Latest trend of pharmaceutical regulation In India

Dr.S.eswara reddy
Joint Drugs Controller (I)

Outline:

- Indian Pharmaceutical Industry
- Introduction CDSCO
- Introduction to Drugs and Cosmetics Act and Rules
- Measures taken for strengthening
- Latest trend of Ph. regulations
- Conclusion

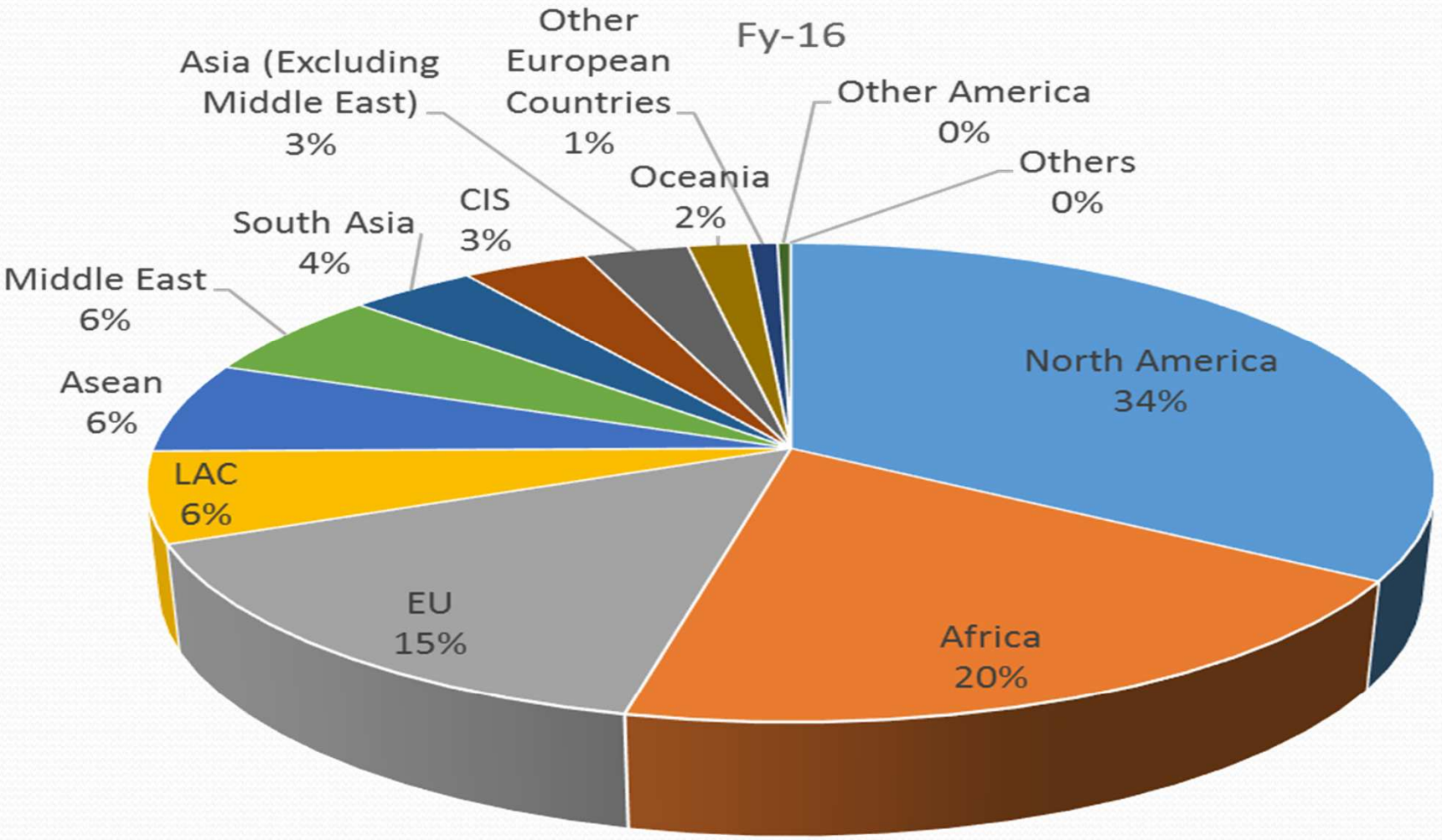
Indian Pharmaceutical Industry – A Profile

Size of the Industry	**USD 32 Billion**
Export	USD 17 Billion
Domestic market	USD 15 Billion
Growth Rate	13-14 %
Imports	USD 6 Billion
Exported to	More than 200 countries
Volume of Production	3rd Largest in the world
Value of production	13th in the world

Indian Pharmaceutical Industry – A Brief Profile

Type of Manufacturing Unit	Number of Units (Approx)
Formulations	4900
Active Pharmaceutical Ingredients	1500
Vaccines	30
Medical Devices	350
Miscellaneous (Surgical dressings, Blood banks, Disinfectants etc)	2850
Other Industry	
Cosmetics	2300
Ayurveda, Unani	4800
Homeopathy	1000
Whole sale and Retails	800,000

India's Contribution to Global Health Care



INDIAN PHARMACEUTICAL INDUSTRY : EXPORT

Indian Pharmaceutical Industry – Global Presence

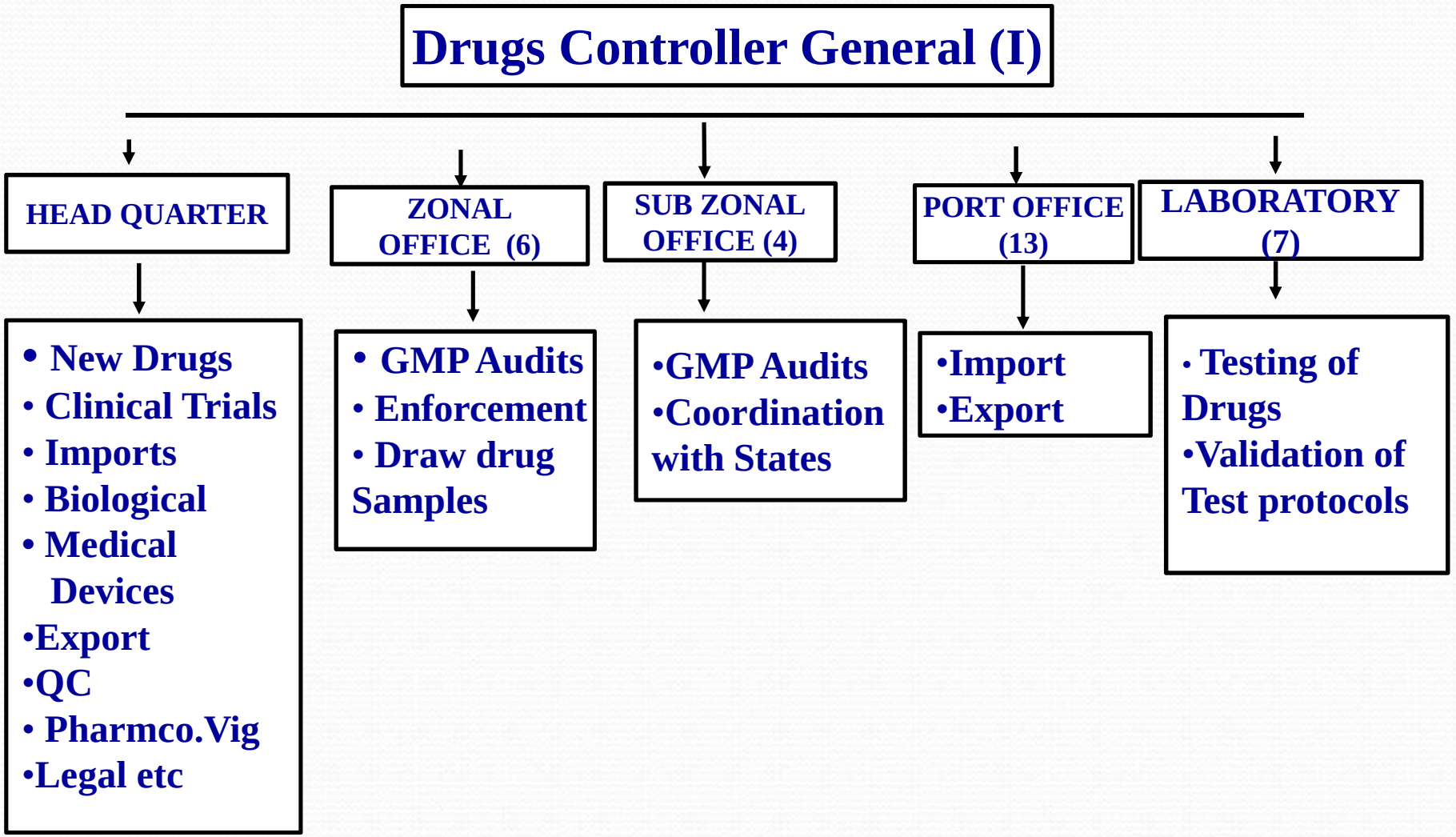
USFDA Approved sites (Formulations + API)	650 (Approx)
EDQM approved sites	253 (Approx)
COPP holding sites	1300 (approx)

Central Drugs Standard Control Organisation

CDSCO

- National Drug Regulatory body
- Under Ministry of Health and Family Welfare
- Headed by Drugs Controller General Of India
- On behalf of Central Government
- Functional NRA by WHO
- Nodal agency for all international activities
- Coordinate with States

Central Drugs Standard Control Organization



CDSCO – Structure

Drugs Controller General of India

Joint Drugs Controller

Deputy Drugs Controller

Assistant Drugs Controller

Drugs Inspectors/Technical Officers

Assistant Drugs Inspectors

Contractual Technical Staff

Drugs and Cosmetics Act and Rules

- **Drugs fall under the Concurrent list of the Constitution**
- **The Act is a Central Act, enforced by both Central and State Govt.**
- **Extended to Whole of India**

Drugs and Cosmetics Act and Rules

Objective:

To ensure safety, efficacy and quality of

- Drugs
- Biologicals
- Medical Devices
- Cosmetics
- Veterinary Drugs.

Implementing Authorities:

- **Central Government:**
  - Central Drugs Standard Control Organization(CDSCO)

- **State Governments:**
  - State Drug Licensing Authorities

Drugs and Cosmetics Act and Rules:

Central Responsibilities:

- New Drug Approvals/Medical Devices
- Import of Drugs/Medical Devices
- Clinical Trails
- Standards for Drugs
- Amendments to Act and Rules
- Pharmacovigillance

State Responsibilities:

- License for Manufacture, Sale and Distribution
- Monitoring quality of Drugs and Cosmetics
- Investigations and Prosecutions

Drugs and Cosmetics Act

Principle:

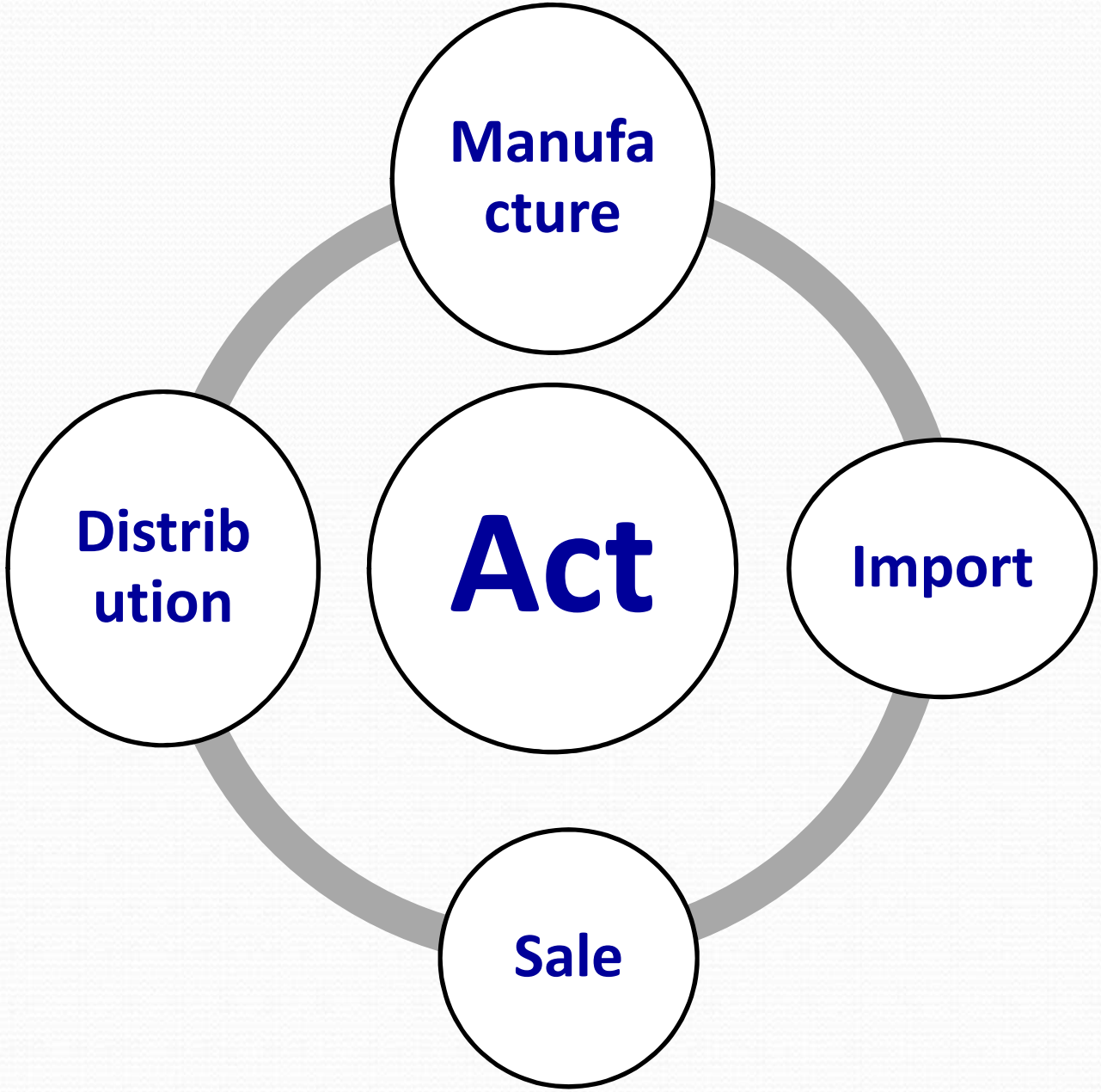
"through system of licensing"

Basic Philosophy:

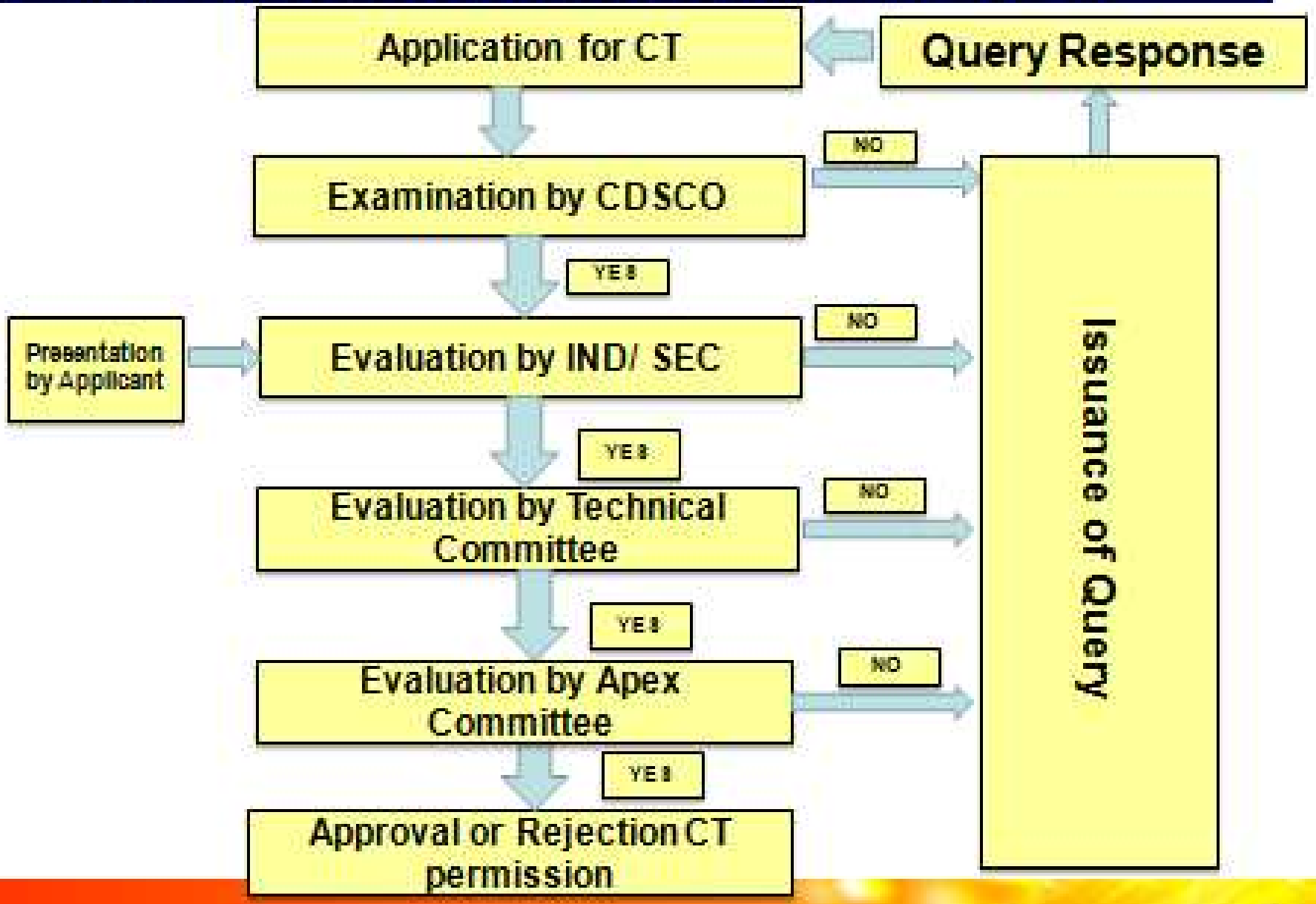
- Manufacturers are responsible for quality of drugs manufactured by them
- Regulatory Agencies will monitor the quality of drugs by

- Periodic inspections of the manufacturing and sales premises for confirmation to the provisions of Drugs & Cosmetics Act
- Monitoring the quality of drugs moving in the market by carrying out post market surveillance.

Drugs and Cosmetics Act



Evaluation of IND/ New Drug Applications for CT



Import of Pharmaceutical products

- Registration of the product with National Regulatory Authority mandatory before import into the country
- Overseas manufacturing sites have to comply to the WHO requirements of GMPs
- Registration is valid for three years
- Site registration fee -1500 USD, product fee-1000 USD
- Provisions for Site inspection
- Site Master File, DMF, Labels
- Review time 9 months
- Quality check at the port of entry

Export of Pharmaceutical products

- Valid license to manufacture drugs for export
- Common GMP Standards for domestic and export purpose
- Products have to comply with the requirements of the importing country
- Joint inspection of the facility by the Central and State authorities carried out for issue of WHO GMP certificate
- Quality check (Label Verifications) of the drugs at the port of exit
- Written confirmation certificate issued for export of APIs to EU countries

Measure Taken

- **STRENGTHENING OF DRUG REGULATORY SYSTEMIN THE COUNTRY.**

- Manpower of CDSCO increased from 111(as on April, 2008) to 474
- States also increased manpower around 20-50%
- Capacities of labs increased
- International cooperation with other overseas regulatory agencies through MoU
- Training to drug regulators on GMP, GLP, GCP

Measure Taken

- **STRENGTHENING OF DRUG REGULATORY SYSTEMIN THE COUNTRY.**
  - Established National Drugs Regulatory Academy
  - Strengthened Pharmacovigillance program
  - International Harmonization
    - Observer status in ICH
    - Member in ICMRA
    - MoU with USFDA, MHRA, PMDA, Russia, China etc

A MoC was signed between CDSCO and Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, Japan on December 11, 2015 at CDSCO (HQ), New Delhi. DCG(I) and other Senior officers of CDSCO during signing of the MoC.

