**

**This Act may be cited as the "Reliable and Effective Growth for Regenerative Health Options that Improve Wellness " or the "REGROW Act".**

SEC. 351B. Approval for cellular therapies.

**(a) Conditional approval of cellular or tissue therapeutic:**
Not later than 1 year after the date of enactment of this section, the Secretary shall establish a program to conditionally approve a cellular therapeutic product if the sponsor of such product demonstrates preliminary clinical evidence of safety, and a reasonable expectation of effectiveness, without initiation of phase III investigations.

**(b) Additional requirements for conditional approval**:
A conditionally approved product under subsection (a) shall, for a 5-year conditional use period, be manufactured, introduced into interstate commerce, and used consistent with the regulations in effect at the time of such use, including good manufacturing practices, without the approval of an application under section 351(a), if all of the following apply:

# REGROW ACT introduced in Senate of the United States

## Key Points:

- Such cells or tissues are **adult human cells or tissues**

- Such cells or tissues have been evaluated to examine **immunogenicity** and **do not provoke a significant unintended immune response in the recipient.**

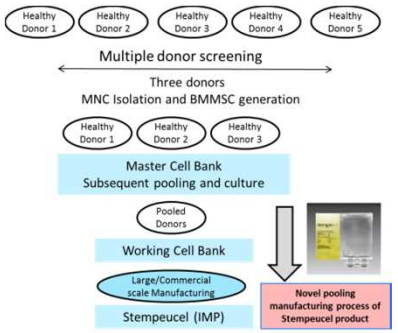
- Such cells or tissues are—
  (A) **minimally manipulated for a non homologous use;** or
  (B) **more-than-minimally manipulated for a homologous or non homologous use, but are not genetically modified.**

- Such cells or tissues are produced for a **specific indication.**

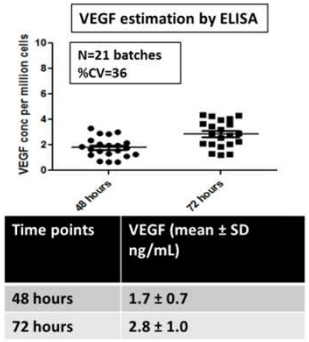
- **Within 5 years of the safety and effectiveness determination described in this section**, the sponsor of the conditionally approved new product prepares and submits an application for approval of a biological product under section 351(a), **demonstrating potency, purity, safety, and efficacy of the use**. The Secretary may permit continued use of such product until the Secretary completes the review of the application and makes a determination. **Upon a determination by the Secretary not to approve the application, use of the cellular therapeutic shall not be permitted**

- **During the conditional approval period**, and before approval of an application under section 351(a), the **sponsor shall prepare and submit annual reports and adverse event reports to the Secretary** containing all the information required for approved biological products.

# Stempeucel® for CLI due to Buerger's Disease – Case scenario for approval in India

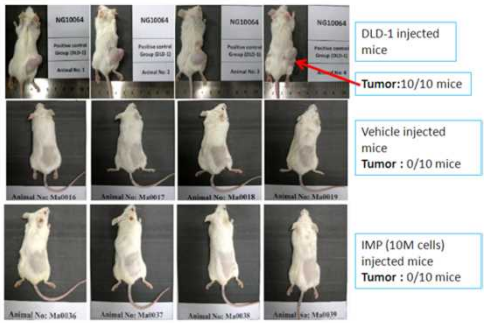



**Stempeucel® Product**



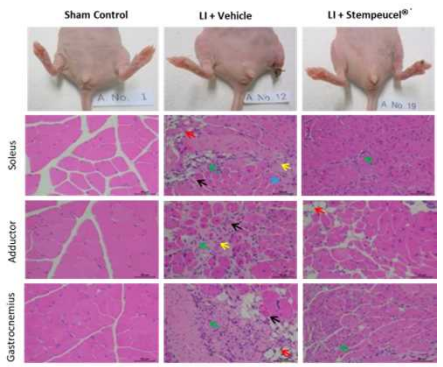

| Time points | VEGF (mean ± SD ng/mL) |
|---|---|
| 48 hours | 1.7 ± 0.7 |
| 72 hours | 2.8 ± 1.0 |

