AMDM 2015 Focus Meeting

Update on Japanese *In Vitro* Diagnostics Regulations

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1

Agenda

I. Overview of Japanese IVD Regulation

II. Revised Points of Pharmaceuticals and Medical Devices Act

III. Current Topics

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3

Role of MHLW and PMDA

- **Ministry of Health, Labor and Welfare (MHLW)**

  Planning basic policy, enforcement of administrative measures based on the law

  Ex.
  - Final judgment on approval of pharmaceuticals and medical devices
  - Issue emergency safety information and direct product withdrawal from market

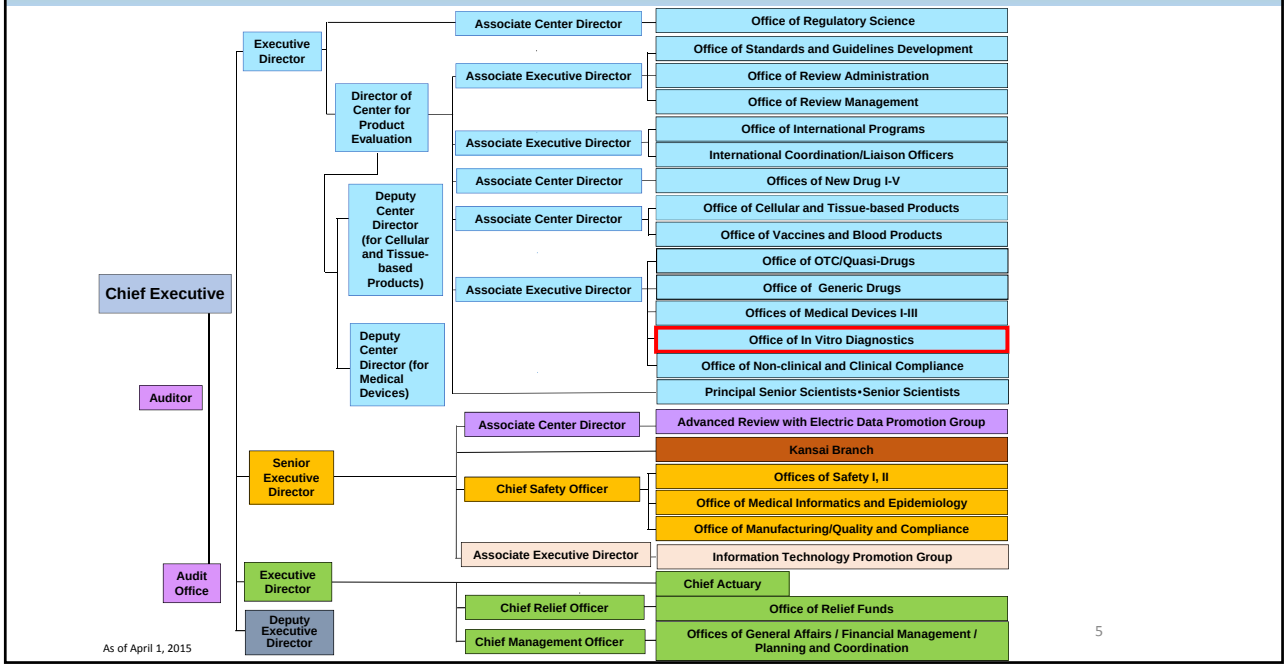
- **Pharmaceuticals and Medical Devices Agency (PMDA)**

  Review, examination and data analysis

  Ex.
  - Scientific review of pharmaceuticals and medical for marketing authorization
  - Consultation on the development of pharmaceuticals and medical devices
  - GMP/GLP/GCP inspections
  - Collection and analysis of adverse Event Reports

4

Organization of PMDA



IVD reagents and IVD equipments (1)

➢Pharmaceuticals and Medical Devices Act (PMD Act)
: Article 2 Definitions

Medical Devices

- devices to be used for the diagnosis, treatment or prevention of humans or animals, to effect on the body structure or function of humans or animals (Clause 4)

Drugs

- Substances (other than quasi-drugs) which are intended for use in the diagnosis, treatment or prevention of diseases in humans or animals, and which are not equipment, dental materials, medical supplies, sanitary materials or programs (Clause 1 ⅱ)