MoU was signed between CDSCO and MHRA , UK at CDSCO (HQ) on October 5, 2015. The delegates of MHRA were led by Sir Michael Rawlins, Chair, MHRA.

Drugs Controller General of India meeting the Deputy Commissioner, Global Regulatory Operations and Policy, USFDA Mr. Howard R Sklamberg on March 17,2015 at CDSCO (HQ), New Delhi.

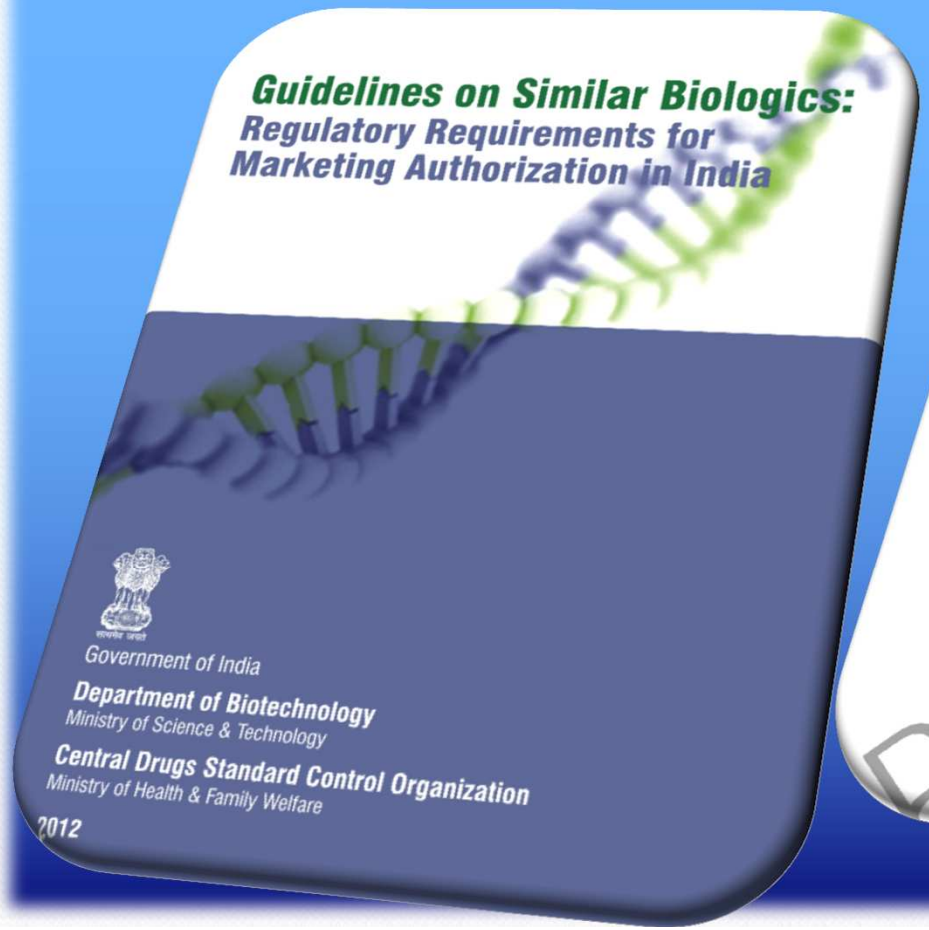
Recent Changes in Regulations

- Provision for compensation /medical management in case of death/injury during Clinical Trial
- Provision for inspection of Clinical Trial Sites
- Registration of Ethics Committees
- Registration of Cosmetics
- No regulatory approval for Academic Research(CT)
- Track and Trace system (Draft)
- Export to ICH countries exemptions
- Prohibition of testing of Cosmetics on animals
- Single window clearance for import of drugs

IT enable services

1. SUGAM app (Online application system) launched by CDSCO
   - Drug import registration
   - Registration for medical devices
   - Online registration of Cosmetics
   - Ethics committee registration
   - Track the status of submitted application.
   - Online review
   - Online query reply
   - Online approval

Recent Guidelines on biological products:



Strengthening of Drug Regulatory System

- Rs 1750 Cr (300 USD Mi)
- Rs 900 Cr for CDSCO and Rs 850 Cr for States
- Major Components:
  - Manpower – 1000 for CDSCO, 2500 for States
  - New labs- 6 for CDSCO and 10 for States
  - E-Governance
  - National Drug Regulatory Academy
  - 8 Mini labs, 20 mobile vans
  - Up gradation of existing labs and offices

Conclusion:

- Adequate regulations
- Inadequate trained man power
- Quality Medicines at affordable Price
- Hub for Generic Medicines
- Supply to UN, WHO etc
  - Vaccines
  - Antiretroviral drug (HIV Drugs)
  - TB and Anti-malarial Drugs
- International co-operation through MoUs


Thank you

Keynote Speech I

Outline of Japan's Pharmaceutical Regulation

1st India-Japan Medical Products Regulation Symposium

18th May 2016

Toshiyoshi TOMINAGA, Ph.D.
Associate Executive Director for International Programs,
Pharmaceuticals and Medical Devices Agency (PMDA)
JAPAN

Outlines

I. New Drug Review

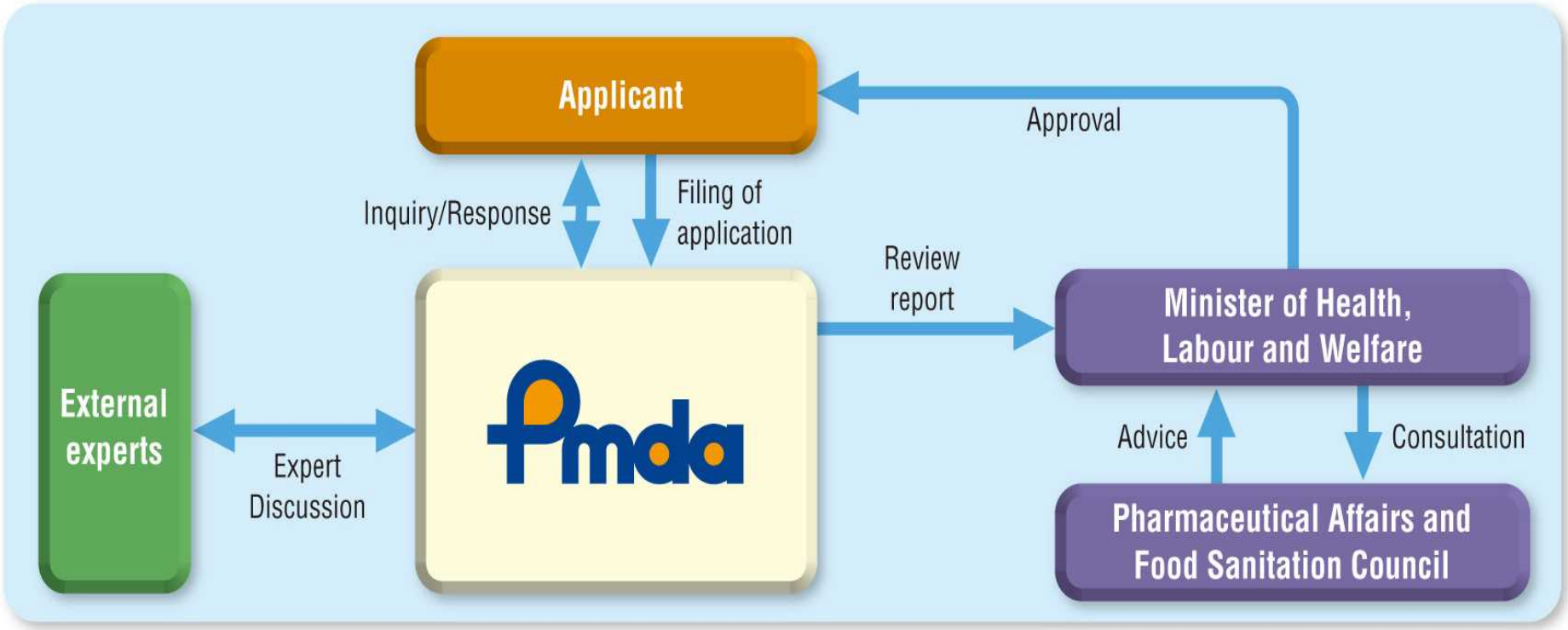
II. Consultation

III. Post-market Issues

IV. International Harmonization

I. New Drug Review

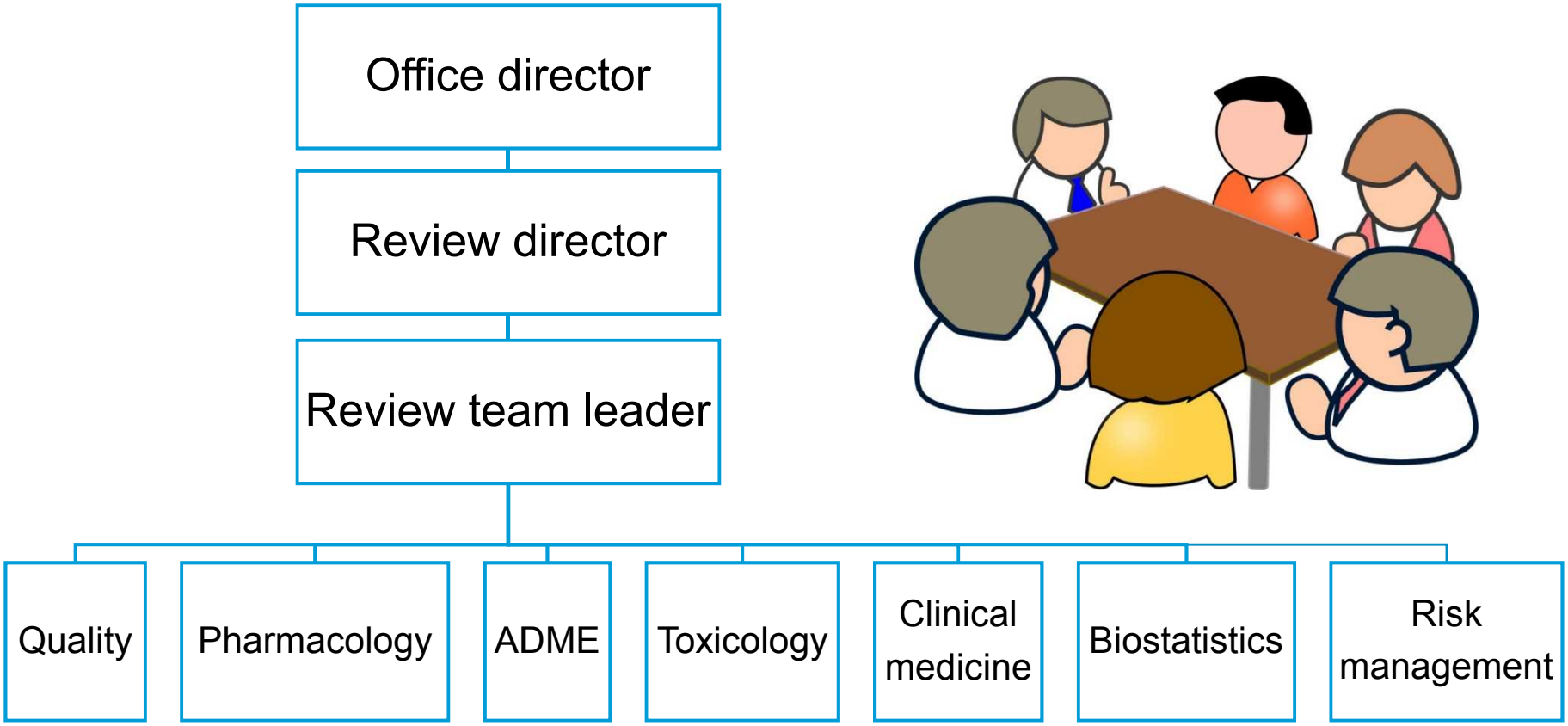
NDA Review Process in Japan



New drug review offices	
New Drug I	Gastrointestinal drugs, drugs for metabolic disorders (including DM and osteoporosis) etc.
New Drug II	Cardiovascular drugs, antithrombotics, antidementia drugs etc.
New Drug III	Central and peripheral nervous system drugs, anesthetics, sensory organ drugs etc.
New Drug IV	Antibiotics, antiviral drugs, respiratory tract drugs, anti-allergy drugs etc.
New Drug V	Antineoplastic drugs
Cellular and Tissue-based Products	
Vaccines and Blood Products	

Other related offices		
Advanced Review with Electronic Data Promotion Group		
Generic Drugs	OTC	Medical Devices I, II, III
Non-clinical and Clinical Compliance	Manufacturing/Quality and Compliance	
Safety I, II	Medical Informatics and Epidemiology	
Standards and Guidelines Development		

Review Team in Offices of New Drug



Review team leader→average year of employment: 8-10 years
review sub leader→average year of employment: 3-7 years

New Target of Review Time

- New Drugs（Priority）

2nd mid-term plan

3rd mid-term plan

Fiscal Year	Percentile	Review Time
2013	50 %（median）	9 months
2014	60 %	9 months
2015	60 %	9 months
2016	70 %	9 months
2017	70 %	9 months
2018	80 %	9 months

7.2 months (Result)

- New Drugs（Standard）

2nd mid-term plan

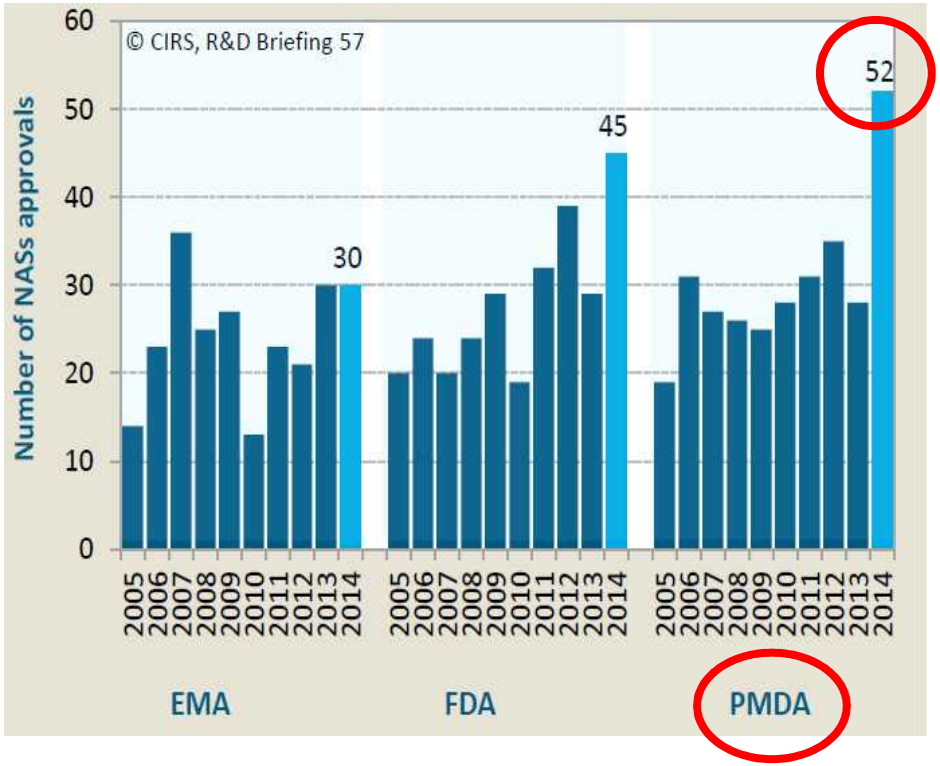
3rd mid-term plan

Fiscal Year	Percentile	Review Time
2013	50 %（median）	12 months
2014	60%	12 months
2015	70%	12 months
2016	70%	12 months
2017	80%	12 months
2018	80%	12 months

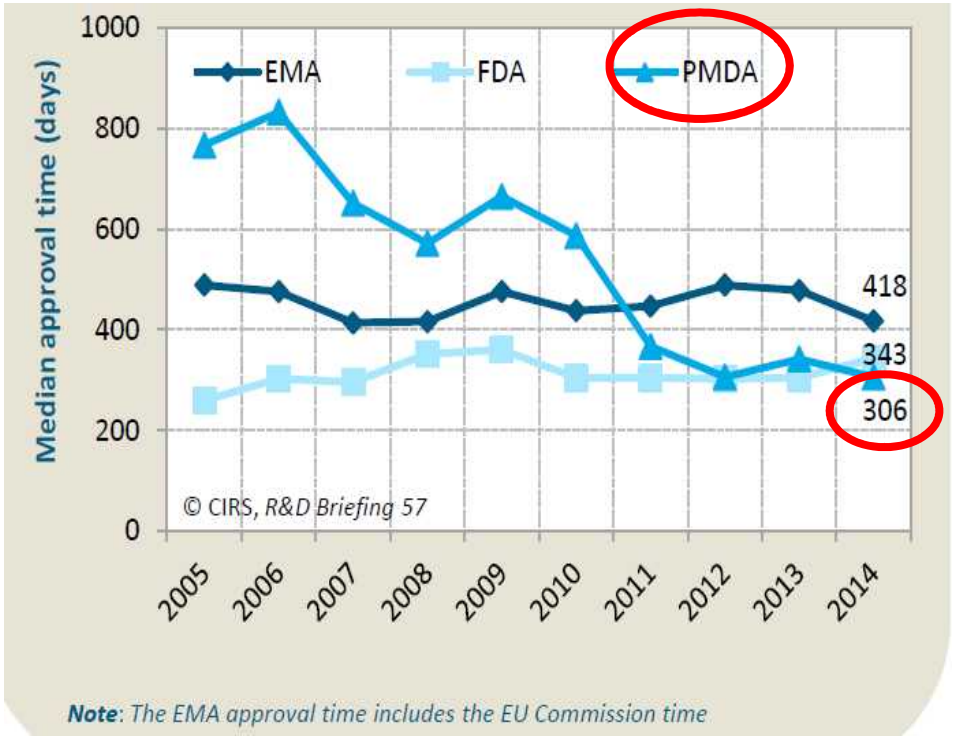
11.3 months (Result)