***In Vitro* Validations**

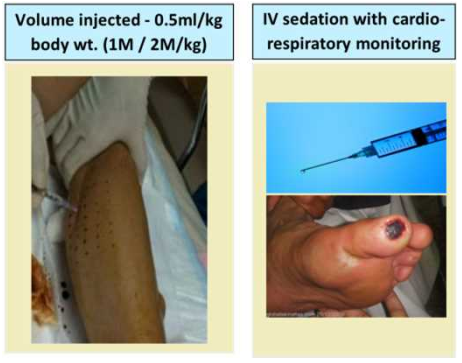



**Preclinical Safety**

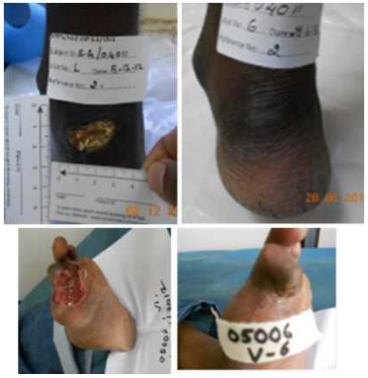
**Preclinical Efficacy**




**Clinical Trials – Phase I & II**




**Approved for limited marketing**




**Stempeucel® approved for limited marketing after phase 2 trial**

# INDIA - JAPAN PARTNERSHIP
# "PHARMACEUTICAL INDUSTRY & BILATERAL COOPERATION"

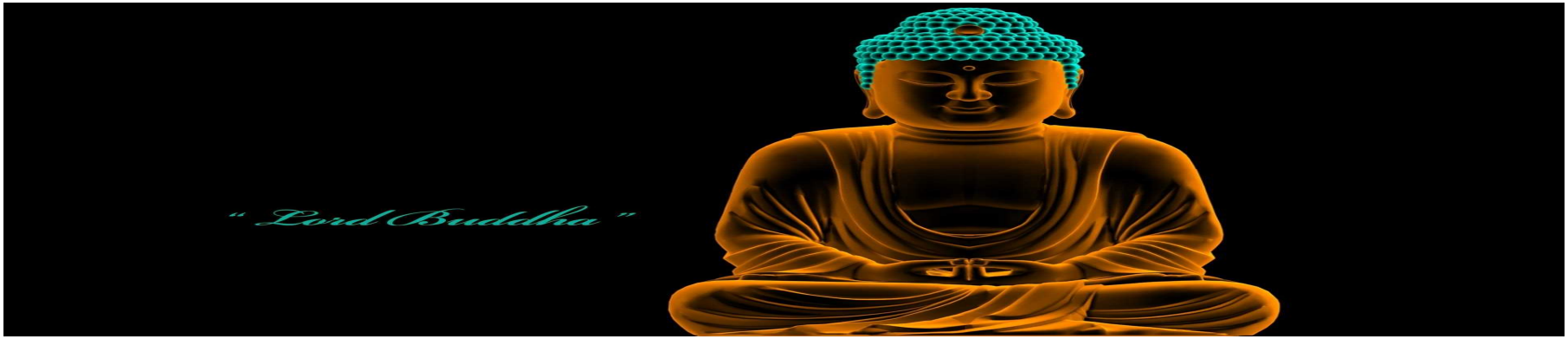
**18th May, 2016**

**Dr Gurpreet Sandhu**

# Contents

# Historical Bondage

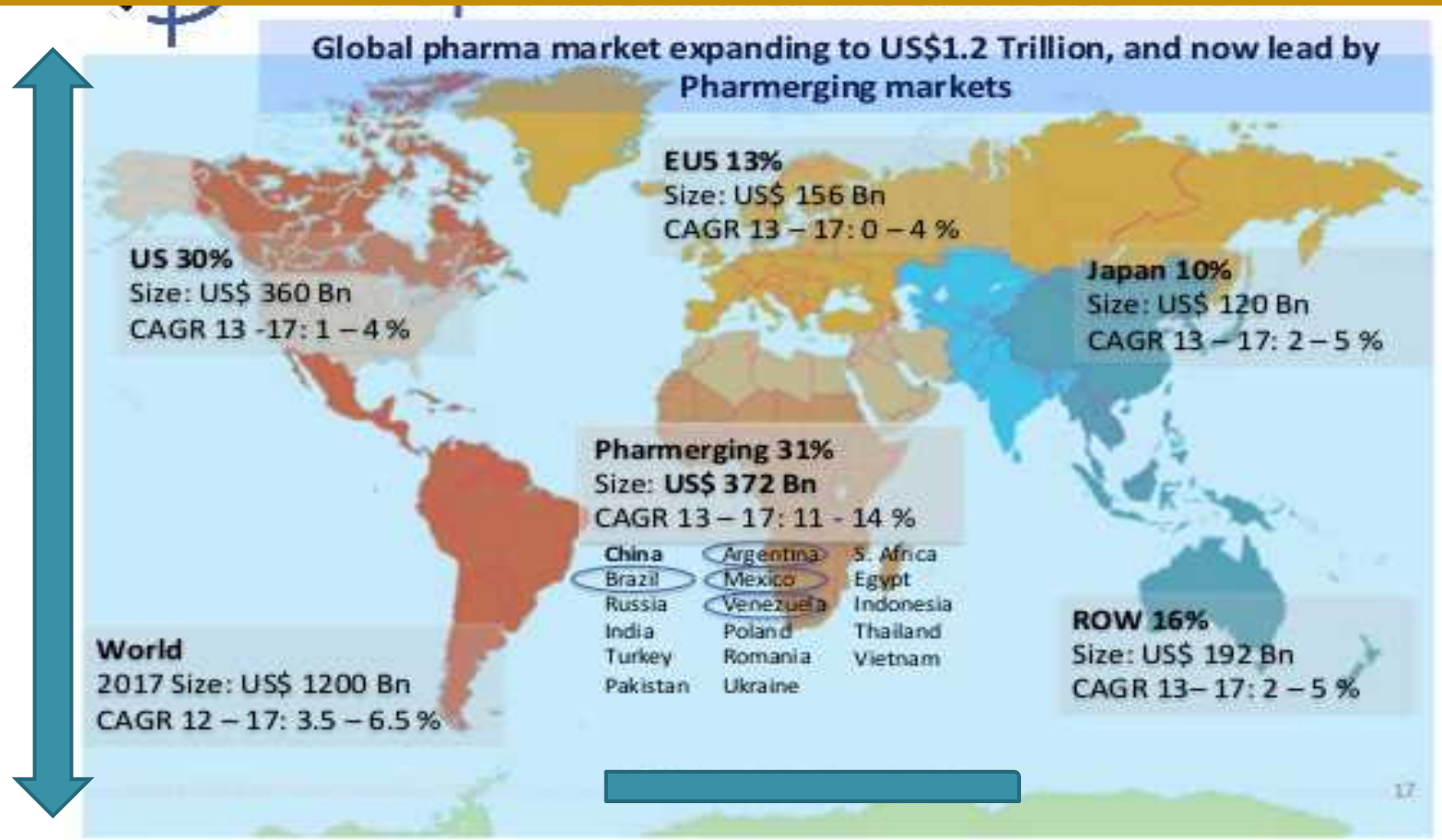





Cultural Heritage : Buddhism - common base.

- Trading to Manufacturing -- Suzuki, Sony, Toyota, and Honda.
- Today – Japan, playing role in all walks of life.
- Japan Brands present in every Indian Household : SONY, PANASONIC, HITACHI, DIAKIN, SANSUI, TOYOTA, SUZUKI & HONDA.

