Cancer immunotherapy: Regulatory implications in Japan

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CONTENTS

• PMDA’s Policy and Trend
• R&D and approvals of cancer immunotherapy products
• Perspectives on cancer immunotherapy review (micro & micro)
• Accelerated Developing Programs (CMC Consideration)
• New Regulations for Cellular and Tissue-based Products (incl. immuno-cell therapy)
Pharmaceuticals and Medical Devices Agency

Kansai Branch

Major Services
- Scientific Review for Drugs & Medical Devices
- GCP, GMP Inspection
- Consultation on Clinical Trials
- Safety Measures
- Relief Services

Unique Three-pillar System Securing Nation’s Safety

Review

Japanese citizens

Safety

Relief
3rd 5-year mid-term Plan of PMDA (FY2014-2018)

Major challenges

- Shortening the time to approval
- High quality review/consultation services
- Enhancing safety measures
- Globalization

Specific measures

- Accelerated review process
  (Improvement of approval predictability)
- Improvement of prior assessment
  (substantial acceleration of approval review process)
- Readiness for introduction of RMP
- Drastic improvement of consultation service
  • Improvement of pharmaceutical affairs consultation service on R&D strategy
  • Improvement of clinical trial consultation service
- Utilization of medical inf. database
- Introduction of approval system with condition/period for Regenerative Medicines

Advanced Review/Consultation System

Goal

- Improvement of pharmaceutical affairs consultation service on R&D strategy
- Improvement of clinical trial consultation service

Human Resources with excellent skills (751 staffs → 1065 staffs)
### Accelerating Review Period

#### Total Review Period New Drug

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<th>Year</th>
<th>Standard Review Period (mo.)</th>
<th>Priority Review Period (mo.)</th>
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<table>
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<th>Year</th>
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<tr>
<td>2018</td>
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</table>

- **Regulatory**: Orange
- **Applicant**: Blue
- **Target Period**: Gray
- **Number of applicant**: Yellow
PMDA Staff Size

Yearly Staff Size Breakdown:

- Administrative part
- Safety Department
- Review Department
- Planned

Yearly Staff Numbers:

- 2004.4: 256
- 2005.4: 291
- 2006.4: 319
- 2007.4: 341
- 2008.4: 426
- 2009.4: 521
- 2010.4: 605
- 2011.4: 648
- 2012.4: 678
- 2013.4: 708
- 2014.4: 753
- 2018: 1065
• Conversion from old fashioned products (ex. BCG vaccine, interferons) to molecular target based medicines, gene-cellular products
Approval of nivolumab in July 2014

• **Nivolumab** was received orphan drug designation in Japan and is indicated for treatment of radical unresectable advanced or recurrent malignant melanoma patients of chemotherapy history (including dacarbazine).

• Approval was based on Phase II study conducted in Japan:
  
  **ORR [90% CI] (RECIST) : 22.9% [13.4%, 36.2%]**

• Response rate of nivolumab exceeded reference threshold response rate of (12.5%), which was set on the basis of the clinical trial results of traditional dacarbazine.
Foreign clinical trials (Phase III) of nivolumab

CheckMate -066
• A randomized blinded comparative Phase 3 study evaluating nivolumab versus dacarbazine (DTIC) in patients with previously untreated BRAF wild-type advanced melanoma was stopped early because an analysis conducted by the independent Data Monitoring Committee (DMC) showed evidence of superior overall survival in patients receiving nivolumab compared to the control arm.
• The trial enrolled 418 patients who were randomized to receive either nivolumab 3 mg/kg every two weeks or DTIC 1000 mg/m² every three weeks. The primary endpoint was overall survival. Secondary endpoints included progression free survival and objective response rate.
  (BMS社 release 資料 June 2014)