Number of New Drug Approved and Review Speed

Number of NAS (New Active Substance) s approved by ICH agencies by approval year



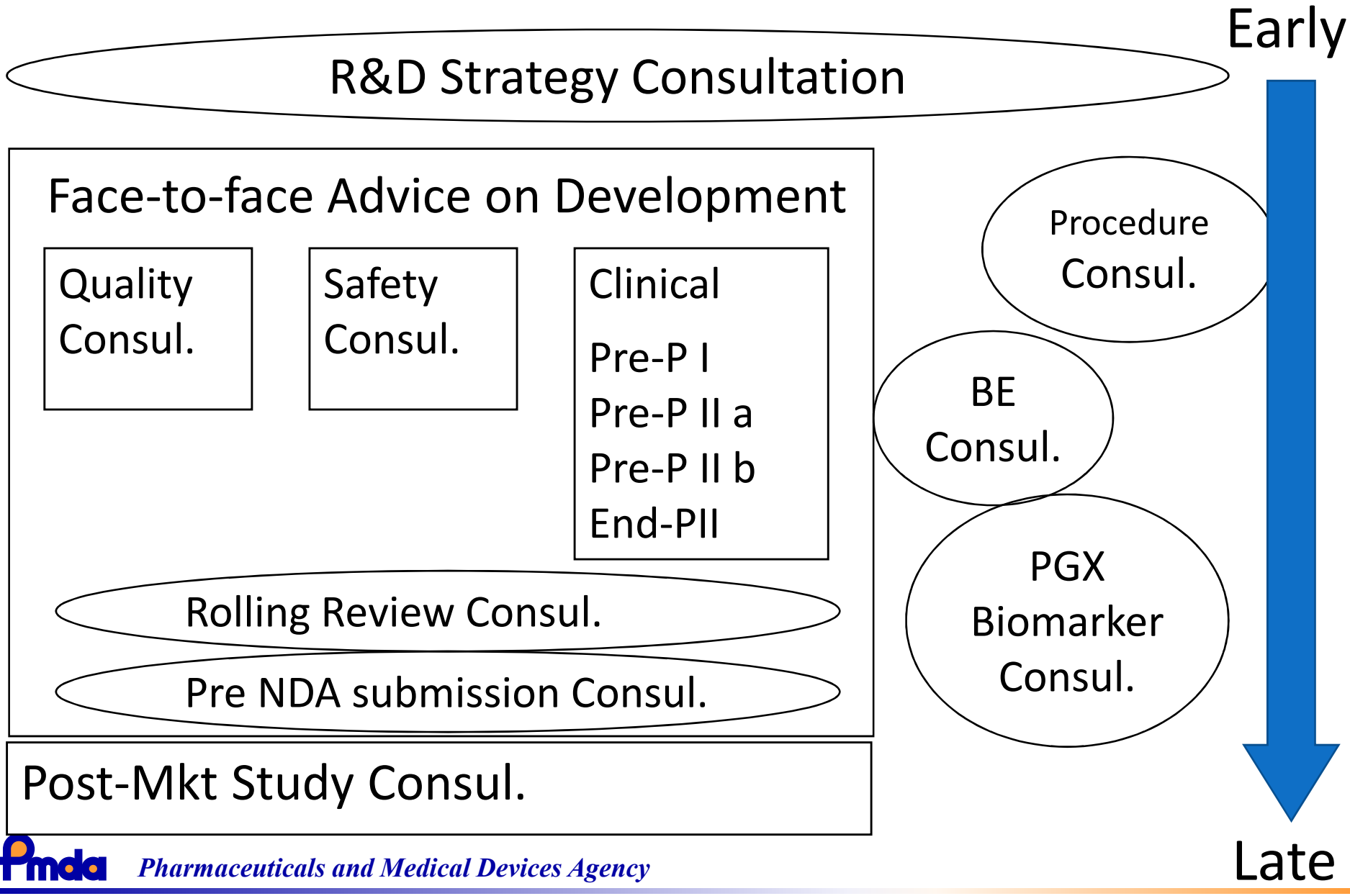
Median approval times for NASs approved by ICH agencies by approval year



http://cirsci.org/sites/default/files/CIRS_R&D_57_ICH_%20approval_%20times_2005-2014_%2006072015.pdf

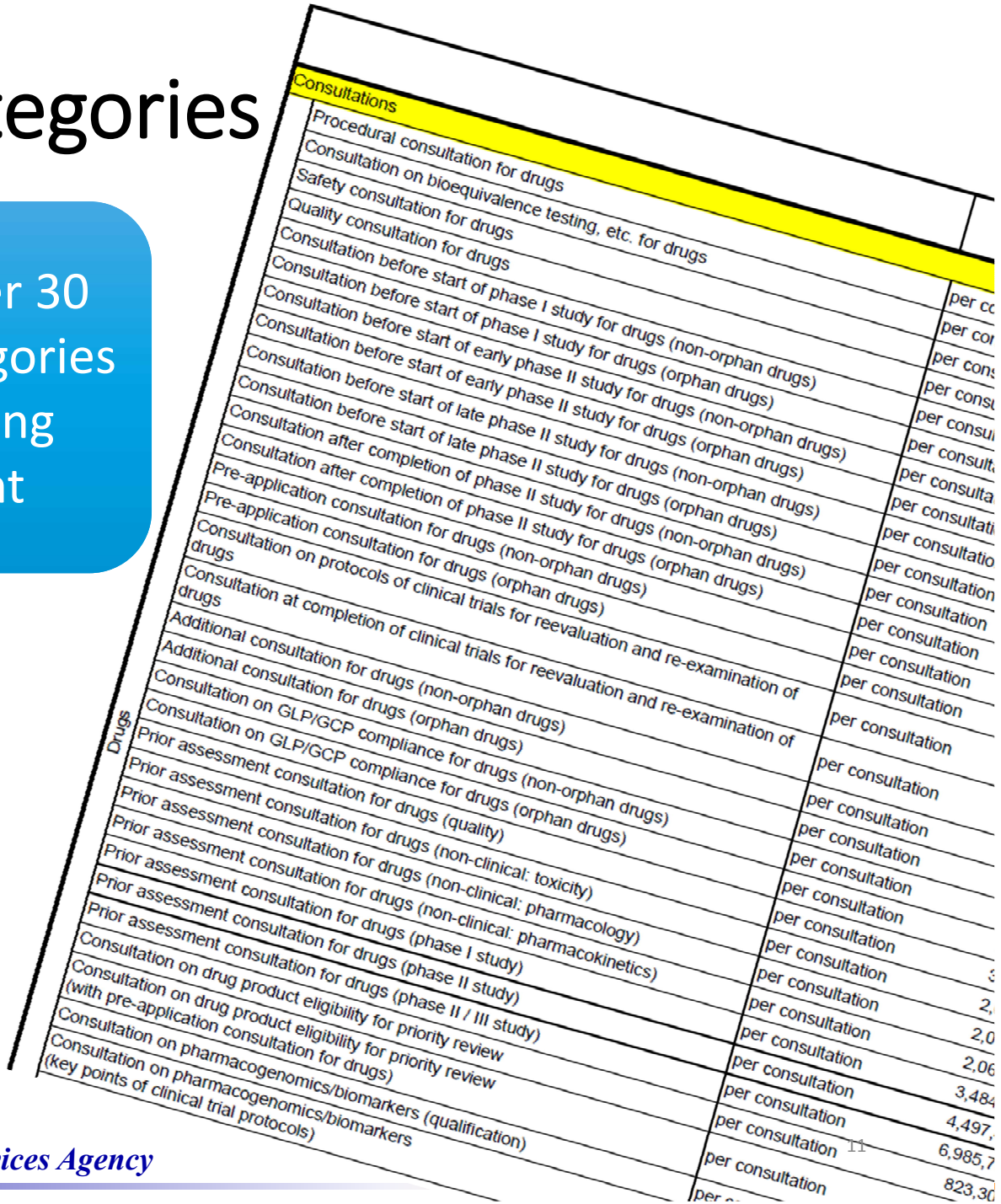
II. Consultation

PMDA's Consultation Menu



Consultation Categories

Currently, there are over 30 PMDA consultation categories to meet the need during product development



Consultations	
Drugs	Procedural consultation for drugs
	Consultation on bioequivalence testing, etc. for drugs
	Safety consultation for drugs
	Quality consultation for drugs
	Consultation before start of phase I study for drugs (non-orphan drugs)
	Consultation before start of phase I study for drugs (orphan drugs)
	Consultation before start of early phase II study for drugs (non-orphan drugs)
	Consultation before start of early phase II study for drugs (orphan drugs)
	Consultation before start of late phase II study for drugs (non-orphan drugs)
	Consultation before start of late phase II study for drugs (orphan drugs)
	Consultation after completion of phase II study for drugs (non-orphan drugs)
	Consultation after completion of phase II study for drugs (orphan drugs)
	Pre-application consultation for drugs (non-orphan drugs)
	Pre-application consultation for drugs (orphan drugs)
	Consultation on protocols of clinical trials for reevaluation and re-examination of drugs
	Consultation at completion of clinical trials for reevaluation and re-examination of drugs
	Additional consultation for drugs (non-orphan drugs)
	Additional consultation for drugs (orphan drugs)
	Consultation on GLP/GCP compliance for drugs (non-orphan drugs)
	Consultation on GLP/GCP compliance for drugs (orphan drugs)
	Prior assessment consultation for drugs (quality)
	Prior assessment consultation for drugs (non-clinical: toxicity)
	Prior assessment consultation for drugs (non-clinical: pharmacology)
	Prior assessment consultation for drugs (non-clinical: pharmacokinetics)
	Prior assessment consultation for drugs (phase I study)
	Prior assessment consultation for drugs (phase II study)
	Prior assessment consultation for drugs (phase II / III study)
	Consultation on drug product eligibility for priority review
	Consultation on drug product eligibility for priority review (with pre-application consultation for drugs)
	Consultation on pharmacogenomics/biomarkers (qualification)
	Consultation on pharmacogenomics/biomarkers (key points of clinical trial protocols)

Pharmaceutical Affairs Consultation on R&D Strategy

Valley of Death

-Shortage of funds, Knowledge on Regulation and Developmental Strategy

Pmda Strategic Consultation

Basic Research

Pharmaceuticals and Medical Devices candidates originating from Japan

Quality Study

Non-Clinical Study

Clinical Trial

(Up to POC studies)

Practical Use

Innovative Products originated from Japan

* Further studies are handled by the Regular Consultation

Consultation on quality or toxicity study of biologics, cell- and tissue-based products

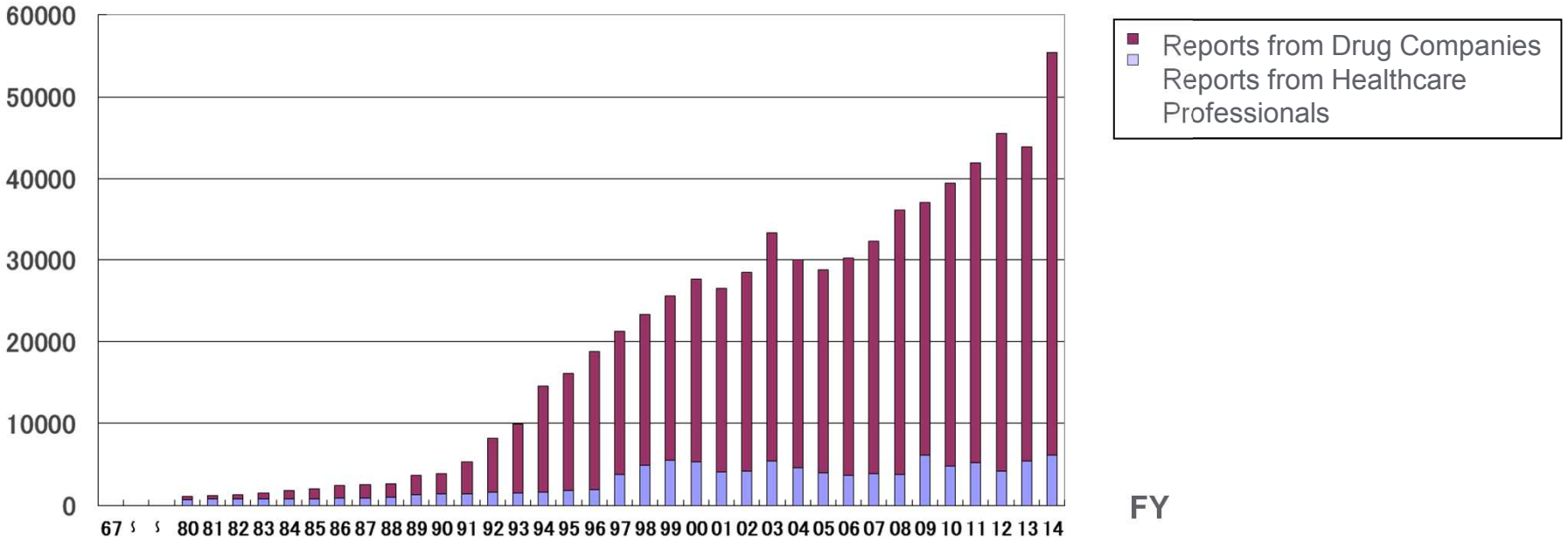
Consultation on endpoints or sample size of early clinical trial

Hideo Utsumi DIA Annual Meeting (2012)

III. Post-market Issues

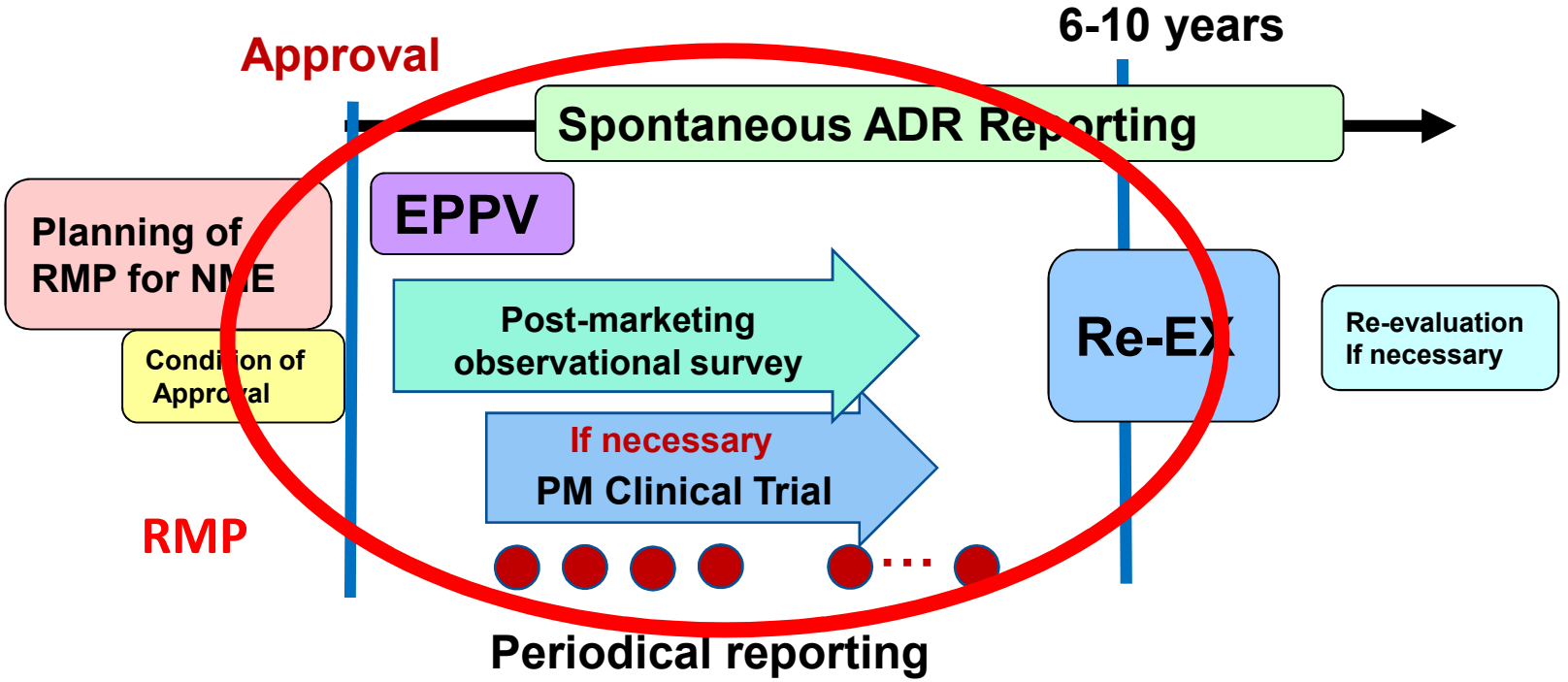
Spontaneous Serious ADR Reporting

- MHLW and PMDA gather ADR reports from drug companies and also directly from health care professionals.
- In FY2014, about 55,000 serious ADR cases were reported.



Tomiko Tawaragi DIA EuroMeeting (2016)

Overview of Japanese Pharmacovigilance Framework

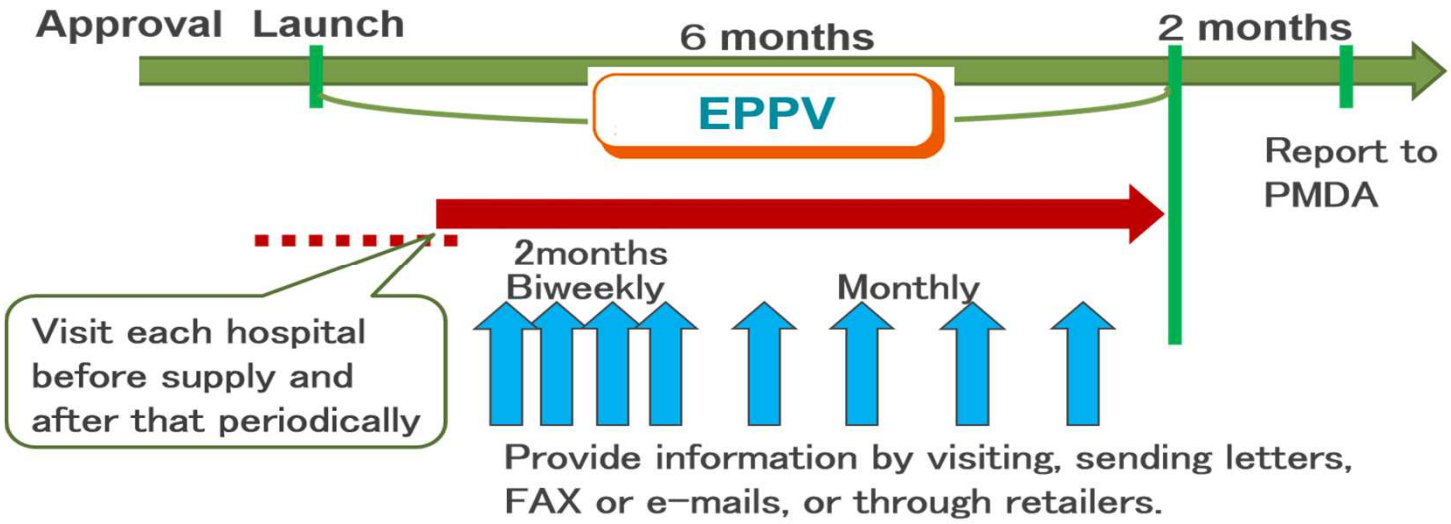


EPPV : Early Post-marketing Phase Vigilance
(6 months intensive monitoring)
RMP : Risk Management Plan
Re-EX : Re-examination

Tomiko Tawaragi DIA EuroMeeting (2016)

Early Post-marketing Phase Vigilance （EPPV）

- Monitoring ADRs is critical in the first 6 months after the launch of a new drug.
- Marketing authorization holders are required to provide the safety information to health care professionals (HCP) and to collect ADR information intensively for the time frame by visiting hospitals periodically.