# Projection 2017



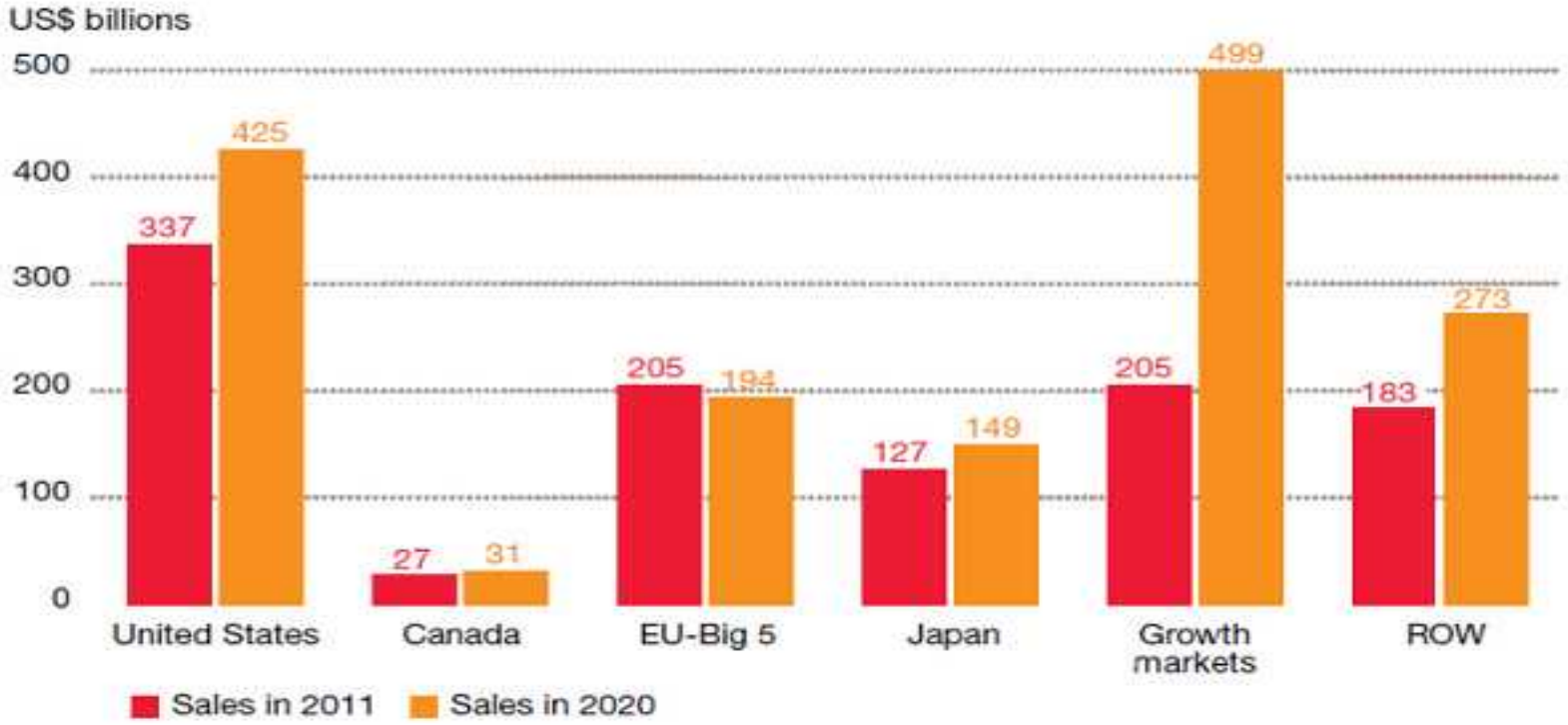
# Emerging Markets:
# -- Future Growth



- Pharma industry to generate 30 percent of its total sales in emerging markets by end of 2016.
- Healthcare spending in emerging markets has overtaken that of the EU 5 (Germany, France, Italy, Spain, and UK).
- Change in Life Style disease patterns, has provided additional opportunities to Pharma Players.
- Major increase in Therapies -- Diabetes, Oncology, Antiviral, Anti-Infective, and Cardiovascular.
- Drug exclusivity reaching its last stage, which in turn help generic Pharma players to expand their Portfolio.

# Pharma Market by 2020






*Source: Business Monitor International*

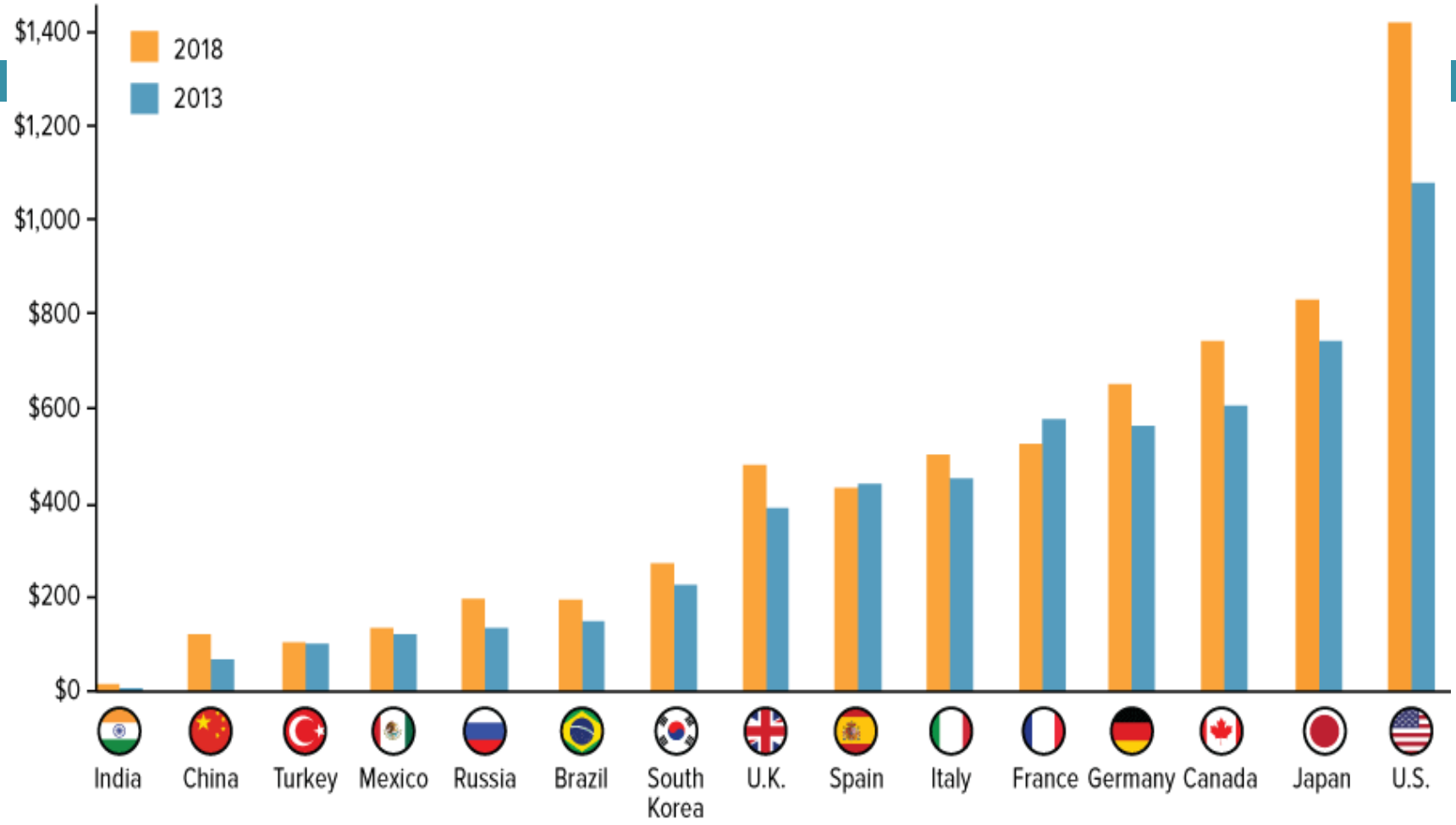
Notes: (1). All sales are expressed in US dollars at constant exchange rates; (2). The growth markets include, in descending order of size, China, Brazil, Russia, India, Mexico, Turkey, Poland, Venezuela, Argentina, Indonesia, South Africa, Thailand, Romania, Egypt, Ukraine, Pakistan and Vietnam. (3) EU-Big 5 is France, Germany, Italy, Spain and United Kingdom.