***In vitro* diagnostic reagents (drugs)**

- drugs which are intended for use in the diagnosis of diseases, and which are not used directly on humans or animals (Clause 14)

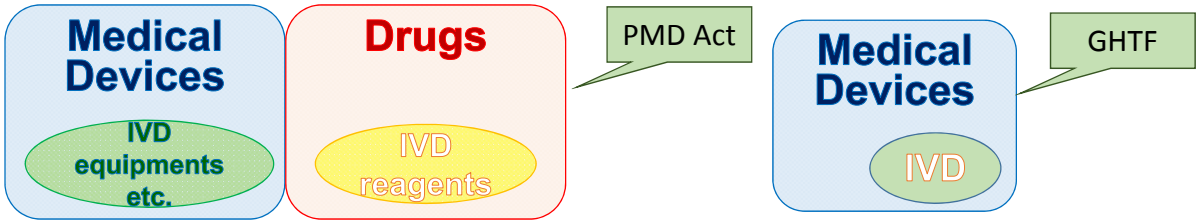
6

IVD reagents and IVD equipments (2)

- Under the Pharmaceuticals and Medical Devices Act (PMD Act)

  * *In vitro* diagnostics reagents(drugs) are categorized as drugs.

  * *In vitro* diagnostics equipments are categorized as medical devices.



- Although IVD reagents are categorized as drugs, IVD reagents are controlled under the similar rules as the medical devices.

  - Risk based classification
  - QMS requirements
  - Essential principle
  - Generic name etc.

7

Classification of IVD reagents

Risk	Class	Risk Level and Examples
Low Risk	**Class Ⅰ**	Its diagnostic information risk is relatively low when used in the diagnosis of disease and which its accuracy in terms of the information which they provide is believed to have a relatively weak impact on life support in comparison with Class Ⅲ Products. These products are recognized by ministerial notification that they have standards and/or standardized measuring method and that they can be calibrated relatively easily upon manufacturing/quality management. OTC products are not included. Example：GOT, GPT, Glucose, LDH, Estradiol
	Class Ⅱ	Its diagnostic information risk is relatively low when used in the diagnosis of disease and which its accuracy in terms of the information which they provide is believed to have a relatively weak impact on life support in comparison with Class Ⅲ Products. OTC products are included. Example：Blood Cell Morphology, Autoimmunity
Other	**Class Ⅲ**	Its diagnostic information risk is relatively high when used in the diagnosis of disease and which its accuracy in terms of the information which they provide is believed to have a relatively strong impact on life support. Example：HIV, HCV, Tumor markers, Microbiology

8

Type of IVD reagents Regulation

Regulation	Category
Self Certification	Class Ⅰ products with self-certification standard
Certification by Registered Certification Body	Class Ⅱ products with certification standard
Approval by MHLW （PMDA's review）	ClassⅢ products, Class Ⅰ / Ⅱ products not conforming standard, Novel products

9

Number of Approvals and Consultations

Number of approvals and review times for IVD

Fiscal Year	FY2010	FY2011	FY2012	FY2013	FY2014
Number of Approvals	191	173	147	166	109
Total Review Times [months]	8.2	7.4	6.0	5.4	5.3
Regulatory Review Times [months]	5.8	4.1	3.4	2.7	2.6