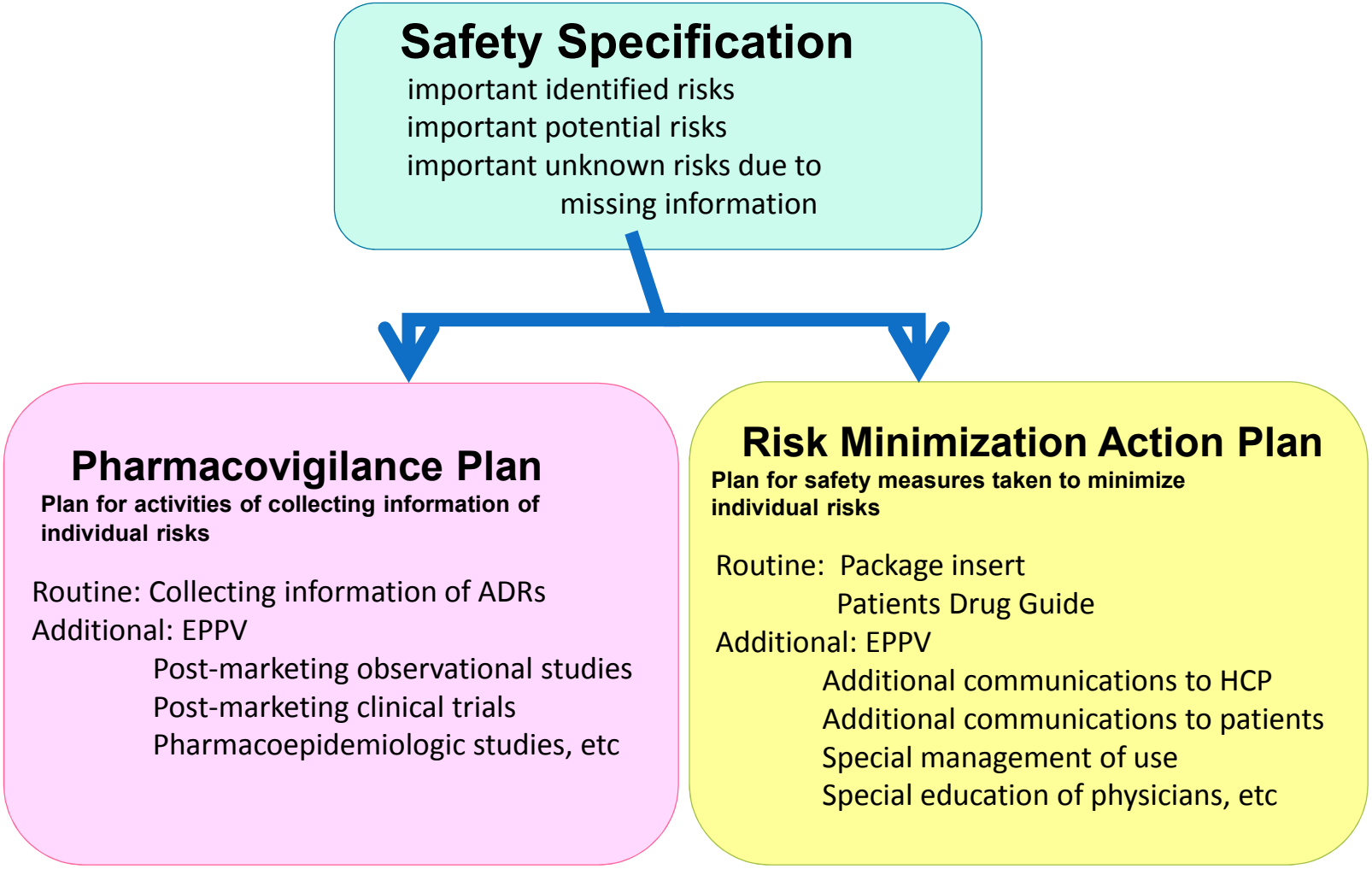
Tomiko Tawaragi DIA EuroMeeting (2016)

Risk Management Plan (RMP)

- In order to conduct an appropriate management of risks of drugs throughout their life-cycle, J-RMP is required for new drugs since 2013 and for some generic drugs since 2014.
- J-RMP is a compact document which consists of the following three elements;
  - Safety specification
  - Pharmacovigilance plan
  - Risk minimization action plan.
- *177* J-RMPs have been posted on the PMDA website.

Tomiko Tawaragi DIA EuroMeeting (2016)

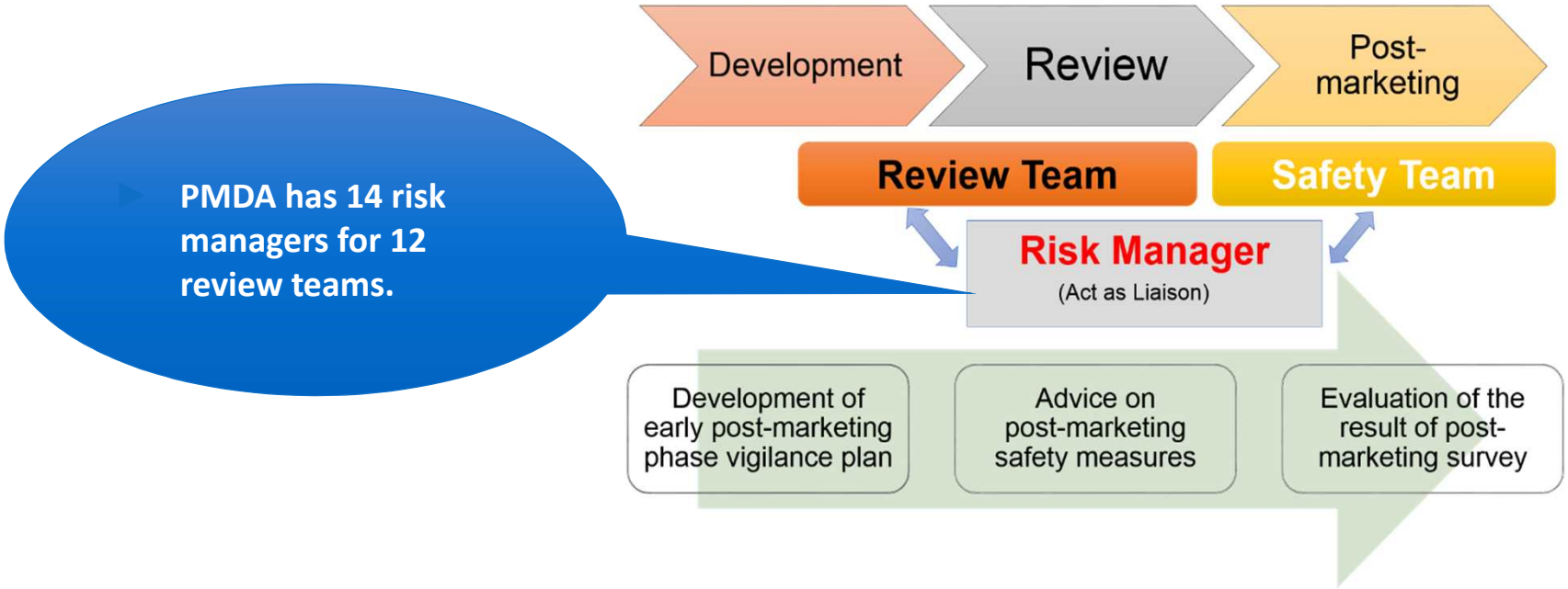
Risk Management Plan (ctd.)



Tomiko Tawaragi DIA EuroMeeting (2016)

Development of J-RMP

- At the time of approval application of new drugs and a part of generic drugs, a draft of J-RMP is required to submit to PMDA. Then, the applicant, PMDA review team, and a risk manager of post-market surveillance team discuss and agree on the J-RMP before the approval.



Tomiko Tawaragi DIA EuroMeeting (2016)

IV. International Harmonization

Examples of Current Global Activities

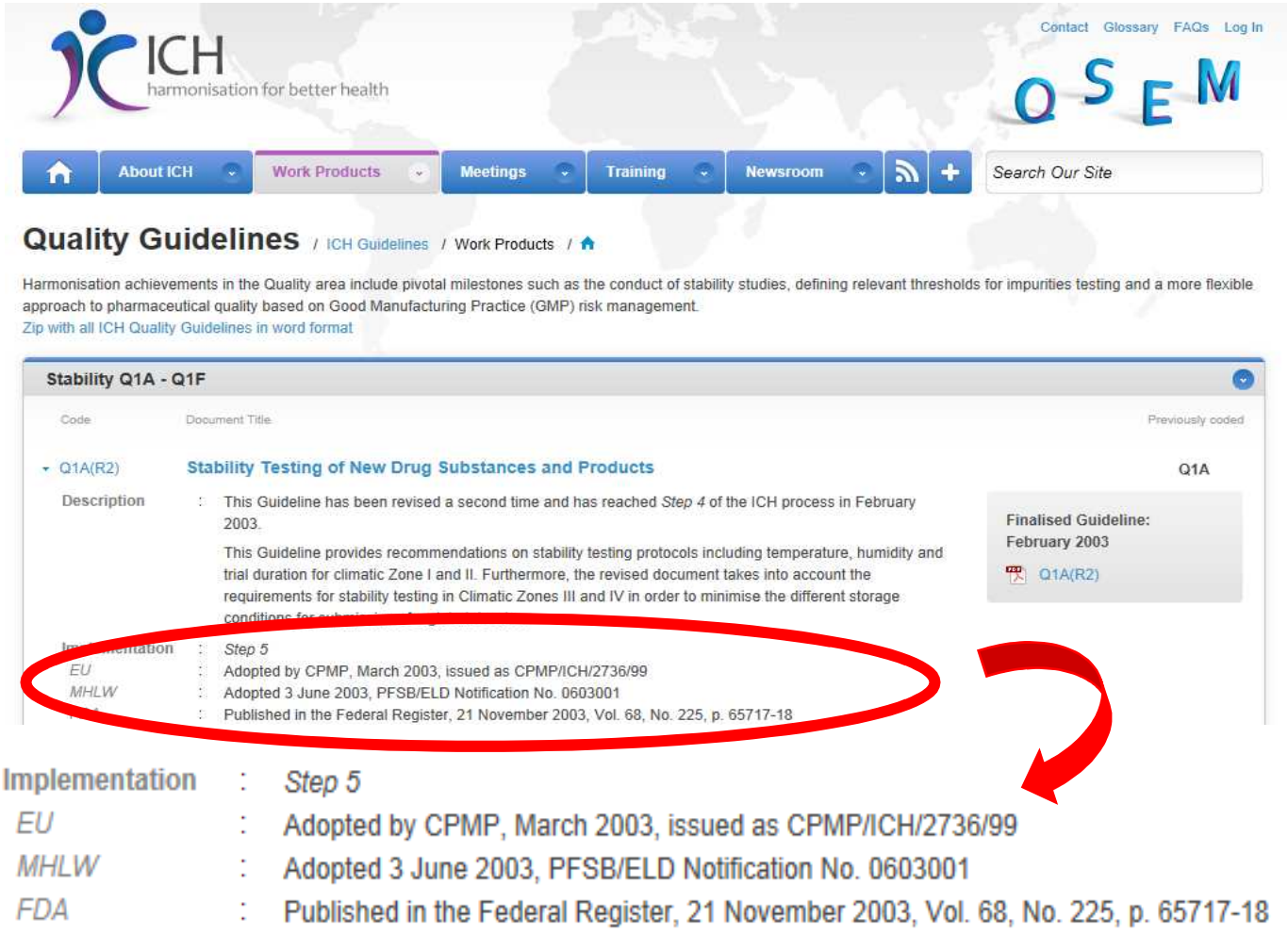
Summit | ICH | IMDRF | PIC/S | ICDRA

APEC LSIF RHSC | PDG | IGDRP | ICMRA

and more…

Abbreviation	Official Name
Summit	International Summit of Heads of Medicines Regulatory Agencies
ICH	International Council on Harmonization →Harmonization of Common Regulatory Standards/Tools
IMDRF	International Medical Device Regulators Forum
PIC/S	Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme
ICDRA	International Conference of Drug Regulatory Authorities
APEC LSIF RHSC	APEC Life Science Innovation Forum Regulatory Harmonization Steering Committee
OECD MAD	OECD Mutual Acceptance of Data
PDG	Pharmacopoeial Discussion Group
IGDRP	International Generic Drug Regulators Program
ICMRA	International Coalition of Medicines Regulatory Authorities

How ICH Guidelines are implemented



Implementation : *Step 5*
EU : Adopted by CPMP, March 2003, issued as CPMP/ICH/2736/99
MHLW : Adopted 3 June 2003, PFSB/ELD Notification No. 0603001
FDA : Published in the Federal Register, 21 November 2003, Vol. 68, No. 225, p. 65717-18

Japanese Guidline

2.1.7.1. 一般的な原薬

試験の種類	保存条件	申請時点での最小試験期間
長期保存試験*	25℃±2℃／60%RH±5%RH 又は 30℃±2℃／65%RH±5%RH	12 カ月
中間的試験**	30℃±2℃／65%RH±5%RH	6 カ月
加速試験	40℃±2℃／75%RH±5%RH	6 カ月

*申請者は、長期保存試験として 25℃±2℃／60%RH±5%RH 又は 30℃±2℃／65%RH ±5%RH どちらの条件で行うかを決定する。

ICH Guideline

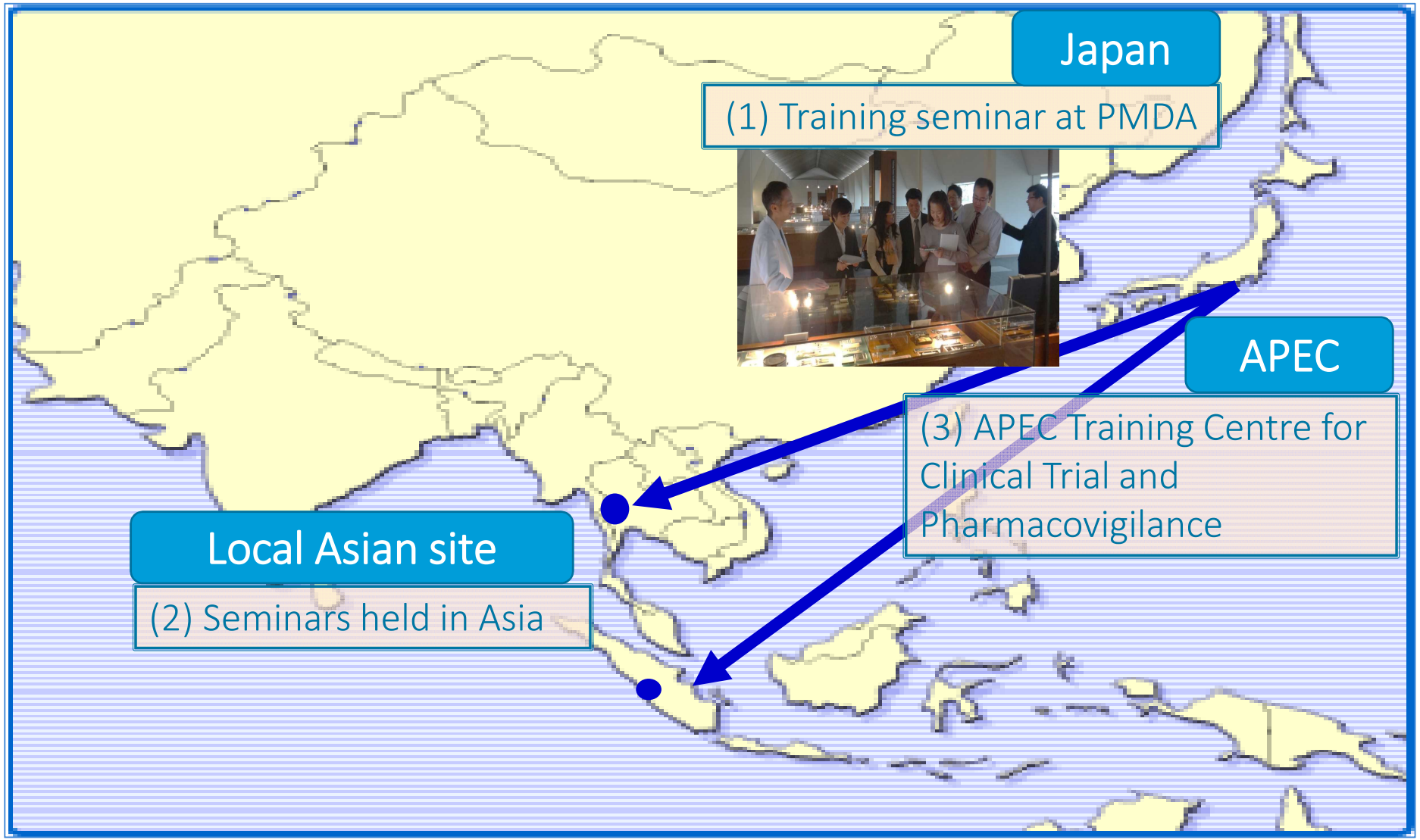
2.1.7.1. General case

Study	Storage condition	Minimum time period covered by data at submission
Long term*	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH	12 months
Intermediate**	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

*It is up to the applicant to decide whether long term stability studies are performed at 25 ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH.

Benefit of International Standards

PMDA Asia Training Center



Thank you for the attention.

DISCLAIMER : The contents of this presentation represent the view of this presenter only, and do not represent the views and/or policies of the PMDA

Trend of regulation on regenerative medicine products in Japan

18 May 2016

Daisaku Sato, Ph.D.