# Current BRICS Scenario




**A cold draft of economic uncertainty is sweeping across the world. The BRICS nations, which fired up global growth, have caught a chill all except `I'.**

## Pharmaceutical Spending per Capita Is Expected to Grow, 2013 vs. 2018




**Source:** Economic Intelligence Unit 2014, IMS Market Prognosis 2014, U.S. Global Investors

By 2018, India will attain 15th Position in PharmaSpending.

# The Rising Sun: Japan



- The annual market size of Japan ~ USD 115 Billion.
- Second largest market behind US Market.
- Annual sale of Generic Drugs still on the lower side ~ USD 7.8 Billion.
- MHLW, promoting the Generic Drugs to reduce Medical Expenses of Patients; target 80 % by 2020.
- Japanese government harmonizing its policies with ICH.

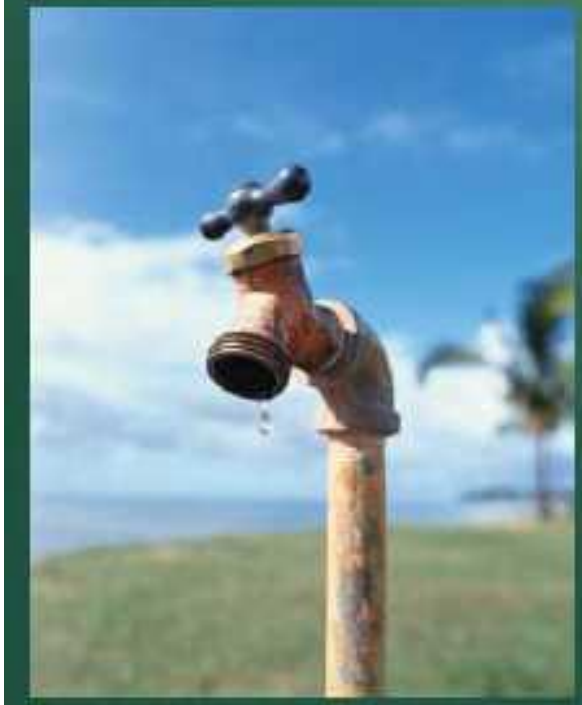
# International Vision



- Companies setting up R&D sites around the world.
  - Chugai -- invest $476m in Singapore
  - Eisai – direct alliance MHRA for its base in UK.
- Ageing population and increased medical needs - pressure on Govt. to focus on Generic Drugs.
  - Generic penetration of 60% in 2017, and 80% by 2020.
- Positive approach - harmonization with EU and US regulatory regimes. The R&D tax credit helping companies to set up shop in Japan.
- Appointing a foreigner (CEO from GSK) for Takeda's top job - An indication in itself that the company is looking to international markets for Expansion.

# ...But feeding grounds are shrinking

| Drying pipeline of blockbusters | Big pharma entering generics | Commoditization pressure |
|---|---|---|



# Japan Pharma ⇨ towards India



Pharma players like Takeda, Eisai, Daichii-Sankyo, Meiji, Mitsui, Otsuka & Asahi Kasei hold working relations in India.