CheckMate -037
• Phase 3 randomized, controlled open-label study of Opdivo (nivolumab), versus investigator’s choice chemotherapy (ICC) in patients with advanced melanoma who were previously treated with Yervoy (ipilimumab).
• Based on a planned interim analysis of the co-primary endpoint, the objective response rate (ORR) was 32% (95% CI = 24, 41) in the Opdivo arm (n=120) and 11% (95% CI = 4, 23) in the ICC reference arm (n=47) in patients with at least six months of follow up.
• ORR was based on RECIST criteria as evaluated by an independent radiologic review committee (IRRC).
  （ESMO 2014 Congress in Madrid BMS社 Sep 2014 より引用）
mAbs & Fusion proteins account for more than 25%

As of September 1, 2013

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<td>Interferons</td>
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<td>Cytokines</td>
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<td>EPOs</td>
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<tr>
<td>mAbs &amp; Fusion proteins</td>
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As of September 1, 2013
Although the target of each category of product varies, common challenges on evaluating safety and efficacy of immunotherapy lay in the characteristics of immunotherapy modulating immune cellular system.

**Anti-Cancer Immunotherapy**
Range of Cancer immunotherapy related Clinical Trials

At this point, we have not observed a clinical anti-tumor effect associated with the immune response against specific cancer antigen.

As of January 2015
Cancer Immunotherapy products to be developed for clinical application

• Immuno-checkpoint modulators
  • PD-1/PD-L1 antibodies
    ✓ Pembrolizumab (MSD) (US breakthrough therapy designated )
  • CTLA-4 antibodies
    ✓ ipilimumab (BMS) Approval : US=March 2011, JP= ?
  • ? CCR-4 antibodies ?
    ✓ Mogamulizumab (Kyowa-Kirin) Approval : JP=March 2012
  • others

• Peptide cancer vaccine
  • some peptide cocktails under clinical trials

• Immuno-cellular therapy
  • T-cell activation, TCR, CAR -gene induction
    ✓ CTL019 (Novartis) (US breakthrough therapy designated )
  • Dendritic cell activation
    ✓ autologous cellular immunotherapy “Provenge “(indicated for advanced prostate cancer )
    approval : US=April 2010
Review Regulations in Japan

- Antibodies (immuno-checkpoint modulators)
- Peptide vaccines
  Regulated as “drug”
- Processed cells (engineered T-cells, Dendritic cells)
  Regulated as “regenerative medical products”
  = ATMPs of EU regulation

An immunotherapy related product won’t alter the way of review and IND process from reviewers perspective.
Micro-perspective: review of cancer immunotherapy products

Cancer drug review philosophy and process won’t change, but will discuss some specific points, considering the natures of immunotherapy
Cancer Immunotherapy related guidelines/guidance for development and review (including peptide vaccines, cellular therapies)

• US FDA
  • Potency Tests for Cellular and Gene Therapy Products (2011.01)
  • Clinical Considerations for Therapeutic Cancer Vaccines (2011.10)
  • Preclinical Assessment of Investigational Cellular and Gene Therapy Products (DRFAT 2012.11)
  • Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products (DRAFT 2013.07)
  • Clinical Considerations for Therapeutic Cancer Vaccines (draft) (2009.9)

• EU EMA
  • GUIDELINE ON POTENCY TESTING OF CELL BASED IMMUNOTHERAPY MEDICINAL PRODUCTS FOR THE TREATMENT OF CANCER (2007.10)

• In Japan
  • Cancer therapeutic peptide vaccine guidance (2012.12 rev.) (Japan Society for Biological Therapy)
  • Cancer Immunotherapy Guidance 2014 (early clinical trials consideration) (under development) under the auspice of Ministry of Health, Labour and Welfare.
Development of Cancer immunotherapy guidance

Contract research organization: Prof. Dr Hiroshi Shiku, Mie University Hospital

- MHLW funded and contracted guidance development project to the leading academic research institutions since 2012 for appropriate and expedited R&D in regulatory point of view.

- Beyond the “drug lag” issue, aiming at developing Japanese originated advanced medical technologies, toward the first clinical application in the world.

- Cancer Immunotherapy Guidance 2014 draft has been developed for early clinical trial consideration and is to be submitted to MHLW.

- Guidance for CMC, Guidance for pre-clinical study and Guidance for late clinical trials will follow.
Pre-clinical Discussions

• To perform pharmacology (on target) studies, testing on tumor growth inhibitory effects, preclinical safety (off target) studies....