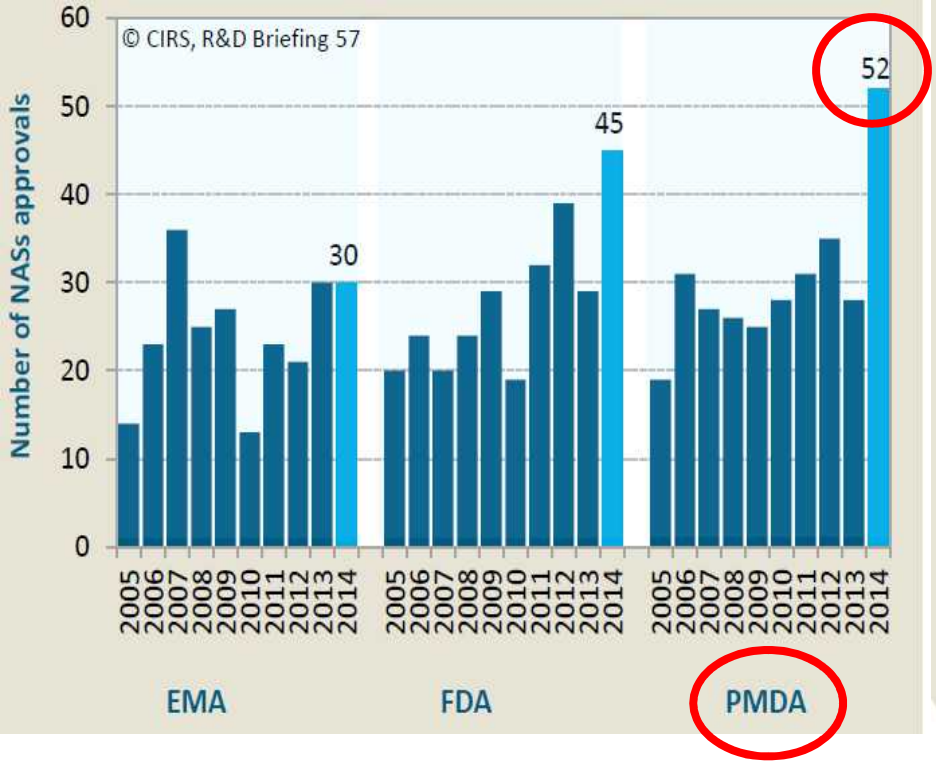
Director, Office of Cellular and Tissue-based Products
Pharmaceuticals and Medical Devices Agency, Japan

Contents

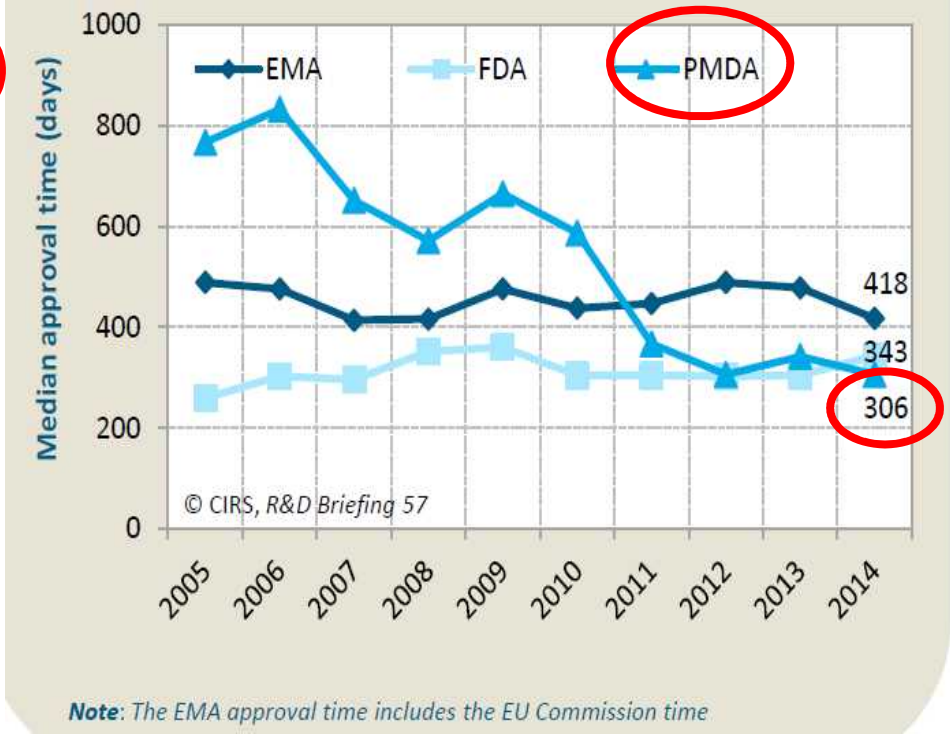
- Introduction
- New regulatory Framework for Cell therapy
- Examples of Review
- Quality System Requirement
- Facilitate Development

Performance of PMDA's NDA review

Number of NASs approved by ICH agencies by approval year



Median approval times for NASs approved by ICH agencies by approval year



http://cirsci.org/sites/default/files/CIRS_R&D_57_ICH_%20approval_%20times_2005-2014_%2006072015.pdf

NEW REGULATORY FRAMEWORK
for
Cell Therapy Products

New Legislative Framework

These two acts were promulgated in November 2013 by the Japanese Diet (Parliament) in line with the **Regenerative Medicine Promotion Act**, in order to reform the pharmaceutical and medical regulation related to regenerative medicine

- **Revision of the Pharmaceutical Affaires Law: The Pharmaceuticals, Medical Devices, and Other Therapeutic Products Act (PMD. Act)**

- The Act on the Safety of Regenerative Medicine

These two acts were enacted on 25 November 2014

Other related governmental policy:

- **Healthcare and Medical Strategy Promotion Act (2014.5)**
- **Japan Medical Research Development Institution Act (2014.5)**

Background for New Legislations (came into effect on 25 November 2014)

1. Needing legal basis for the guideline to secure safety of stem cell therapies
2. Growing need for collaboration between medical institutions and industry from the early stage of development

→ New legislation was needed to enhance safety of regenerative medicine.

→ The Act on the Safety of Regenerative Medicine

3. The existing framework in Pharmaceutical Affairs Law does not fit for the characteristics of regenerative and cellular therapeutic products

→ Definition of regenerative medical products and establishment of new framework were needed.

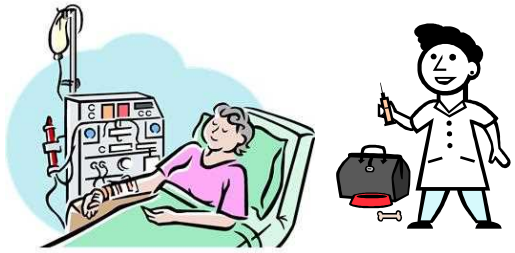
→ Revision of the Pharmaceutical Affaires Law (name changed to The Pharmaceuticals, Medical Devices Act (PMD. Act)

Two Acts regulating regenerative medicine & cell therapy

Regenerative Medicine

MHLW process

All medical **technologies** using processed cells which safety and efficacy have not yet been established



The Act on the Safety of Regenerative Medicine

PMDA process

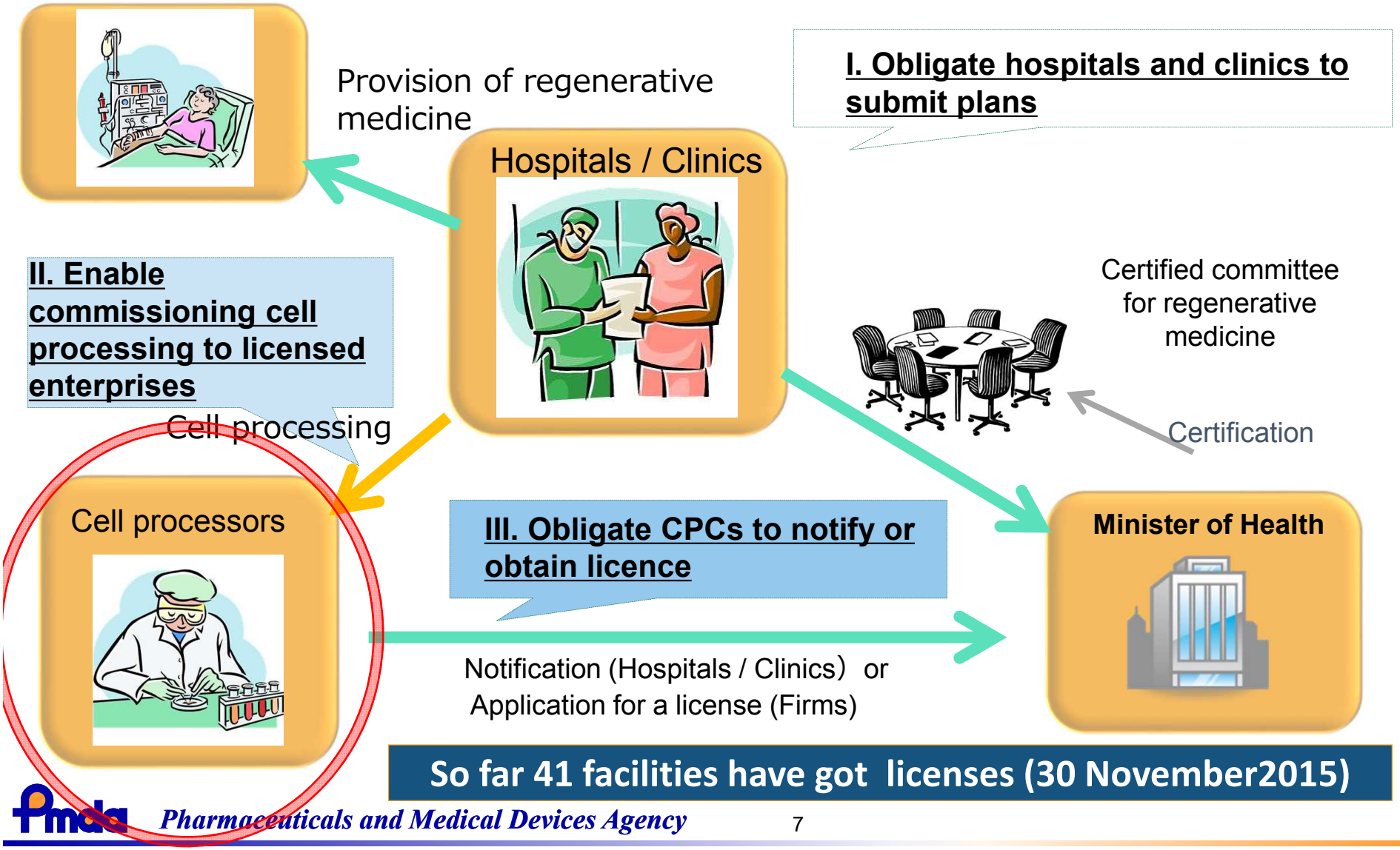
Production and marketing of regenerative and cellular therapeutic **products** by firms

The Act on Pharmaceuticals and Medical Devices (PMD Act)*

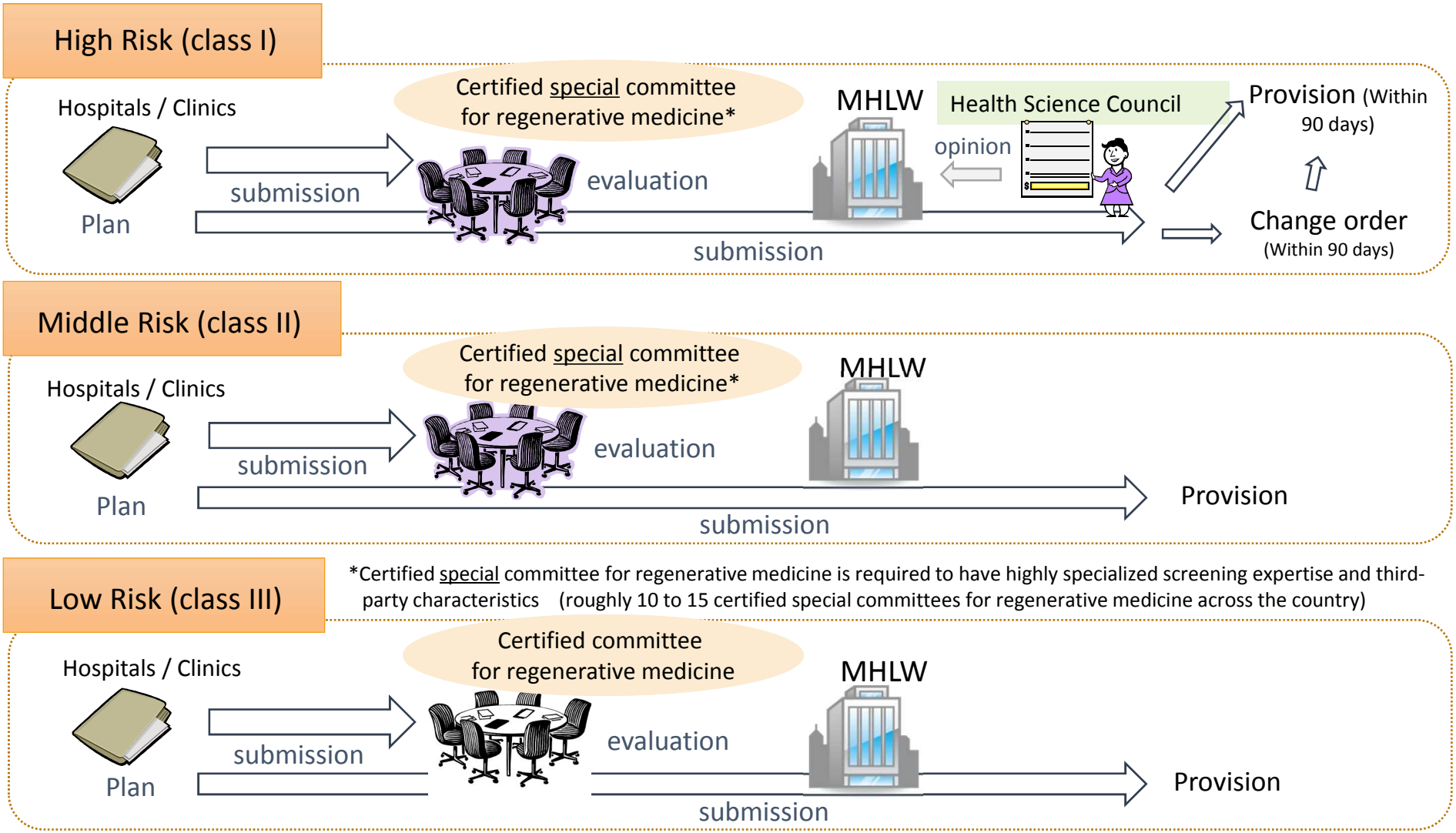
* Two laws will be enacted on 25 November 2014

It may be similar to researcher initiated IND application system

Overview of the Act on the Safety of Regenerative Medicine



Rules for hospitals and clinics



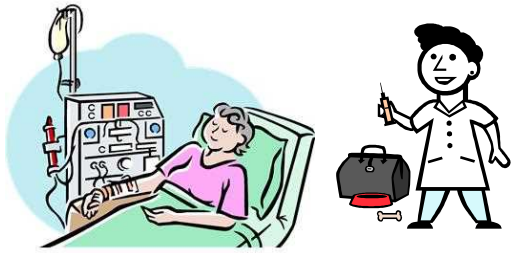
*Certified special committee for regenerative medicine is required to have highly specialized screening expertise and third-party characteristics (roughly 10 to 15 certified special committees for regenerative medicine across the country)

Two acts regulating regenerative medicine & cell therapy

Regenerative Medicine

MHLW process

All **medical technologies** using processed cells which safety and efficacy have not yet been established



The Act on the Safety of Regenerative Medicine

PMDA process

Production and marketing of regenerative and cellular therapeutic **products** by firms

The Act on Pharmaceuticals and Medical Devices (PMD Act)*

* Two laws will be enacted in November 2014

Commercial IND and product approval system

Regenerative medicine & cell therapy in Japan

Medical Care Act (MCA) = The Act on the Safety of Regenerative Medicine.

Pharmaceuticals and Medical Devices Act. (PMD Act.)

Academic Research Purpose

Commercial Product Marketing Authorization Purpose

Medical care

Clinical Research using human stem cells

108 protocols approved

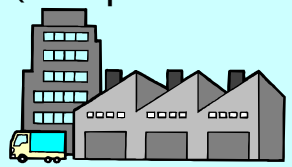
(as of November 2014 - before new legislation)

Under the new legislation, as of 31 January 2016:
79 new clinical research plans,
2634 medical care plans
have been notified to MHLW

Regenerative Medical Products

4 approved marketed products

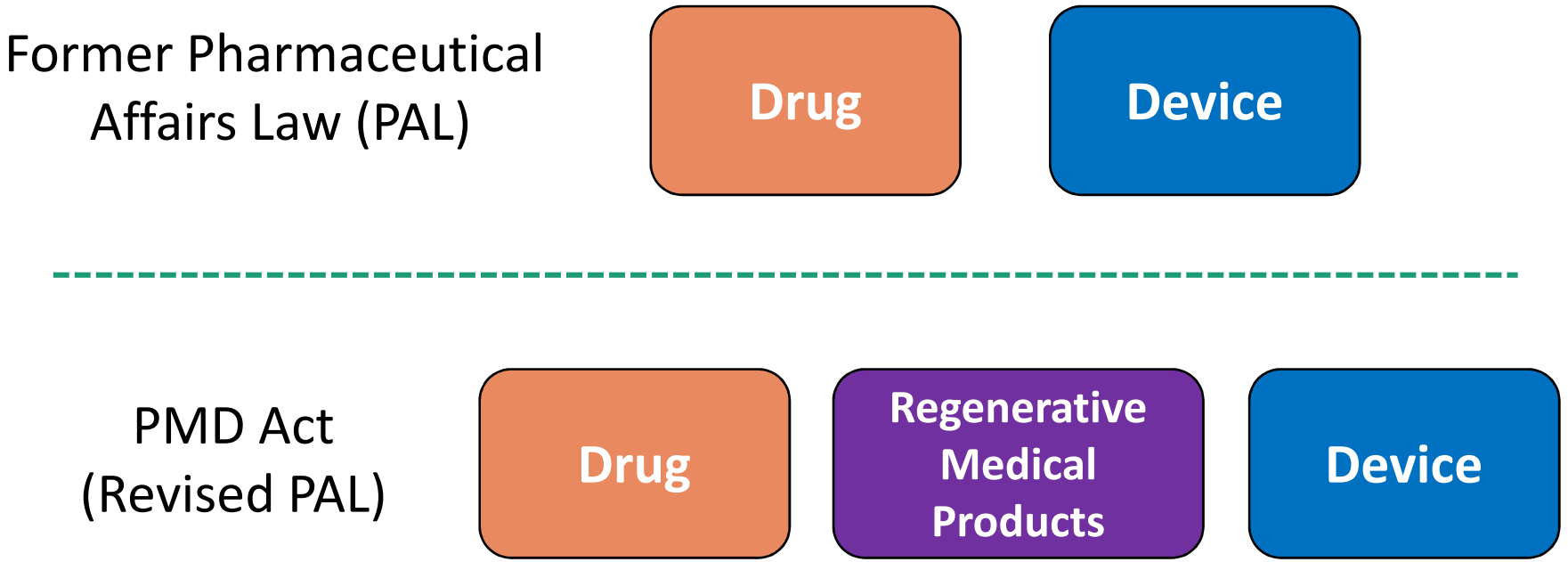
33 clinical trials initiated (including 9 gene therapy products)
(~April 2016)



Covered by MHLW

Covered by MHLW and PMDA

Regenerative Medical Products in the PMD Act



- **Additions for Regenerative Medical Products**
  - Definition and independent chapter for Regenerative Medical Products
  - Introduction of conditional/time limited approval system

Definition of “Regenerative Medical Products” in Japanese Legislation

- **Regenerative medical products** are defined as **processed live human/animal cells** that are intended to be used 1) for either (1) the reconstruction, repair, or formation of structures or functions of the human body or (2) the treatment or prevention of human diseases, or 2) for gene therapy.

Under the Revised PAL (=Pharmaceuticals and Medical Devices Act. (PMD Act.))

・‖.

Cellular and Tissue based Products and Gene therapy Products

・‖.

Advanced-therapy medicinal products (ATMPs)

Regulation (EC) No 1394/2007

Scope of Manipulation("Processed cells") to be regulated

(Definition)

1. **Manipulation to be regulated**
   - Artificial proliferation and differentiation of cells and tissues
   - cell lines
   - drug treatment for the purpose of activation
   - biological properties modification
   - combination with non-cellular components
   - genetic engineering modification
   - Isolation/separation of specific cell by biological and chemical treatment with agents
   - Cells for non-homologous use

2. **Minimal manipulations** such as, treatment with antibiotics, washing, freezing, The gamma ray sterilization, simple isolation/separation without biological and chemical treatment **are not covered by the new regulation**

Blood transfusion (blood products), Hematopoietic stem cell transplantation, Assisted Reproductive Technology, except those derived from genetic engineering, iPS cells, are also excluded from the scope of the regenerative medicine regulation.