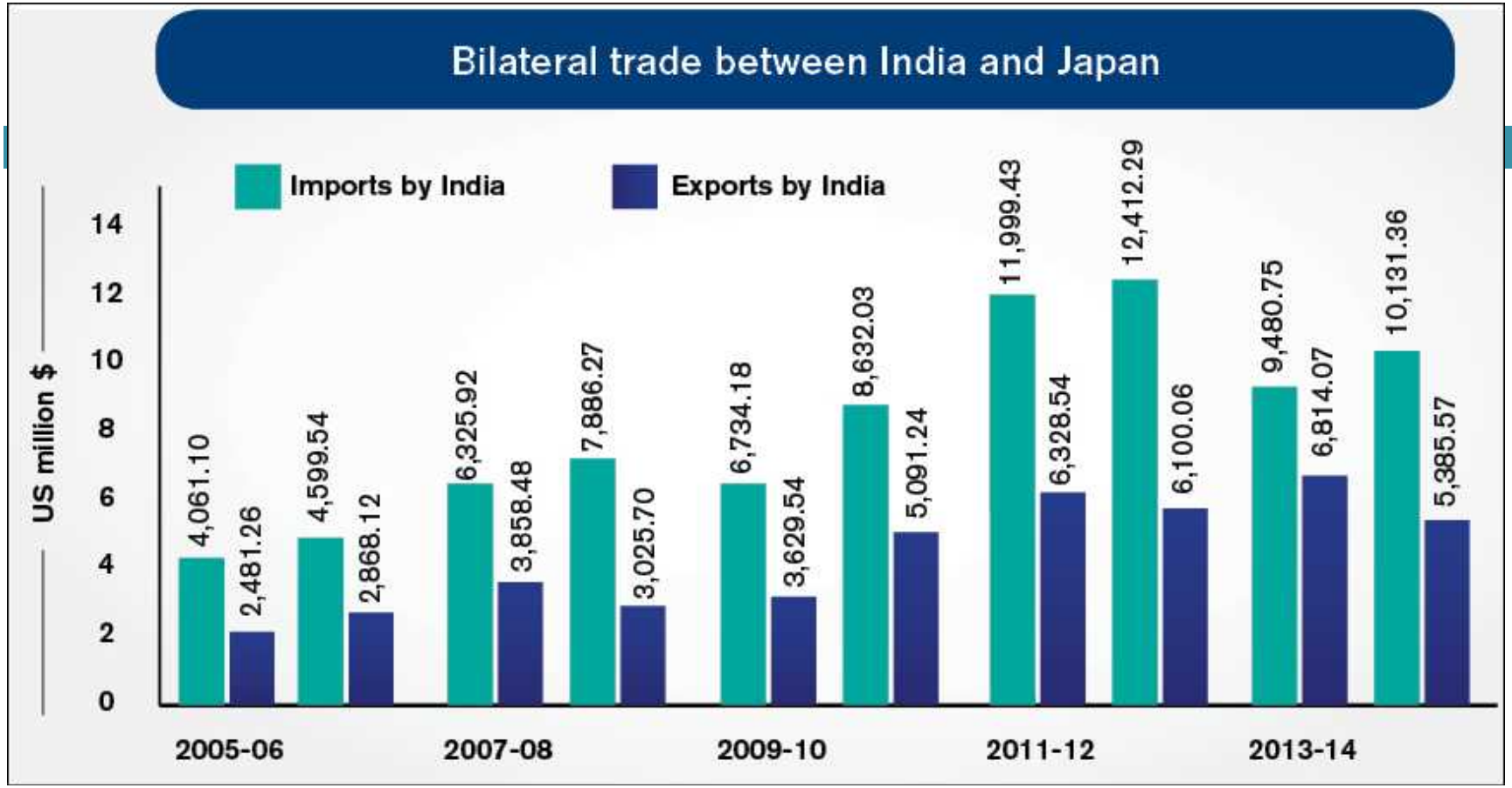
**Areas of Potential Cooperation:**

- **Contract Manufacturing:** Accessibility to FDA infrastructure with cheaper production base .
- **Drug Product:** An area where mutual co-operation can grow. India has already demonstrated -- US, Europe & Emerging Markets
- **R&D:** Indian intellectual strengths to be capitalized.
- **Export / Import:** Medical Devices, High Quality APIs, Biosimilars as their is huge surge of growth in Healthcare sector.

# Bilateral Cooperation



- **MOU signed between PMDA & FDA India on 11th of December, 2015.**
- **Indian big boys putting investments in Japan, like.**
  - Lupin went in for two buyouts : Kyowa in 2007 and I'rom in 2011.
  - SUN Pharma, bought 14 established brands of Novartis in Japan.
  - Zydus in 2007 bought Tokyo-headquartered Nippon Universal Pharmaceutical.
  - Dr. Reddy's Labs, Aurobindo Pharma, Reva Pharma have fortified their investment in the region by setting up offices in Japan.
- **Japanese Companies setting their base in India, either directly or through M&A like.**
  - Meiji, acquired Medrich
  - Otsuka, Joint Venture with Claris Lifesciences
  - Daiichi Sankyo, acquired Ranbaxy but afterwards became a part of "Sun Pharma"
  - Eisai, set up their manufacturing base in South of India.
  - Sumitomo & Mitsui have Trading / Equity Investment model in India.

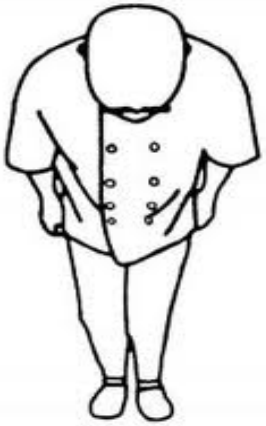

Bilateral trade between India and Japan
Imports by India
Exports by India
US million $
0
2
4
6
8
10
12
14
4,061.10
2,481.26
4,599.54
2,868.12
6,325.92
3,858.48
7,886.27
3,025.70
6,734.18
3,629.54
8,632.03
5,091.24
11,999.43
6,328.54
12,412.29
6,100.06
9,480.75
6,814.07
10,131.36
5,385.57
2005-06
2007-08
2009-10
2011-12
2013-14

# PM "Modi" Exhorts Japan to "Make in India"




- Need to boost investor sentiment
- Look at FDI in a two-fold manner: "First Develop India" vs. "Foreign Direct Investment"
- Ensure "corporate government responsibility" for effective governance
- Boost manufacturing to help growth of the middle class and create jobs
- Develop a growth oriented environment to enhance ease of doing business
- Develop a "3D" outlook: tap democracy, demography and demand
- Channelise India's rich demographic dividend for competitive advantage
- Train manpower in an industry-aligned fashion
- Implement "Digital India" for an informed citizenry
- Rollout a "Look East and Link West" approach
- Envision integrated clusters with roads, rails, airports and associated infrastructure
- Ensure State and Centre coordination for export promotion


ありがとう



# India-Japan: Opportunities for collaboration

18th May 2016

Sudhanshu Pandey, IAS
Joint Secretary,
Department of Commerce, Govt of India

# The Indian Pharma Industry : The Flag Bearer

**India's Exports of Pharmaceuticals during the last Five years (USD billion)**

| 2009-10 | 2010-11 | 2011-12 | 2012-13 | 2013-14 | CAGR% |
|---|---|---|---|---|---|
| 8.95 | 10.7 | 13.3 | 14.7 | 15.04 | 14 |

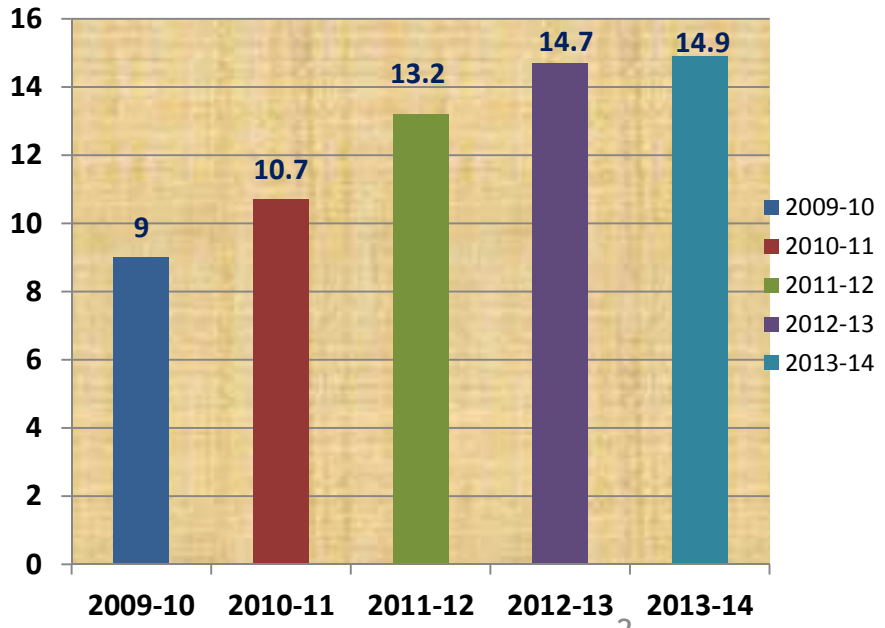
India's share in World Generic Market is 3.3%. excluding India's domestic market)

Over 55% exports of India are to highly regulated markets.