• Consider the species differences related to immune response (MHC) in the animal texting, using human cellular products, humanized antibody

• In-vitro immunogenicity assay using human cells? Toxicity studies in animals close to human?

• Encourage to set up animal modeling to mimic the human mode of action

I will just echo the challenges raised by other regulatory speakers
ORR discussion in early clinical trials

- RECIST criteria has been used for CR, PR, SD, PD in diagnostic imaging for assessing tumor shrinkage.
- When delayed effect is observed, how should we accommodate ORR?
- Is IrRC valuable and usable in the routine clinical trials for assessing immuno-therapeutic substances and cells, instead of RECIST?
Late phase clinical trials

• Confirmatory trials (Phase III)
  • Comparative efficacy with standard care, placebo (Same principle as conventional chemotherapy)
  • Efficacy Endpoint (Same principle as conventional chemotherapy)
    Hard endpoint such as overall survival (OS) should be recommended. (PFS will also be considered like conventional chemotherapy)
  • Statistical test Method
    Discussion on taking into account of Delayed response (Wilcoxon test? Application of Harrington-Fleming?)
FDA’s guidance

“In general, **time-to-event endpoints** are measured from the time of randomization. **Due to delayed effect of the vaccine**, the endpoint curves of the trial results may show **no effect for the initial portion** of the study. If the treatment is effective, **separation of the curves may occur later** in the study after the vaccine effect has become established. **This may violate the proportional hazard assumptions necessary when applying Cox modeling** and may necessitate an increase in sample size to provide sufficient power to test a statistical hypothesis.”

(FDA: Clinical Considerations for Therapeutic Cancer Vaccines(draft)(2009.9)
Successful combination therapy strategy

Higher ORRs were reported in combination of CTLA-4 : ipilimumab and PD-1 : nivolumab

Potential combination therapies

• Some Inter-company co-development programmes have already been on-going

• Conventional course of development:
  ✓ Individual safety assessment in Phase 1
  ✓ Combined safety assessment in Phase 1
    ➢ Discussion: If MOAs of two NMEs are different, can they be exempted?
  ✓ Justification of dosing of each drug product should be demonstrated in Phase 2

• Do we need to apply a new strategy for development or pursue the conventional process (for particularly dosing)?
Macro-perspective: review of cancer immunotherapy products

• In the oncology area, promising new products are awaited, including novel immunotherapy in the future.
• In response to the demand of access, regulators are streamlining review process of such products.
To what extent probability of effectiveness is to be pursued before Marketing authorization?

Question is “What is the socially and scientifically acceptable level of effectiveness for approval?”

For:

• A new product for life threatening disease, which is affected by the *timing of access*

• Breakthrough therapeutics for present unmet medical needs, *longing for treatment*, while paying particular attentions to the safety
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 public health
Early Access schemes of ICH 3 parties

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<thead>
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<th>US</th>
<th>EU</th>
<th>JAPAN</th>
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<td>serious or life-threatening</td>
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<td>Conditional &amp; Time-limited approval for</td>
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<td>Break through therapy &amp;</td>
<td>Pilot Project on Adaptive</td>
<td>Forerunner Review Assignment</td>
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<tr>
<td>Fast Track designation</td>
<td>Licensing</td>
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Various agencies have various approaches to accommodate patient access.
• To approve products based on the limited data, such as surrogate endpoints in exploratory study.

• It applies to certain new drug products in treating **serious or life-threatening illnesses** and that provide meaningful therapeutic benefit to patients over existing treatments.
  • Approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity.
  • The drug product has an effect on a surrogate endpoint that is **reasonably likely to predict clinical benefit** or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity.
  • Approval will be subject to **the requirement that the applicant study the drug further, to verify and describe its clinical benefit** (such as OS).
  • Postmarketing studies would usually be studies already underway.
  • FDA may **withdraw approval**, if a postmarketing clinical study fails to verify clinical benefit; .............
Principle

- **Clinical benefit** is investigated mainly with **survival data in Phase III studies**. When an agent is indicated for **commonly occurring cancer**, submission of **Phase III study data**, which mainly evaluate survival, is **essential for the approval application**.