Limitations of Clinical Trials of Regenerative Medicine to satisfy unmet medical needs

There are some specific limitations for cell therapy products

- Designed for unmet needs under the present treatment (e.g. last line therapy): limited number of patients available for clinical trials
- Difficult to conduct controlled study to demonstrate clinical benefit, in the Japanese medical environment, due to:
  - highly invasive surgical intervention
  - autologous cell collection
- Clinical trial design affected by heterogeneity of quality derived from source materials (including autologous collection and culture procedures)

PMDA's Philosophy (September 2008)

PMDA continues to improve the public health and safety of our nation by reviewing applications for marketing approval of pharmaceuticals and medical devices, conducting safety measures, and providing relief to people who have suffered from adverse drug reactions.
We conduct our mission in accordance with the following principles:

- We pursue the development of medical science while performing our duty with greater transparency based on our mission to protect public health and the lives of our citizens
- We will be the bridge between the patients and their wishes for faster access to safer and more effective drugs and medical devices
- We make **science-based judgments** on quality, safety, and efficacy of medical products by training personnel to have **the latest technical knowledge and wisdom in their field of expertise**
- We play an active role within the international community by promoting international harmonization
- We conduct services in a way that is trusted by the public based on our experiences from the past.

Benefit and Risk Balance Assessment

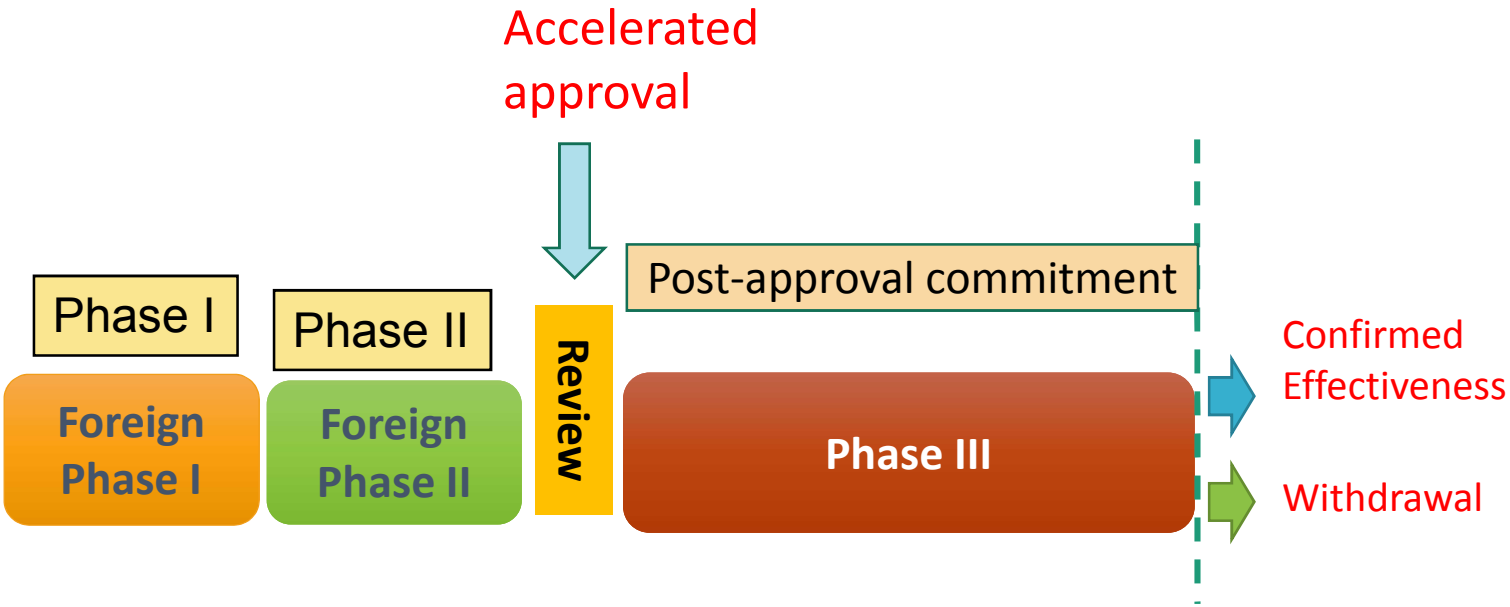
- Discussion of acceptable level of clinical effectiveness vs. patient access to the new therapy
- Weighing acceptable risk against expected benefit
- Based on regulatory sciences in terms of social responsibility for pubic health

Evolving Early Access schemes of ICH founding 3 regions

Each agency has similar approaches to accommodate patient access demand.

Type	US	EU	JAPAN
priority	Priority Review Orphan Designation	Orphan Designation	Priority review Orphan Designation
Conditional	Accelerated approval for serious or life-threatening illnesses	Conditional MA MA under exceptional circumstances **Pilot Project on Adaptive path (new)**	Approval for Oncology drug, Orphan drug **Conditional & Time-limited approval for regenerative medicine (new)**
Rolling submission	Break through therapy & Fast Track designation	**PRIME (new)**	**Forerunner Review Assignment (new)**

US Accelerated approvals and development



(drugs for life-threatening disease and unmet medical needs)

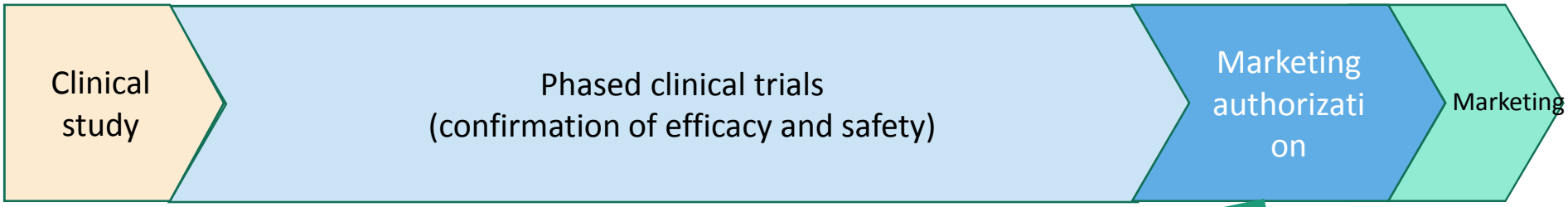
- To approve products based on the limited data, such as surrogate endpoints in exploratory study.
- Similarity to accelerated approval of USFDA * The product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit (ref.)

Ref.) USFDA--Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses (57 FR 58958, Dec. 11, 1992

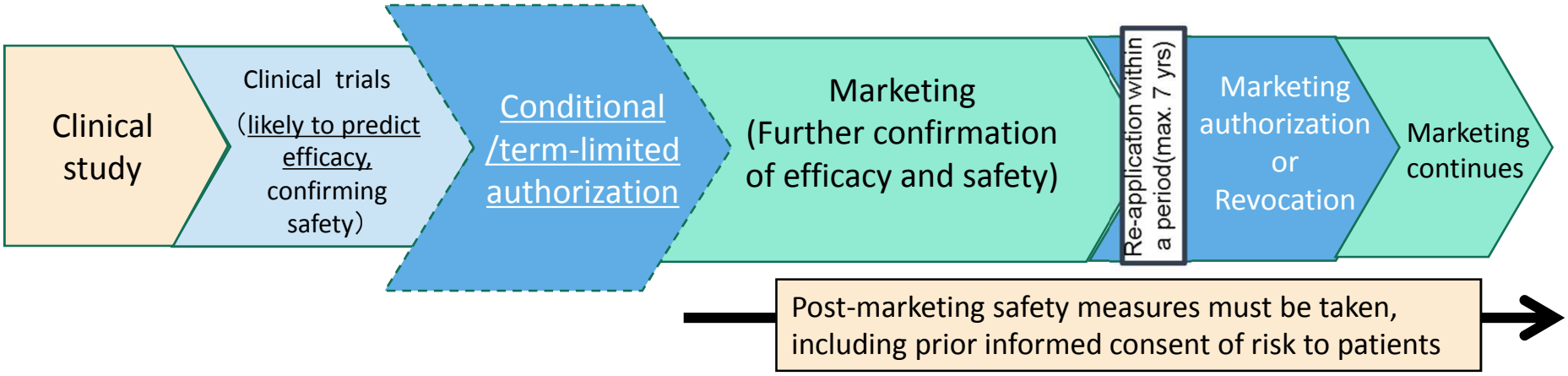
Expedited approval system under PMD Act

< Drawback of traditional PAL approval system >
Long-term data collection and evaluation in clinical trials, due to the characteristics of cellular/tissue-based products, **such as non-uniform quality** reflecting individual heterogeneity of autologous donor patients

[Traditional approval process]



[New scheme for regenerative medical products]



Public no-fault Indemnity system for patient injuries associated with products approved under PMD Act.

Very Japan specific regulation!!

	Biological device	Regenerative medical products
Conditional and time limited approval	NA	√
Adverse Drug Reaction Relief Fund	NA	√
Infection Relief Fund	√	√

Private Insurance products will be available for clinical studies under the Act on the Safety of Regenerative Medicine

Further acceleration……

Strategy of SAKIGAKE
(Forerunner review assignment system)

厚生労働省
Ministry of Health, Labour and Welfare

▸HOME ▸What s New ▸Related Sites Links ▸Japanese
search

Strategy of SAKIGAKE

(Japanese)

The Ministry of Health, Labour and Welfare (MHLW) has formed the "Strategy of SAKIGAKE" by Ministry Project Team to lead the world in the practical application of innovative medical products (Press release (in Japanese) This PT has been launched to plan strategies as a package covering from basic research to the practical application with related divisions within the MHLW.

The Strategy of SAKIGAKE consists of two measurements as follows and covers from basic research to clinical research/trials, approval reviews, safety measures, insurance coverage, improvement of infrastructure and the environment for corporate activities, and global expansion.

- SAKIGAKE Designation System: promoting R&D in Japan aiming at early practical application for innovative pharmaceutical products, medical devices, and regenerative medicines.
- Scheme for Rapid Authorization of Unapproved Drugs: accelerating the practical application of unapproved/off-label use of drugs for serious and life-threatening diseases by expanding the scope of the Council on Unapproved Drugs/Off-label Use to include unapproved in Western countries if it satisfies certain conditions and by improving the environment for companies to undertake development of such drugs.

The MHLW will implement these policies during the budgetary request process in FY2015, but some of them which are ready will be executed in 2014 ahead of schedule.

＜Materials＞
- Strategy of SAKIGAKE (PDF:379KB)
- Summary of Strategy of SAKIGAKE (PDF:587KB)

- MHLW drew up a new strategy to lead the world in the practical application of innovative medical products in 2014.

http://www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/140729-01.html

SAKIGAKE Designation System

– To put innovative products into practice in Japan first in the world –

Designation Criteria

- Medical products for diseases in dire need of innovative therapy
- Applied for approval firstly or simultaneously in Japan
- Prominent effectiveness can be expected based on non-clinical study and early phase of clinical trials

Designation Advantage

1. Prioritized Consultation [Waiting time: 2 months→1 month]

2. Substantialized Pre-application Consultation [de facto review before application]

3. Prioritized Review [12 months → 6 months]

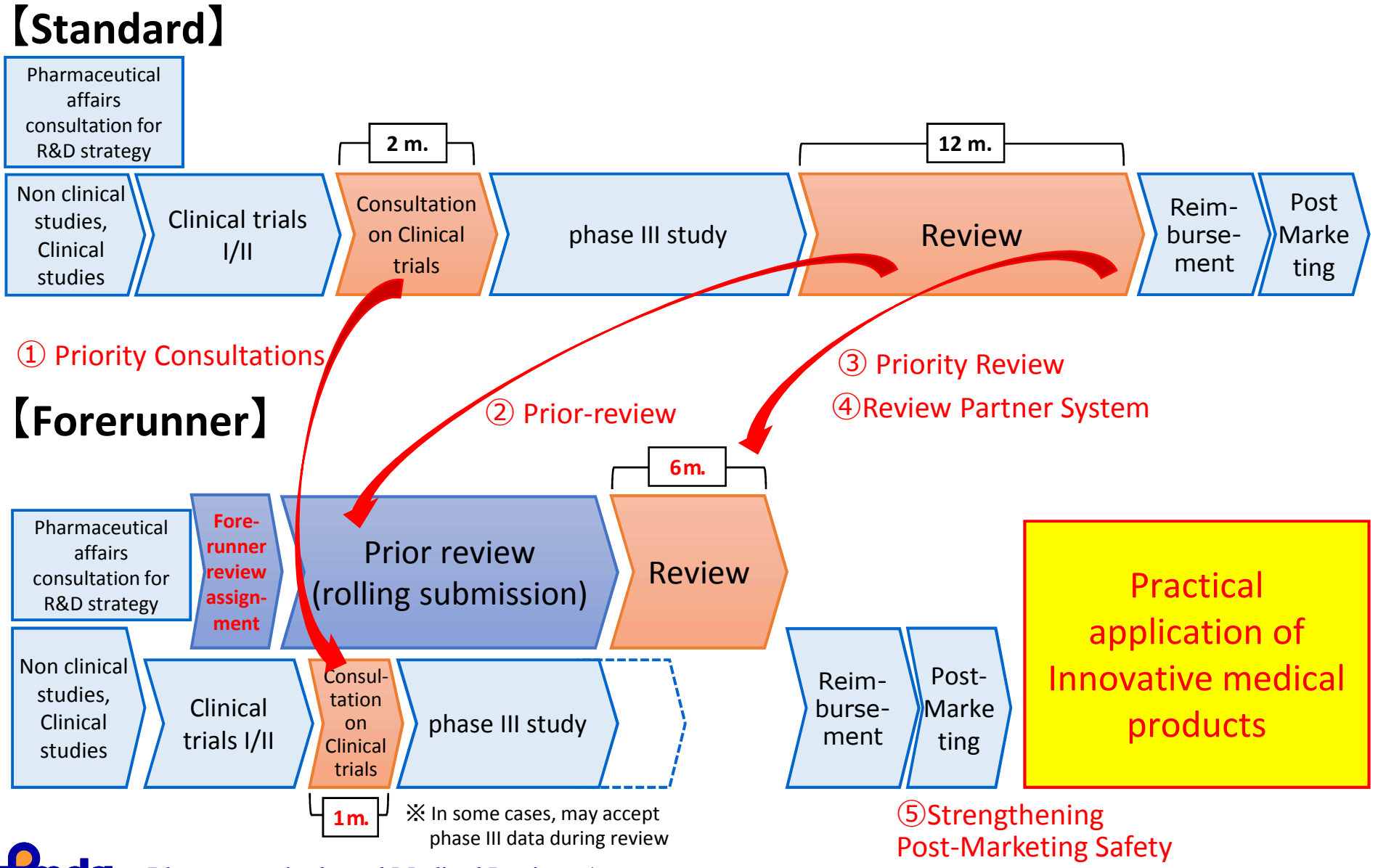
4. Review Partner [PMDA manager as a concierge]

5. Substantial Post-Marketing Safety Measures[Extension of re-examination period]

Designation Procedure

1. Initiation by applicant 2. Initiation by the MHLW

General Timeframe of Forerunner Review Assignment



Assignment on 10 February 2016 regenerative medical products

Name of medical products	Proposed indication	Name of applicant
STR01 (Autologous bone marrow-derived mesenchymal stem cell)	Nerve syndrome and dysfunction caused by spinal cord injury	NIPRO Medical Co., Ltd. /Sapporo Medical Univ.
G47Δ (Growth-controlled oncolytic herpes simplex virus type 1)	Malignant glioma	Daiichi Sankyo Co., Ltd. / Institute of Medical Sciences, University of Tokyo
autologous cardiac progenitor/stem cells	Pediatric congenital heart disease (single ventricle physiology)	Japan Regenerative Medicine Co., Ltd. /Okayama University

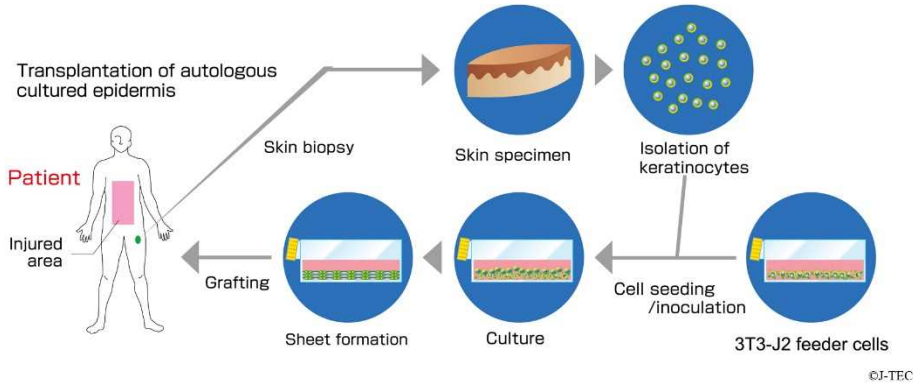
Examples of Product review

(specific points to consider for cell therapy products)

Two authorized products under PAL

Ref. Japan Tissue Engineering Co., Ltd. (J-TEC), HP

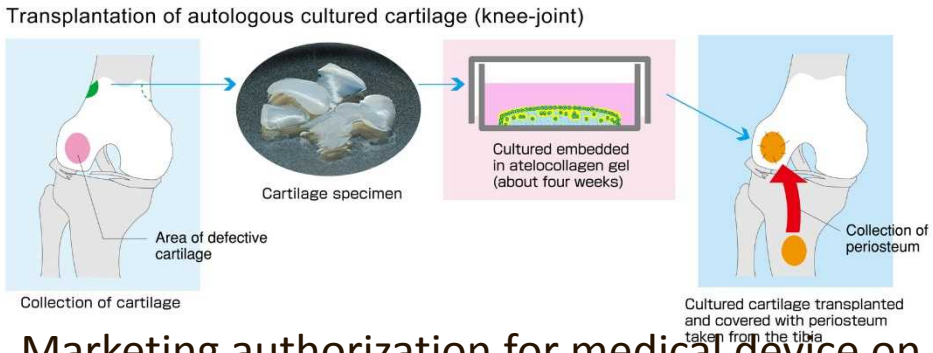
Autologous Culture Epidermis ***JACE***



Indication: serious burns treatment (limited to the burns of more than 30% of the body surface area)

Marketing authorization for medical device on 29 October 2007
(submission: 6 October 2004)

Autologous Cultured Cartilage ***JACC***



Indication:
Relief of symptoms of traumatic cartilage defects and osteochondritis dissecans (exclude osteoarthritis) for knee joints. (limited to a defect area of over 4cm2 with no alternative therapy.)

Marketing authorization for medical device on 27 July 2012
(submission: 24 August 2009)

Two of the new product approvals under the new regulation (Update)

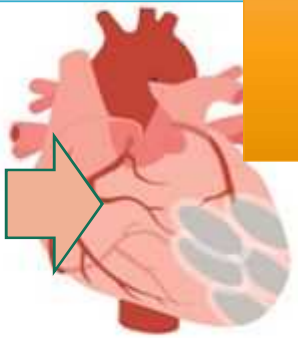
- In September and in October 2014, two new product applications for marketing authorization were filed by PMDA.
- They were approved on 18 September 2015.

Licensed by Mesoblast, Ltd. (Osiris Therapeutics, Inc.)