U.S.A the largest exports destination followed by UK

Largest exporter of formulations in terms of volume during 2010 with 14% market share *Source: UN COMTRADE*

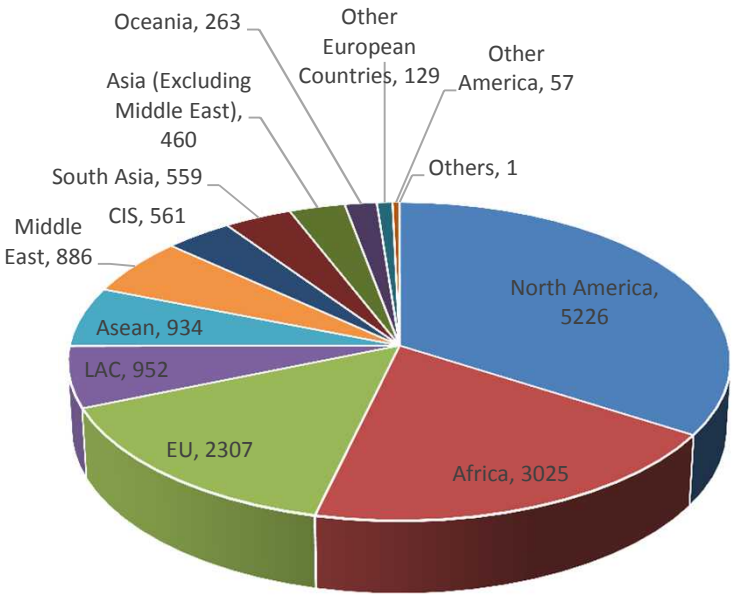
**India's Exports of Pharmaceutical (values in USD bn)**



# India's Contribution to Global Health Care

*Values in $ million*

| Region | Fy-16( April-feb) | Contbn% |
|---|---|---|
| North America | 5226 | 34.03 |
| Africa | 3025 | 19.69 |
| EU | 2307 | 15.02 |
| LAC | 952 | 6.20 |
| Asean | 934 | 6.08 |
| Middle East | 886 | 5.77 |
| CIS | 561 | 3.65 |
| South Asia | 559 | 3.64 |
| Asia (Excluding Middle East) | 460 | 3.00 |
| Oceania | 263 | 1.71 |
| Other European Countries | 129 | 0.84 |
| Other America | 57 | 0.37 |
| Others | 1 | 0.01 |
| Grand Total | 15358 | 100.00 |




CREDIBLE AFFORDABLE SUSTAINABLE

# Strengths of Indian Pharmaceuticals

| | | |
|---|---|---|
| 1 Global Pharmacy for Generic Medicines | 2 Manufacturing Hub of the World | 3 Emerging Flagship Industry of India |

| | |
|---|---|
| 1 | ☞ Finished generics supplied from India account for 20% of the global generics market.<br>*Source: PricewaterhouseCoopers, The changing dynamics of pharma outsourcing in Asia* |
| 2 | ☞ More Than 90% of WHO Prequalified API [ARVs, Anti-tubercular & Anti-malarials ] are sourced from India. |
| 3 | ☞ It is estimated that 70% of the patients belonging to 87 developing countries received medicine procured from India by<br>☞ The United Nations Children's Fund (UNICEF)<br>☞ International Dispensary Association (IDA)<br>☞ the Global Fund and<br>☞ the Clinton Foundation. |
| 4 | ☞ Medicine Sans Frontiers also purchases 80% of its ARVs, for its projects in over 30 countries, from India.<br>*Source: Ellen F.M. 't Hoen, LL.M., The Global Politics of Pharmaceutical Monopoly Power, AMB 2009* |
| 5 | ☞ Indian generic ARVs approved by the US Food and Drug Administration (US FDA) also resulted in cost-savings of an over 90% of the ARVs for PEPFAR. |

# Accreditations Of India

| Authority | Name of Regulatory Agency | Nos. |
|---|---|---|
| USA | **Companies** filed DMFs with U.S. FDA (As on 31st march 2015) | **430** |
| | No of **Sites** (Bulk drugs + Formulations) Registered with US FDA (as on april2015 ) | **605** |
| | Total **No Of DMF's** (Type II Active) Filed from India (as on Dec 2015) | **3820** |
| | **ANDAs(As on Dec 2015 )** | **3455** |
| | Formulation **companies** with USFDA approvals. | **53** |
| EUROPE | Number of CEPs received (as of Feb 2016) | **1354** |
| | Number of companies with CEPs | **220** |
| | Number of Molecules for which CEPs have been filed with EDQM | **371** |
| | No of Sites registered with EDQM In India(As on Feb 2016) | **630** |
| | UK MHRA (Medicines Healthcare Regulatory Agency), Market authorizations as on March 2015 | **1554** |

# 6 Indian companies are amongst the top 20 Generic Companies

| Rank | Company | Country | 2014 In $ billion | GR% |
|---|---|---|---|---|
| 1 | Teva Pharmaceutical | Israel | 9.1 | -1 |
| 2 | Novartis | Switzerland | 8.6 | 4 |
| 3 | Actavis | Ireland / USA | 6.6 | 6 |
| 4 | Mylan | USA | 6.6 | 10 |
| 5 | *Sun Pharma india* | India | 4.5 | 68 |
| 6 | Aspen | South Africa | 3 | 13 |
| 7 | Hospira | USA | 2.6 | 12 |
| 8 | Sanofi | France | 2.4 | 11 |
| 9 | Fresenius | France | 2.3 | +/- |
| 10 | *Lupin india* | India | 2 | 19 |
| 11 | *Dr.Reddy's india* | India | 1.8 | 10 |
| 12 | Apotex | Canada | 1.7 | -2 |
| 13 | STADA Arzneimittel | Germany | 1.6 | -1 |
| 14 | *Aurobindo india* | India | 1.6 | 75 |
| 15 | *Cipla India* | India | 1.4 | 17 |
| 16 | Krka Group | Slovenia | 1.3 | 1 |
| 17 | Valeant Pharmaceuticals | Canada | 1.2 | -17 |
| 18 | *Zydus Cadila India* | India | 1.2 | 28 |
| 19 | Par Pharmaceutical Companies | USA | 1.2 | 20 |
| 20 | Nichi-Iko Pharmaceutical | Japan | 1.2 | 12 |
| | Total of Top 20 | | 74.2 | 7 |

| Country | Companies in top 20 |
|---|---|
| India | 6 |
| USA | 4 |
| France | 2 |
| Canada | 2 |
| Japan | 1 |
| Germany | 1 |
| Switzerland | 1 |
| Slovenia | 1 |
| South Africa | 1 |
| Israel | 1 |

# Opportunities for Collaboration

# Overview of Pharmaceutical Situation in Japan

- The new targets of Generic Unit Share in the Japan market (Basic Policy which was approved by Cabinet in June 2015) continuously increased
- Initially it was to accomplish a 60% unit share by the end of March, 2017
- Then later revised to accomplish over 70% unit share by the end of June 2017
- Finally revised again to accomplish over 80% unit share between April 2018 and March 2021

**The difficulties and Counter Measures needed to achieve the " Generic 80% Share" target**

Insufficient manufacturing capacity, and the need for expansion to meet new Generic demand.