- If **clinical development** if an anti-malignant tumor agent is **in progress abroad**, **utilisation of foreign study data** should be considered and a clinical development plan should be drawn referring to ICH E5 so that **the development in Japan will be fast**.

Exemption

- If the **number of patients** indicated for the treatment is **considerably limited** with a scientific justification, this does not apply.

- If the agent is applicable to an **orphan medicinal product** (Article 77-2 of PAL), it is possible to conduct a clinical study with the limited number of the available subjects.

- If there is an adequate reason for expecting a **superior clinical benefit** at the end of **Phase II studies**, it is possible to make an application before Phase III data become available and to obtain an approval. **Within certain period of time**, the clinical benefit and appropriateness of Phase II approval need to be verified with **Phase III data**.
Current situation of adaptive licensing in Japan-US-EU
More in the future?

- Superior clinical benefit at Phase II study
- Orphan designation applicable

Crizotinib is one of the examples of PII approval with PM commitment of Phase III study

Orphan drug designation is not difficult process for oncology field (except for cytotoxic substances) as long as rational explanation is made to scope the type of carcinoma, based on its expected effect.
Forerunner Package Strategy (Sakigake)

Strategy of SAKIGAKE

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. 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:507KB)

http://www.mhlw.go.jp/eng/health-medical/140729-01.html
Forerunner Review Assignment System (Sakigake)

Forerunner Review Assignment System is a system to put innovative medicines/medical devices/regenerative medicines originated from Japan into practice.

**Designation Criteria**

Medical products for diseases in dire need of innovative therapy and satisfies the following two conditions:

1. Having developed firstly in Japan and anticipating an application for approvals (desirable to have PMDA consultation from the beginning of R&D)
2. Prominent effectiveness (i.e. radical improvement compared to existing therapy), can be expected based on the data of mechanism of action from non-clinical study and early phase of clinical trials (phase I to II)

Not limited to life-threatening and regenerative medicine
• Shorten review time, using rolling submission of data as “prior review” during P-III
• Similar to breakthrough therapy designation of USFDA
• Come into effect in early 2015
Overall picture of CMC development

【Typical Development】

Non-Clinical Study

Phase 1

Phase 2

Accelerated approval review timeline

Clinical Study

Approval

Post-Approval

Process Validation

Control Strategy

Target product Profile

Establishment of Design Quality and Product Quality by CMC study

Process Parameters

Quality Attributes

CQA

CPP

Consistency

Equivalency

Knowledge Control/Quality Risk Management

Investigational Product GMP

GMP
Overall picture of CMC activities through the product life cycle
In case of immune cell therapy development in Japan

New regulations for cellular and tissue based products (“regenerative medical Products”) will be applied.
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)**
Two Acts regulating regenerative medicine & cell therapy

MHLW process  →  Regenerative Medicine  →  PMDA process

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

The Act on the Safety of Regenerative Medicine

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 Hospital exemption system of the EU
Definition of “Regenerative Medical Products” in Japanese Legislation

- **Regenerative medical products** are defined as processed 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
The Pharmaceuticals and Medical Devices Act (PMD Act)

- Separate category and definition of “regenerative medical products”

Difficult to gather and evaluate the data for efficacy of regenerative medical products in a short time due to heterogeneity of cells.

To secure timely provision of safe regenerative medicines, a new regulatory framework is needed.

Expedited approval system for regenerative medical products

After the safety is confirmed and the results predict likely efficacy, the product will be given conditional, time-limited marketing authorization in order to enable timely provision of the products to patients.
How to expedite R&D and review for cellular and tissue based product

- Designed for unmet needs under the present treatment: limited number of patients available for CT
- Difficult to conduct controlled study to demonstrate “true end point” of clinical benefit
- Heterogeneity of Quality affected by source materials

Would it take long time for CTs and review if regulator pursues the conventional drug pathway too much?
Expedited approval system under PMD Act

[Traditional approval process]

Clinical study → Phased clinical trials (confirmation of efficacy and safety) → Marketing authorization → Marketing