Conditional approval in Canada and New Zealand

1. Bone marrow mesenchymal stem cells (MSCs) for GVHD **(normal approval)**
2. Skeletal myoblast sheet for serious heart failure due to ischemic heart disease **(conditional and time-limited authorization** – 5 years, conducting post-marketing efficacy studies**)**

Review Time less than 12 months)



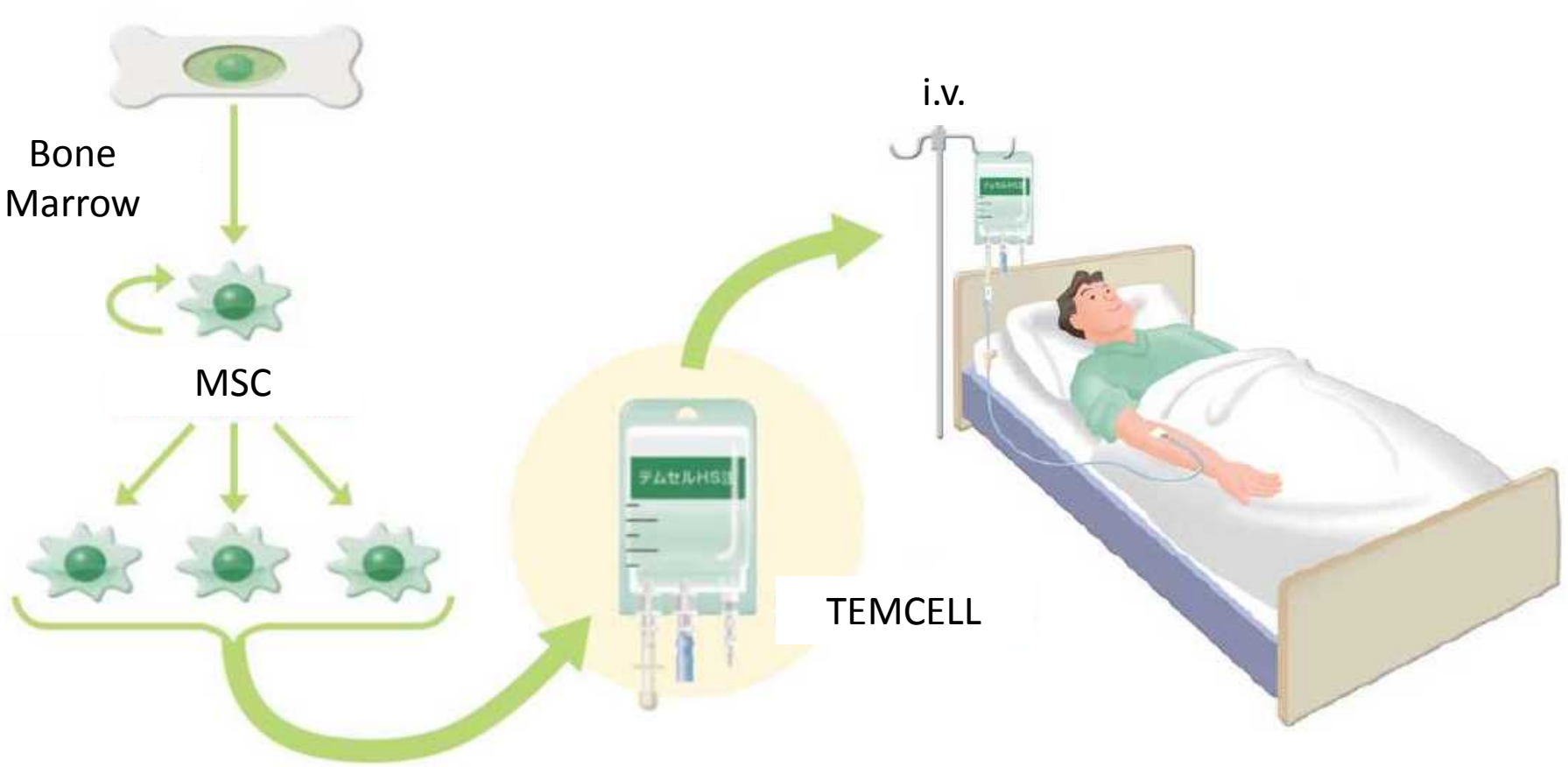
Note: Figures quoted from the company press release docs

TEMCELL

- Target: Steroid refractory acute GVHD
  - Fatal and Rare disease (approx. 1000-2000/y)
- Product: Allogeneic MSC
- Manufacturer JCR Pharmaceuticals Co., Ltd
- Resources and technology imported from Mesoblast, Ltd. (Osiris Therapeutics, Inc.)
  - Prochymal® (Brand Name)
    - Conditional approval in Canada and New Zealand

http://www.jcrpharm.co.jp/news/20151126_3991

TEMCELL Route of Administration



http://www.mhlw.go.jp/stf/shingi2/0000104129.html

TEMCELL Clinical Studies

■Japan

- JR-031-201/202 study(Phase I/II)

  Single arm clinical trial, 14 subjects. Grade II-IV.

- JR-031-301 study (Phase II/III)

  Single arm clinical trial, 25 subjects. Grade III-IV.

■ Foreign (Prochymal®)

- 280 study

  Placebo-controlled RCT, 216 adults and 28 pediatric subjects.

  Grade B-D.

- 275 study

  Single arm clinical trial, 75 pediatric subjects.

First approval of conditional and time-limited authorization

HeartSheet

- Target:

  Serious heart failure due to Ischemic Heart Disease

  - Chronic and Poor prognosis (NYHA Class III or IV, LVEF<35%)

- Product: Autologous skeletal myoblast

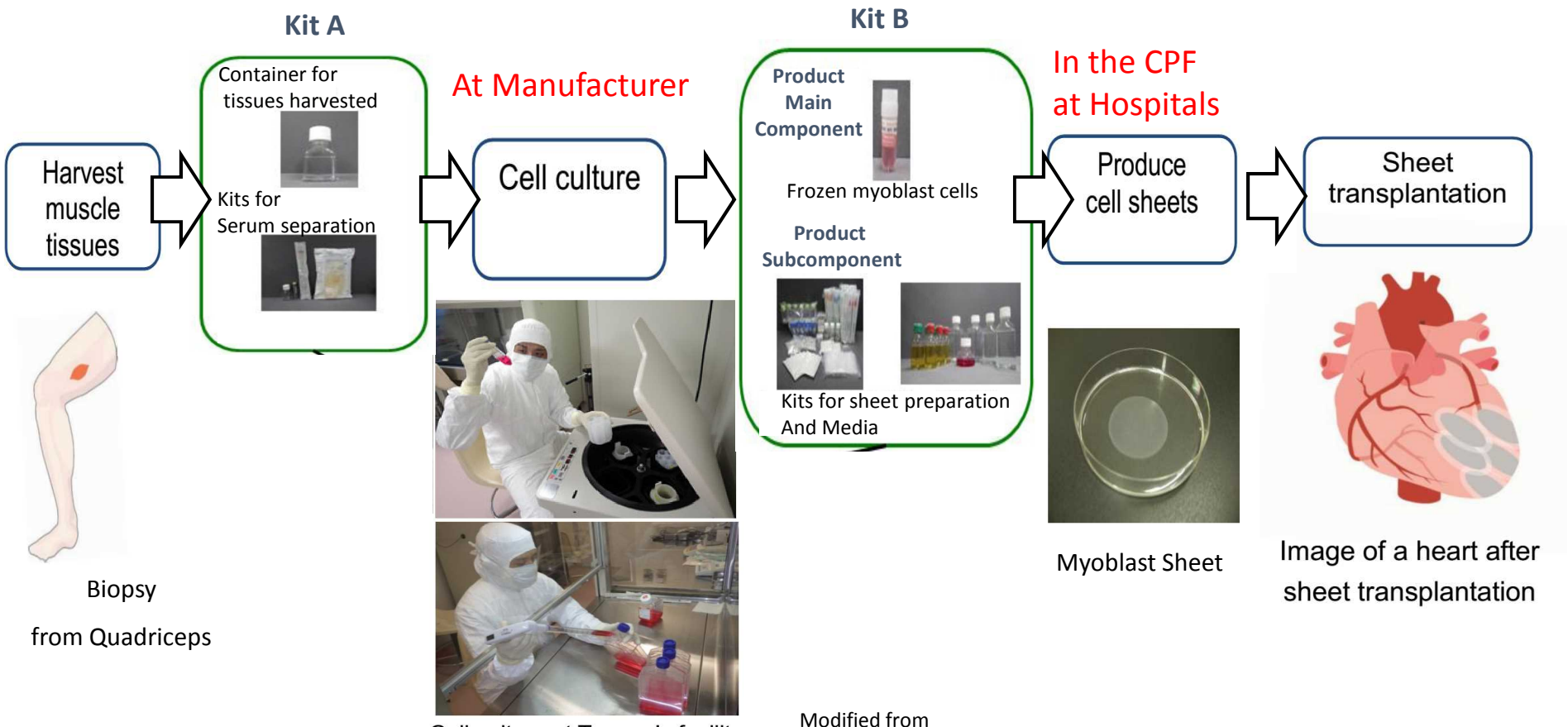
- Manufacturer: Terumo Corporation

- Manufacturing

  - Biopsy from Quadriceps
  - Final product is manufactured at Cell Processing Facilities (CPF) in hospitals

HeartSheet
Manufacturing and Final Products

■ Process to Sheet Transplantation



Modified from
file:///C:/Users/Nori/Documents/ATMP%20Cluster/20160421/Terumo%2020141031.pdf
http://www.terumo.com/about/pressrelease/2015/20150902.html

Summary of Review

- Efficacy evaluation
  - LVEF (RI, CT, Echo) => surrogate endopoints
  - Comprehensive clinical evaluation

    >>Improvement of clinical symptoms
  - Survival (External control comparison)

  >> Skeletal Myoblast Sheet: All subjects survived

>> Conditional and time-limited approval

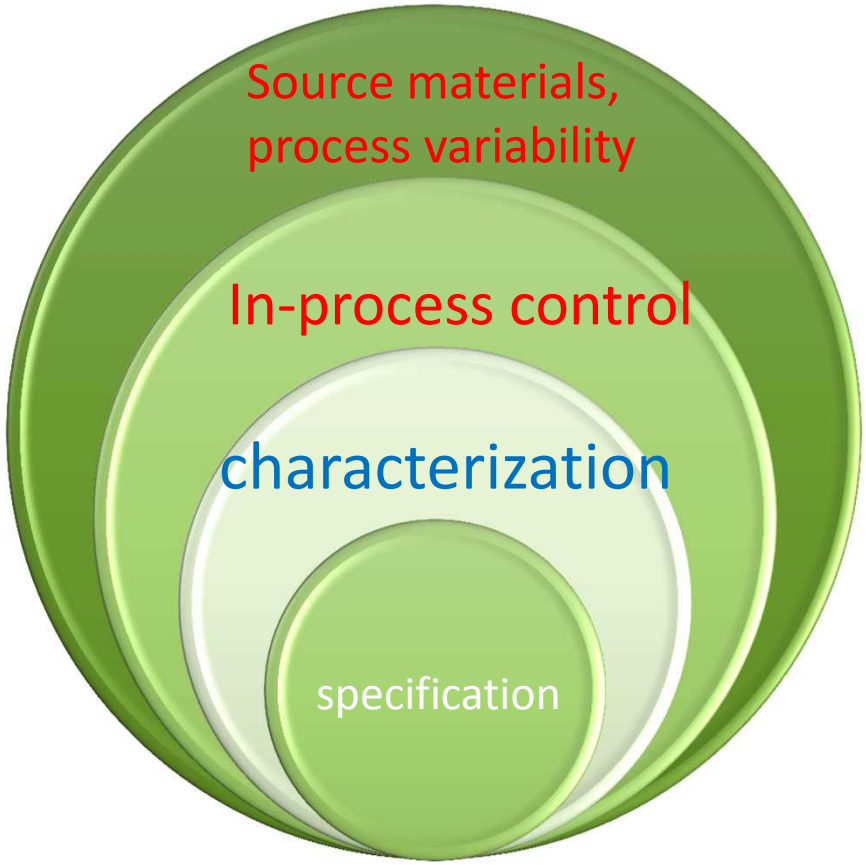
■ Post-marketing evaluation

- Concurrent external control comparison
  - Endpoint: Survival => true endpoint
  - Skeletal Myoblast Sheet: 60 subjects
  - Control: 120 subjects

Ref.) Konishi A, Sakushima K, Isobe S, Sato D., First Approval of Regenerative Medical Products under the PMD Act in Japan. ***Cell Stem Cell***. 2016. 18(4): 434-435

Quality concept of hCTPs

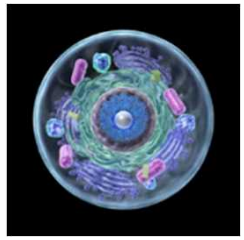
Bio-pharmaceuticals



hCTPs

- **Difficult to cover every aspect of quality by specification**
- **Limited information can be obtained from characterization and specification**
- **Much more rely on in-process control to control quality**

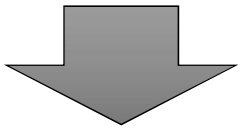
Safety assessments for cellular/tissue-based products



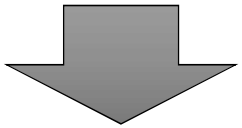
1. Inadvertent transformation
2. Effect by active-substances produced from-cells or tissues
3. Effect on normal cells or tissue
4. Inadvertent formation of ectopic tissue
5. Undesirable immunological reactions by products
6. Tumorigenicity or Carcinogenicity
7. Safety evaluation based on guidance for products for gene therapy, when the products have transgenes.
8. General toxicity
9. Effects on vital organs
10. Safety evaluation on impurities from manufacturing processes

General considerations for general toxicity study

Cellular/Tissue based product	Products for gene therapy
➢ Species differences in biological reaction ➢ Heterogenous immune responses ➢ Inappropriateness of conventional TK/ADME study	➢ Species differences in infectivity or transduction efficiency ➢ The determination of NOAEL ➢ Dose-limiting toxicity ➢ Worst-case scenario



Hazard Identification



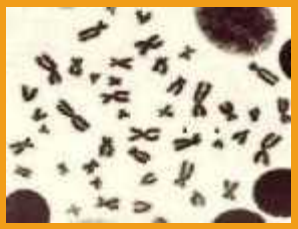
Hazard Identification
Risk assessment

Testing for tumorigenicity

in vitro Testing

- Karyotype

  → Genetic stability



- Soft agar colony formation assay

  → Proliferation independent on adhesion

in vivo Testing

- Testing using immuno-deficient animals

  → Tumorigenicity in vivo

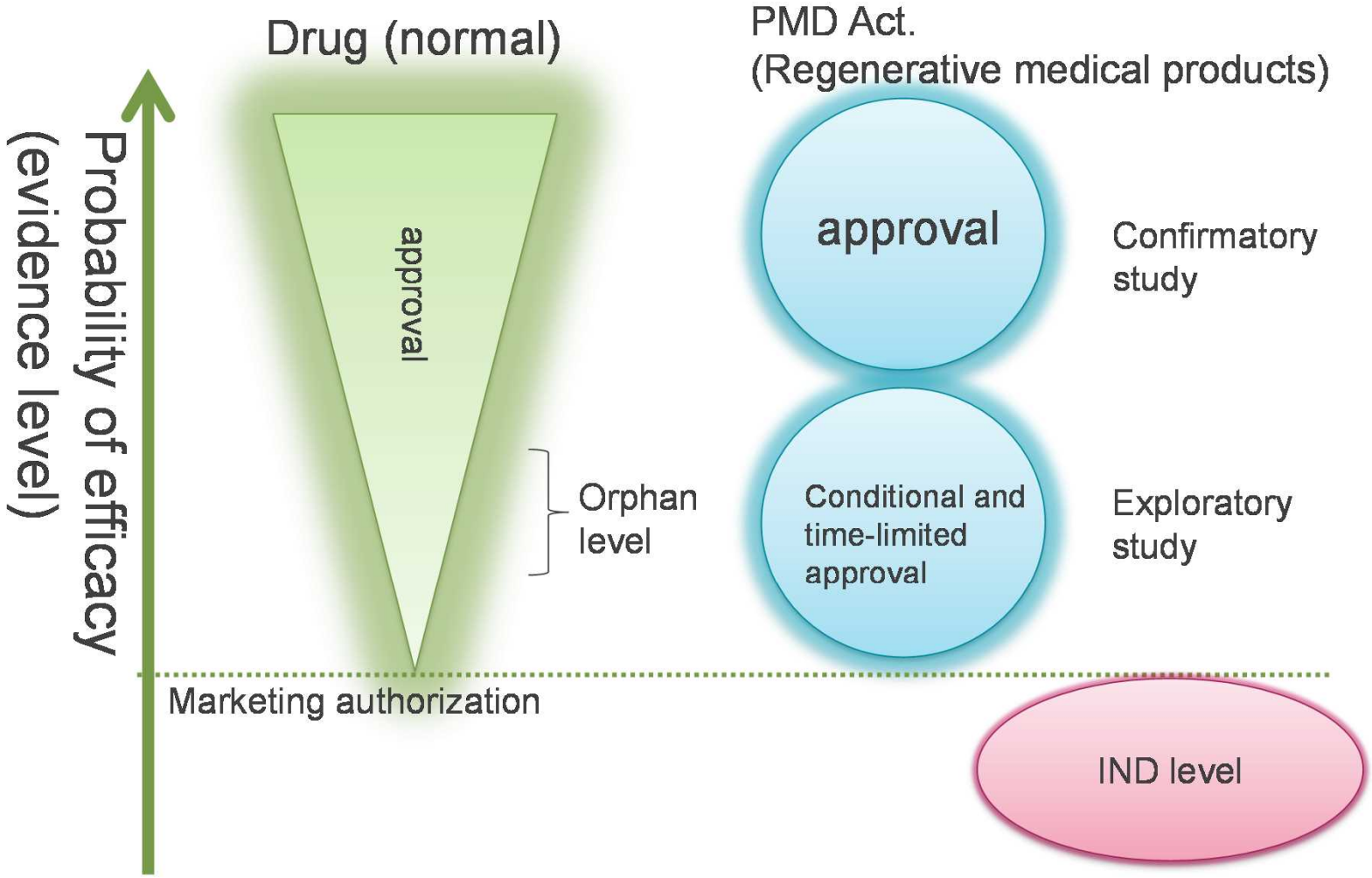
The necessity should be considered on a case-by-case basis depending on the product characteristics.

Safety and Efficacy evaluation of limited number of subjects in the trial for conditional approval

- Challenge on new designs and statistical methodologies for small population
- How to secure evidence level
  - Design : controlled? / blinded? possibility?
  - Clinical endpoint (efficacy) : clinical significance, objectiveness, surrogacy, etc.
- At least, Maximize the information from a single subject in terms of safety and efficacy.
- Post-marketing study, further confirmatory study?