The immediate necessity for additional investment into plants and manufacturing equipment

Sawai (in Nov 2015) started operations of a 2nd R&D Laboratory with an investment of USD 55 million.

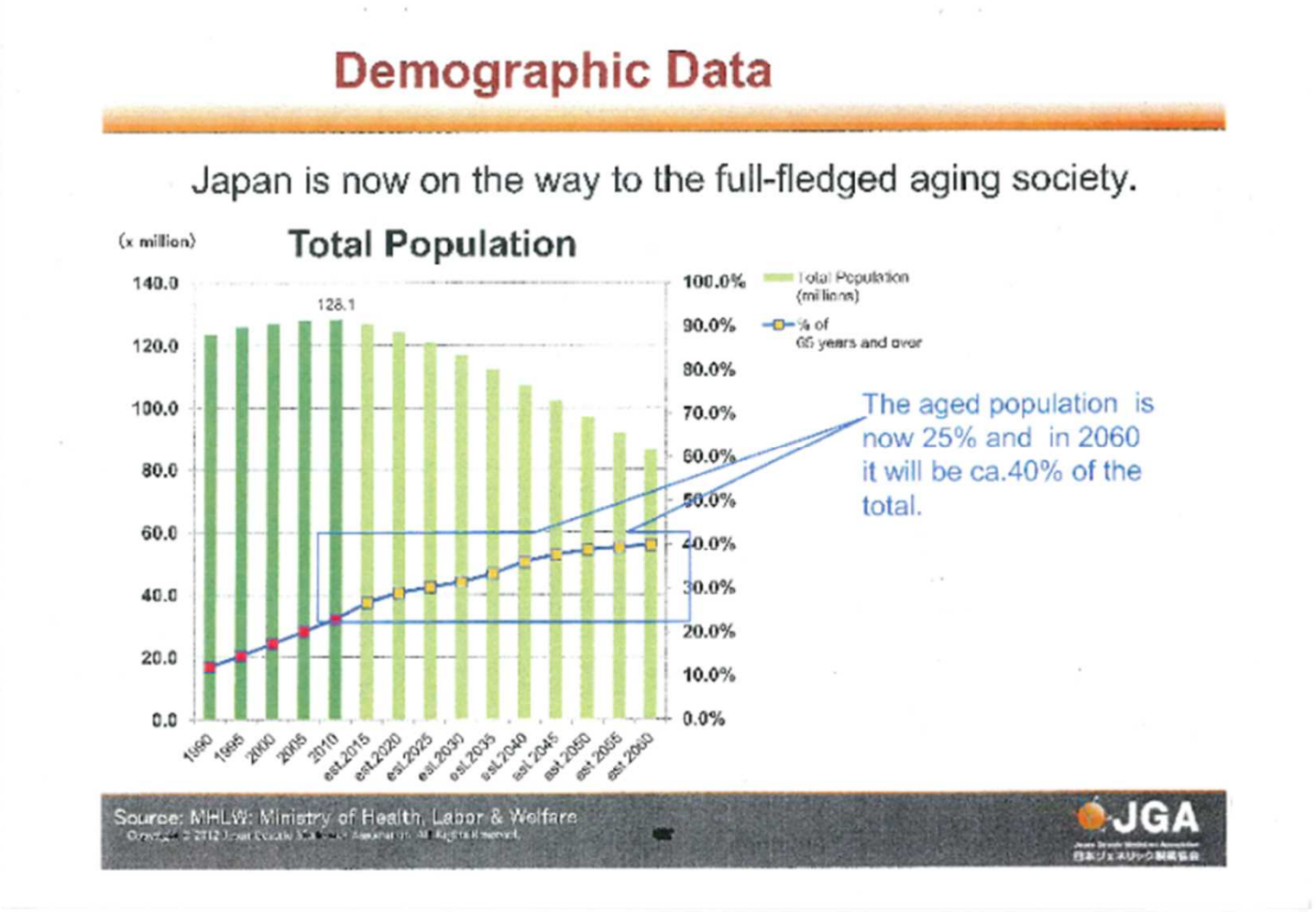
Purpose is to increase as well as strengthen new product development capability and production capacity

In light of the revised target of 80% Generics, they have added an additional USD 182 million more to invest into expansion (from USD 400 million to now USD 582 million).

They have now increased the original investment plan/budget to USD 400 million by end of fiscal year 2017.

Source: Mainichi Shimbun Dec 7th 2015

This chart shows the decrease of demand of pharmaceutical drugs due to the future decline of the Japanese population



Due to so many generic drugs available for each original drug (e.g. 40 products), there is a burden of inventory management as it is required by regulation to have all strengths (same as what the Innovator has registered) for each product (e.g. 5mg, 10mg and 20mg)