< 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

[New scheme for regenerative medical products]

Clinical study → Clinical trials (likely to predict efficacy, confirming safety) → Conditional/term-limited authorization → Marketing (Further confirmation of efficacy and safety) → Re-application within a period (max. 7 years) → Marketing authorization or Revocation → Marketing continues

Post-marketing safety measures must be taken, including prior informed consent of risk to patients
Cellular product specific quality considerations

- Evaluation of Q/S/E
- Selection of Cells that are Suitable for Reprogramming etc.
- Relevant Pluripotency to Differentiate into the Target Cells, Potency of Self-Renewal
- Serving Innovative treatments for Sevier Diseases, Marked loss of QOL or Lack of Existing Relevant Therapies
- Relevant Cells Can Be Processed (e.g. differentiate) to Desired Product

I will just echo the challenges raised by other regulatory speakers

- Characterization, Stability
- Source: Biological Features
- Inactivation and/or Elimination of Undifferentiated Cells
- Ch: Cell
- Sta: Source Biological Features
- Rer: Stability

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Clinical trial consultations contribute to streamlining and expediting the expected review process of PMDA. Some critical points to be looked into during the expected review are shared with the consultation sponsors in advance, e.g.:

- clinical endpoint justification in the PII & PIII studies,
- number of subject population for that endpoint with statistical robustness,
- dosing for Japanese in case of different Japanese/western tolerability, etc.
Outcome of the PMDA Science Board

Cellular & Tissue-based Products
- Current Perspective on Evaluation of Tumorigenicity of Cellular and Tissue-based Products Derived from iPSCs and iPSCs as Their Starting Materials (Aug. 21, 2013)

Pharmaceuticals, Biologics
- Summary of Discussion on Non-clinical Pharmacology Studies of Anticancer Drugs (Dec. 10, 2013)
- Summary of the discussion on assessment of the current status of personalized medicine relating to drug development and review (Mar. 11, 2014)

The Science board outcome is to be contributed to resolve questions expected in the scientific consultation during development.
Pharmaceutical Affairs Consultation on R&D Strategy

For small biotech companies and academic research organizations

Valley of Death
- Shortage of funds, Knowledge on Regulation and developmental strategy

Basic Research
- Pharmaceuticals and Medical Devices candidates

Strategic Consultation
- Quality Study
- Non-Clinical Study
- Clinical Trial (Up to POC studies)

Practical Use
- Innovative Products

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 (744)
- Pre-Consultation (900)
- Face-to-Face Consultation (258)
(7/1/2011 – 9/30/2014)

Further studies are handled by the Regular Consultation
International Collaboration (Win-Win Relationship)
## Global Activities

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<th>Official Name</th>
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<td>Summit</td>
<td>International Summit of Heads of Medicines Regulatory Agencies</td>
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<tr>
<td>ICH</td>
<td>International Conference on Harmonization</td>
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<tr>
<td>IMDRF</td>
<td>International Medical Device Regulators Forum</td>
</tr>
<tr>
<td>PIC/S</td>
<td>Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme</td>
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<td>HBD</td>
<td>Harmonization By Doing</td>
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<tr>
<td>ICDRA</td>
<td>International Conference of Drug Regulatory Authorities</td>
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<tr>
<td>APEC LSIF RHSC</td>
<td>APEC Life Science Innovation Forum Regulatory Harmonization Steering Committee</td>
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<tr>
<td>OECD</td>
<td>OECD Mutual Acceptance of Data</td>
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<td>PDG</td>
<td>Pharmacopoeial Discussion Group</td>
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<td>International Generic Drug Regulators Pilot</td>
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<td>ICMRA</td>
<td>International Coalition of Medicines Regulatory Authorities</td>
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*and more...*
Regular oncology sector teleconference among FDA, EU, CA and PMDA

• MOU between the Chinese SFDA (present CFDA) and the Japanese MHLW, under which PMDA supports cooperative activities
• ** MOU concluded between Interchange Association and East Asia Relations Commission, but is being implemented through cooperation of related organizations.
Thank you for your attention

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Regenerative medicine literature available in English