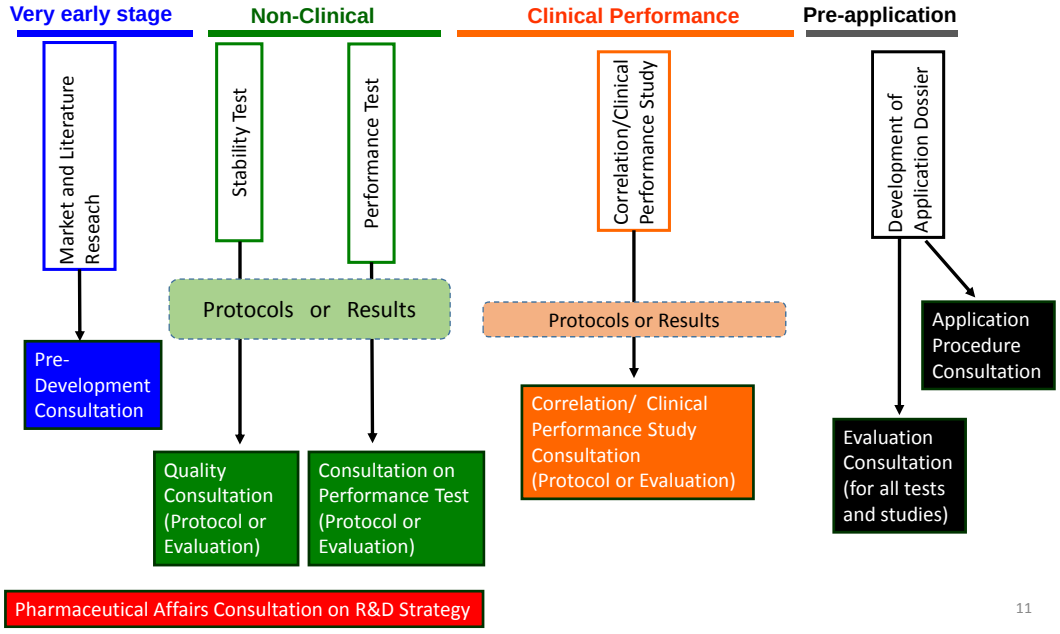
Number of consultations conducted for IVD

Fiscal Year	FY2010	FY2011	FY2012	FY2013	FY2014
Number of Consultations	7	5	8	7	25

*Source: PMDA annual report FY2014

10

PMDA's Consultation Menu (2014.11.25～)



Collaboration plan to accelerate review of IVD

(issued on 31 March 2014)

This plan from FY 2014 to FY 2018 aims to shorten and standardize the review periods of IVD approval through the collaboration of Japanese regulatory authorities and industries by;

1. Taking measures to improve the quality of review process
   Training for applicants, Efficient consultation service, Standardization of review process

2. Setting standard review periods
   80th percentile value out of application cohorts of IVD reagents should satisfy each targeted overall review period from application to approval. (13 months for IVD with consultation with external experts and 7 months for normal IVD)

3. Increase of reviewers

4. Managing progress of this plan
   Regulatory authorities and industries will check its progress regularly and take necessary action(s) to ensure proper implementation.

12

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13

Background on Revision of Pharmaceutical Affairs Law

- High demands to market innovative drugs and medical devices as well as advance R&D of cellular and tissue therapeutic products in a timely manner
- Needs for stronger safety measures
- The Japan Revitalization Strategy

14

Brief Overview of Revision of PAL

- Points of this revision are to;
  1. Strengthen safety measures regarding drugs and medical devices
  2. Revise medical device regulations based on its characteristics
  3. Introduce cellular and tissue therapeutic product regulations based on its characteristics
- The law has been renamed as "Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics" **= "*PMD Act*"**.
- The chapter for medical devices/IVDs is prepared separately.

→ PMD Act has been put into effect on 25 November 2014

15

Summary of Main Revisions Related to IVD Reagents

1. Marketing Authorization Holder (MAH) of IVD reagents is re-defined.
   (It was not distinguished from MAH of drug under PAL.)

2. Manufacturer of IVD reagents should be registered, not licensed or accredited.

3. QMS inspection is performed per product family, not on individual product.
   Product family of IVD reagents are categorized in the following;
   A)Radioactive IVD reagents
   B)Other IVD reagents than those in A)