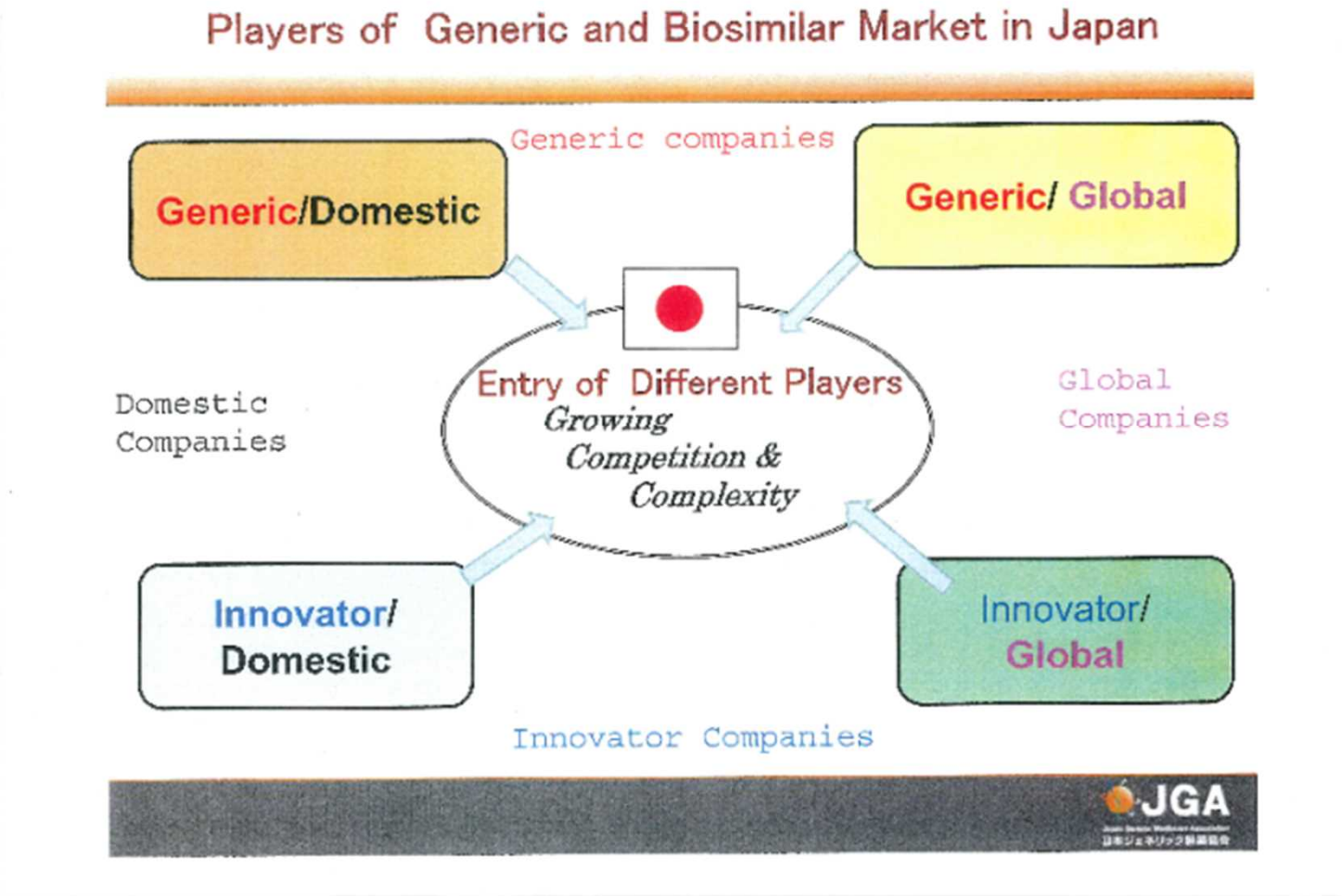
The necessity of all dosage forms/strengths creates difficulty in inventory management for pharmacies. MHLW is reviewing this issue.

Sizes of most generic companies are small or medium (approx. 200 companies)

MHLW comments that there are too many Generics companies and has suggested for consolidation/integration/M&A to reduce the number of companies and create larger entities

This is abut 10 times the average of European Union countries.

# High possibility of entry into the Japanese market by global generic or bio-similar company



# Some examples of India's involvement in Japan market recently

- A Japanese company acquired Indian company for manufacturing products in India and supply to Japan.(Meiji Seika acquired Medreich in February 2015.)
- - An Indian company acquired a Japanese company which manufactures API's and final products in India in order to sell them in Japan.(Lupin acquired 100% of stock of Kyowa Yakuhin in November, 2008.)
- -A Japanese company established a branch office, plant and laboratory in India and manufactures API's and products to supply them in Japan.(Eisai established a branch office in April, 2004 and a plant and lab in March, 2007 in India.)

- Japanese company established a joint venture company with a foreign generic company to sell generic and long listed-products in Japan.
  ( A joint venture company of Takeda and Teva have started their business from April, 2016.)

- These are the types of collaboration that we encourage and hope to continue and develop between India and Japanese companies.

# Examples of current trends and alliances APIs and/or Intermediates

Japanese Innovator transfers their API or Intermediates/process/technology to an Indian plant.

This way, Japanese Innovators are able to reduce the cost due to Generics competition

# Importing of APIs or Intermediates from India : Some Facts

47.5% of Japanese GE drug companies use APIs which are imported from overseas

The shares by country of imported APIs were published in 2013 to be 22.5% from Italy, 15.7% from Korea, 14.0% from China and 10.2% from India.

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(Source : Road Map (5-year plan), MHLW 2013)

## Opportunities and Partnership possibilities between India and Japan

Fact: India can make formulations to meet the Japanese quality and aesthetic requirements

A few ways to succeed are as follows:

A. Investment into own plant or

B. Acquisition of existing plants or pharma company

C. Contract manufacturing

Manufacturing Site Transfer (When an Innovator or Generic Company transfers their formulation process and manufacturing to an Indian facility)

New Generic formulation co-development

# A. Investment into own Plant

Eisai India was established in 2007.

And now imports into Japan from their Vizag plant around 1 billion tablets per year

This includes long listed products ( such as Aricept/ Donepezil). Eisai first reported planned to export Intermediates and gradually also APIs

In fact, now they succeeded in doing both and additionally have made formulations for Japan

# B. Acquisitions

Lupin (strategy targeting APIs first): Now has a few formulations in Japan.

More are under development and also several products made in Japan (ex-Kyowa) are being transferred to the Lupin India plant. We expect a growing number of formulations from India in future

Meiji (acquisition of Meidrich, India): Wherein their strategy/goal is to manufacture long-listed products and develop new GE products for Japan.

# c) Contract manufacturing

*I : Manufacturing Site Transfer*

Cipla : Japanese Innovator Company transferred their process of an old listed product (no longer patented) to Cipla's facility. Site transfer regulation procedure was less complicated and approval received within 3 months. (Jinsoku Ichihen)

*II : Generic Formulation Development*

1. Sun Pharma : Recently got Japanese ANDA approval for anti-pain product (Daiichi's Cravit (Levofloxacin))
2. Cipla : Strategic collaboration with Japanese GE company for co-development of a new GE formulation. In 2013 which was successfully developed and launched as a first GE in 2013. The product continues to be supplied in Japan.

*Others*

Jubliant : Manufacturing a blockbuster generic product for a large Japanese GE company through technology transfer, one more new GE product has been filed in Feb 2016 and two(2) others are under development

# Barriers of entry to the Japanese Market

GMP compliance : Unique and strict requirements. Japanese companies and authorities worry if foreign companies can understand and comply (Change control etc.)

Stable supply : Whether a product can be supplied at the agreed upon delivery timelines. In Japan, companies must sell the GE product for a minimum period of 5 years.

Appearance : Quality demand is very high when it comes to AESTHETICS of tablets and the packaging. i.e. Foreign substances, stain, dust, hair, deformed blister, chipped tablet etc. These might be accepted in the US/EU but *NOT* in Japan.

# THANK YOU!