Evidence Level of Efficacy: Drug (normal) vs. HCT/P

If there is no effective treatment available for the target population of the disease

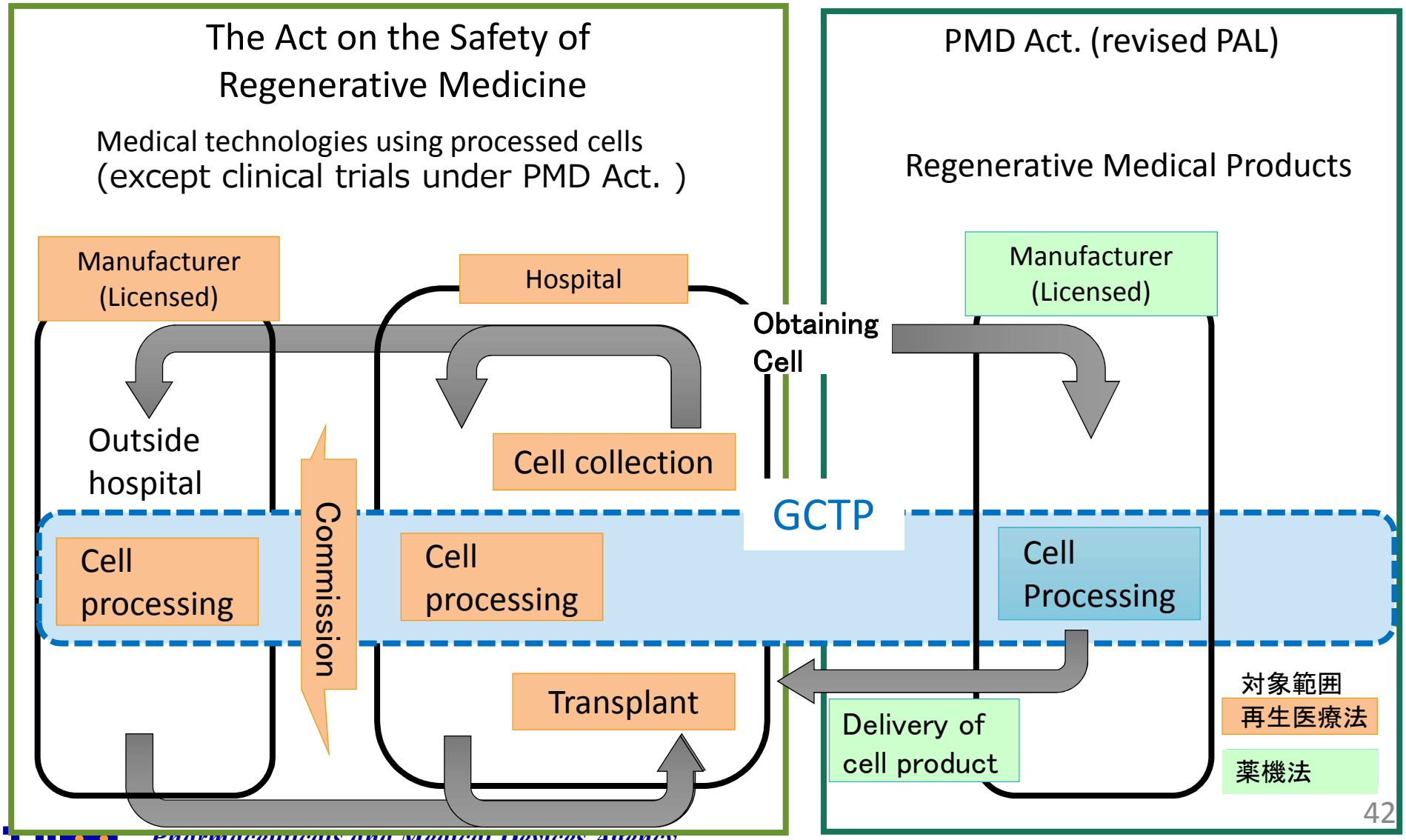


Quality System Requirements

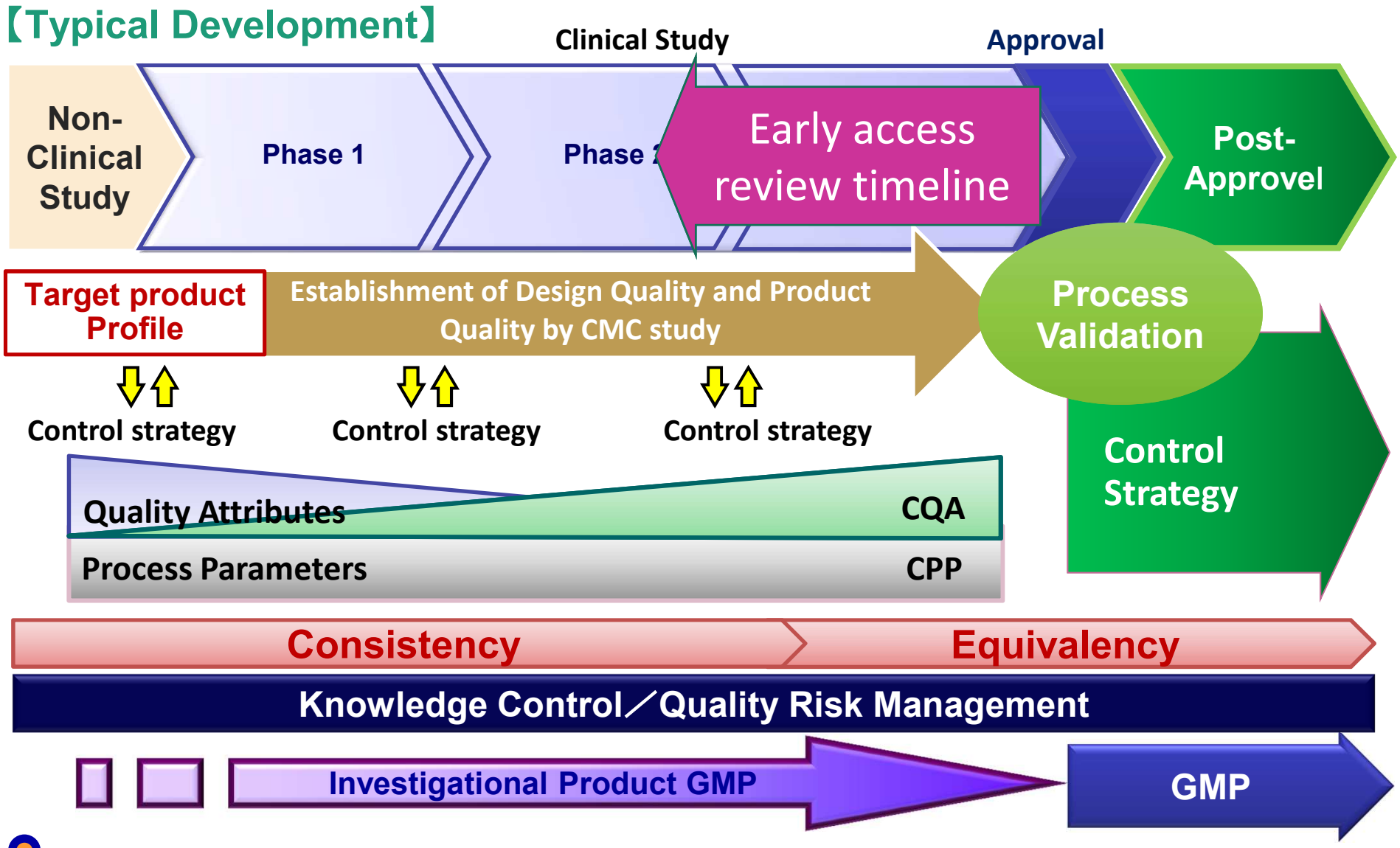
GMP type regulation

Consistent parts of the two Acts

GCTP = Good gene, Cell, Tissue based Product Manufacturing Practice



Overall picture of CMC development



Key Consideration of GCTP

Quality System Requirement for regenerative medical technologies / products, considering the characters of these products; such as raw materials that cannot be sterilized

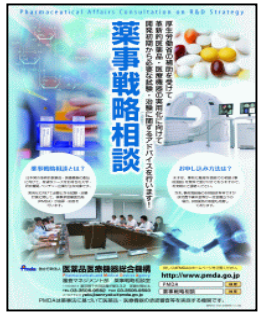
- Quality Risk Management
- Manufacturing Control (Sterility assurance, Prevention of Cross-contamination..)
- Quality control (**Verification / validation**, Quality review)
- Facility requirement

It is necessary to consider whether the risk is manageable,
- not only from the facility point of view,
- but from the effects of the manufacturing operation, such as the evaluation of performance.

Facilitate Development

Scientific Advice Scheme

Pharmaceutical Affairs Consultation on R&D Strategy for scientific advice



Basic Research

Pharmaceuticals and Medical Devices candidates

Strategic Consultation

Quality Study

Non-Clinical Study

Clinical Trial
(Up to POC studies)

Practical Use

Innovative Products

* Further studies are handled by the Regular Consultation

Consultation on quality and battery of pre-clinical, including examining tumorigenicity, biological ingredient safety

Consultation on endpoints or sample size of early clinical trial

Flow of Strategy Consultation

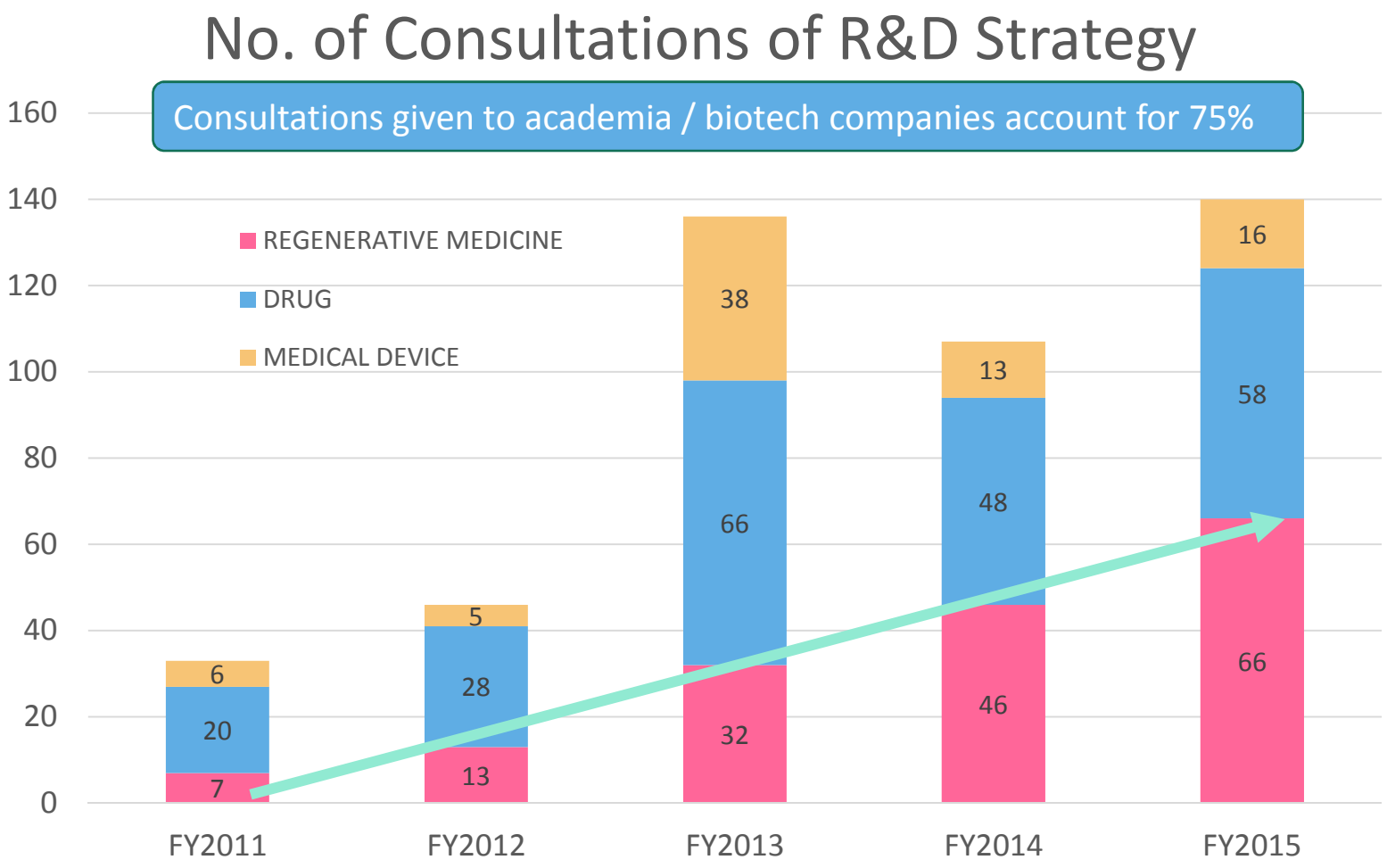
Introductory Consultation (1,149)

Pre-Consultation (1,490)

Face-to-Face Consultation (466)

(7/1/2011 – 3/31/2016)

Pharmaceutical Affairs Consultation on R&D Strategy (face to face)



Related Guidelines for Products Evaluation

Guidelines on Ensuring Quality and Safety of Products Derived from Processed Cell/Tissue

- Autologous (2008)
- Allogeneic (2008)

Guidelines on Ensuring the Quality and Safety of Products Derived from Processed Human Stem

- Autologous Somatic Stem Cells (2012)
- Autologous iPS-like Cells (2012)
- Allogeneic Somatic Stem Cells (2012)
- Allogeneic iPS-like Cells (2012)
- Embryonic Stem Cells (2012)

Points to Considers for the Evaluation of Specific Products

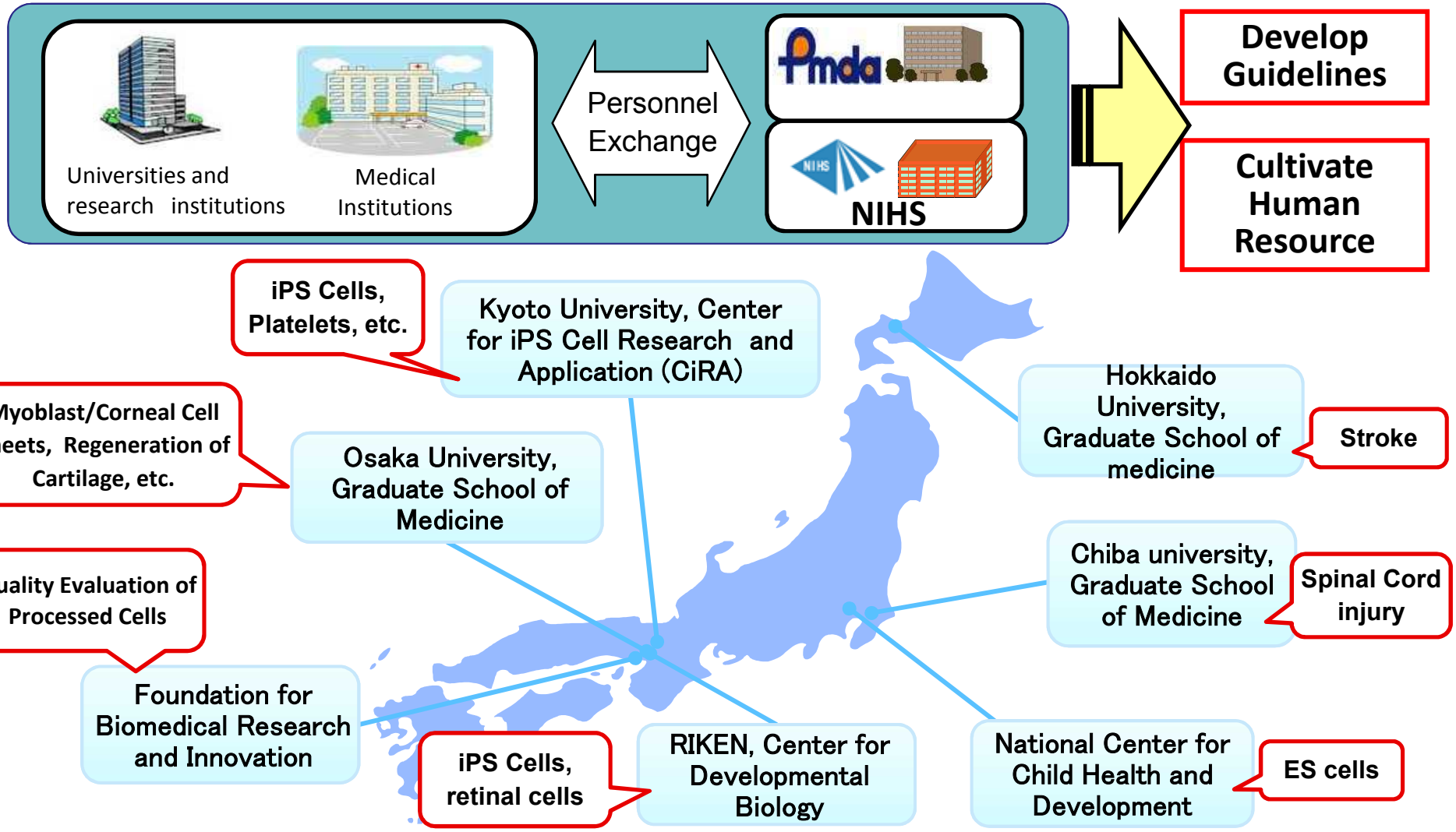
- Cell sheet for heart failure (2010)
- Corneal epithelial cell sheet (2010)
- Corneal endothelial cell sheet (2010)
- Articular cartilage repair (2010)
- Cell sheet for periodontal tissue regeneration (2011)
- Autologous induced pluripotent stem cells-derived retinal pigment epithelial cells (2013)
- Allogeneic induced pluripotent stem cells-derived retinal pigment epithelial cells (2014)

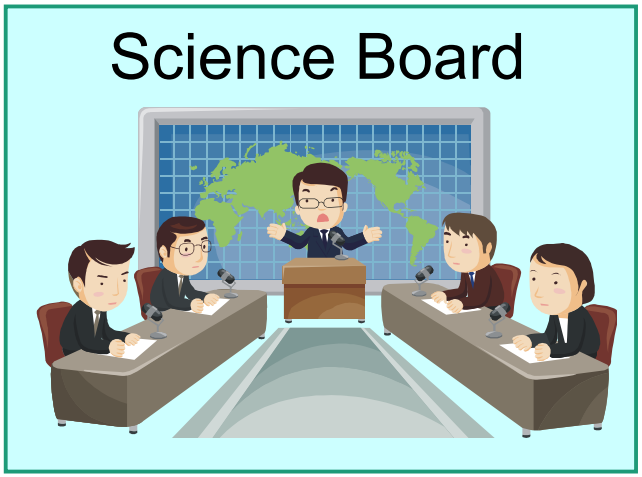
The Science Board Report. PMDA.

- Current Perspective on Evaluation of Tumorigenicity of Cellular and Tissue-based Products Derived from induced Pluripotent Stem Cells (iPSCs)* and iPSCs as Their Starting Materials (2013)

Personnel Exchange to strengthen review human resources to implement new regulation

< Program for Cellular Therapy Products >





Exchange opinions between top-class researchers in Japan and PMDA reviewers on assessment methods of cutting-edge technologies

Cellular and Tissue-based Products Subcommittee

Perspective on how quality/safety of cellular and tissue-based products should be ensured -

- Tumorigenicity
  →*Summary of discussion on tumorigenicity of cellular and tissue-based products derived from induced pluripotent stem cells* was issued. (8/20/2013)*
- Requirements for CPF (Cell Processing Facilities), and others
  - *Summary of discussion on Manufacturing and quality of cellular products during the early development in cell processing facilities (14 August 2015)*

Sharing of Information, Experience and Knowledge is Valuable !!

Thank You for your attention!

Daisaku Sato, Ph.D.

Director, Office of Cellular and Tissue based Products, PMDA, Japan

sato-daiasku@pmda.go.jp

Thanks to my colleagues of Office of Cellular and Tissue-based Products

Literature available in English:

(1) Hara A. Sato D. Sahara Y. New Governmental Regulatory System for Stem Cell–Based Therapies in Japan. ***Therapeutic Innovation & Regulatory Science***. 2014; 48(6): 681-688.

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