4. Pre-marketing application form and its attachments are revised.

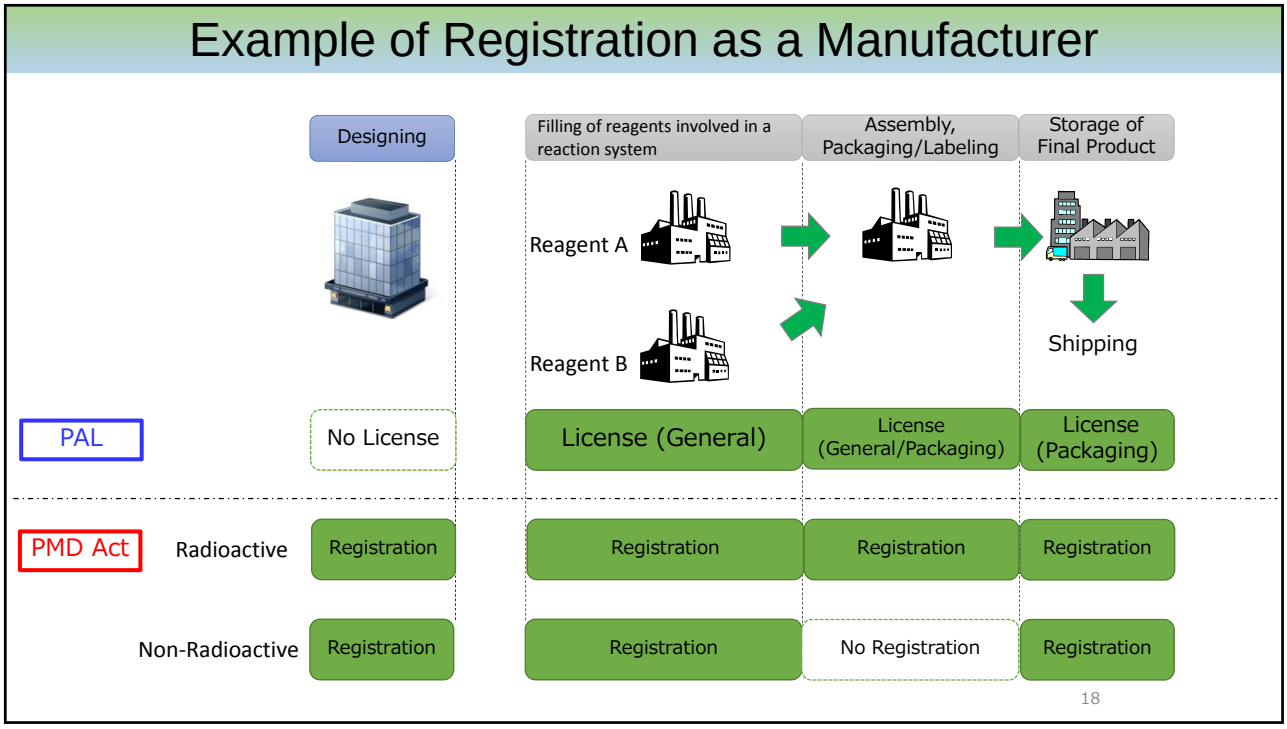
16

Scope of Facilities to be Registered as a Manufacturer

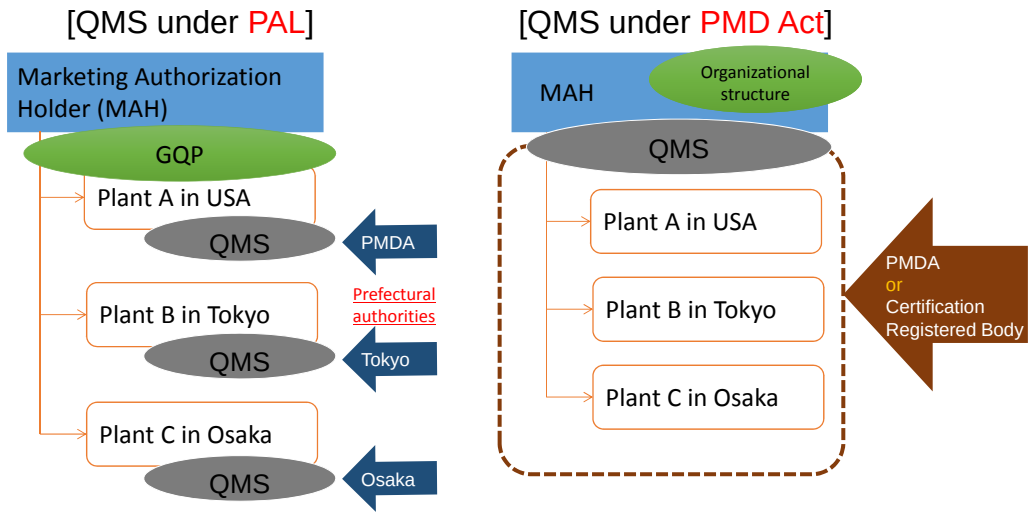
Manufacturing Process	Radioactive IVD reagents	Non-radioactive IVD reagents
Design	X	X
Filling process of reagents involved in a reaction system in final product	X	X
After filling process of reagents before storage of final product	X	NA
Domestic storage site of final product	X	X

17

Example of Registration as a Manufacturer



QMS Inspection is applied to MAH, not each Manufacturer



19

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20

Definition of CoDx in Japan(1)

A companion diagnostics(CoDx) is essential for using the pertinent therapeutic product, and corresponds to either of the following (except *in vitro* diagnostic agents or medical devices intended simply for disease diagnosis, etc.) :

- that is used to identify patients who are expected to respond better to a specific therapeutic product.
- that is used to identify patients who are likely to be at high risk of developing adverse events associated with a particular therapeutic product
- that is necessary for optimizing the treatment including dose, schedule, and discontinuation of a particular therapeutic product

July 2013; Notification on Approval Application for *In Vitro* Companion Diagnostics and Corresponding Therapeutic Products

21

Definition of CoDx in Japan(2)

Q: What examples are there of "*in vitro* diagnostic agents or medical devices intended simply for disease diagnosis" described in Section 1 of this Notification?

A: Examples may include *in vitro* diagnostics that are used for

biochemical assays related to organ functions such as serum creatinine, transaminases, and blood glucose level,

hematological assays such as prothrombin time kit,

bacterial or viral identification and susceptibility tests for infections,

as well as tests used to identify the disease, check the treatment effect, assist in follow-up observation, or evaluate the severity in routine clinical practice.

However, diagnostics of these types may also be judged as CoDx depending on the clinical necessity, etc.

22

Discussion Points of NGS Regulation

- Is each component of NGS MD or IVD reagent in Japan?
- How to evaluate analytical performance of NGS
- How to define validated mutations as indication of corresponding drugs
- How to deal with update of clinical database after marketing authorization of NGS (and corresponding drug)

23

Companion Diagnostics WG

Companion diagnostics (CoDx) working group in PMDA

One of the projects across multi-offices in PMDA

Founded in April, 2012

HP: http://www.pmda.go.jp/rs-std-jp/standards-development/cross-sectional-project/0013.html

24

Common Mistakes Resulting in the Delay of IVD Approval(1)

- Stability Test for Shelf Life

Requirements are specific in Japan;

・Method : QC release test and the criteria described in application form
・Lots : 3 lots
・Repeats : 2 or more
・Time points : 3 times or more; Beginning, Interim, Claimed shelf life or later in real time
・Storage condition : Equal or above the upper limit of the claimed temperature
(This shall not apply in case of refrigerated.)
＊Shipping stability, In use stability; self-assurance

- Clinical Performance Study for Novel Product

Sometimes submitted protocol and clinical data are insufficient in followings;
・Generalisability
・Positioning of the product
・Difference from previous product
・Medical environment difference from foreign countries etc.

25

Common Mistakes Resulting in the Delay of IVD Approval(2)

- Clinical Performance Study for Companion Diagnostics (CoDx)

1) CoDx-negative cases (i.e. patients not enrolled in clinical trial) also should be evaluated in clinical performance study.

・Confirming the test was conducted appropriately

・Validating true negative (not false negative)　etc.

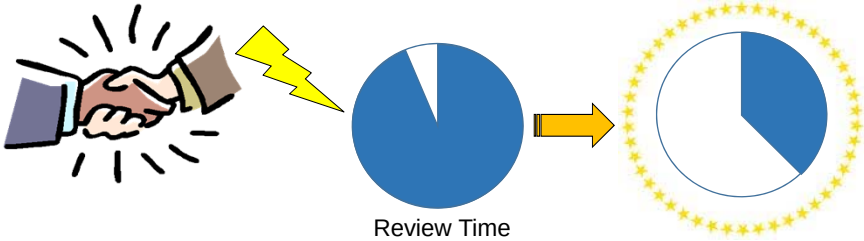
2) In some cases, CoDx testing results of exploratory clinical trials are required.
(e.g. if clinical cut off is defined in the exploratory clinical trial)

26

Take home message

To further shorten the review period, we need・・

- Applicant's cooperation
  - appropriate evaluation of the IVDs
  - suitably-preparation of application documents
- Oversea manufacturer's cooperation
  - giving accurate information to Japanese distributors
  - quick response to inquiry from Japan
- Joining the meeting with PMDA (as necessary)



27

Thank you very much for your attention !

http://www.pmda.go.jp/