IVD (clinical investigation requirements) (Japan)

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Introduction of Japanese IVD regulation

Regulatory differences between IVD and LDT in Japan

IVD

The PMD Act

- Tests conducted using approved in vitro diagnostic products and medical devices
- Marketing authorization holder assure the quality and precision of the products

Based on the PMD Act, the quality, accuracy and performance of the product is ensured by the government and the third-party certification bodies.

Under the jurisdiction of Pharmaceutical Safety and Environmental Health Bureau of the MHLW

LDT: Laboratory Developed Test

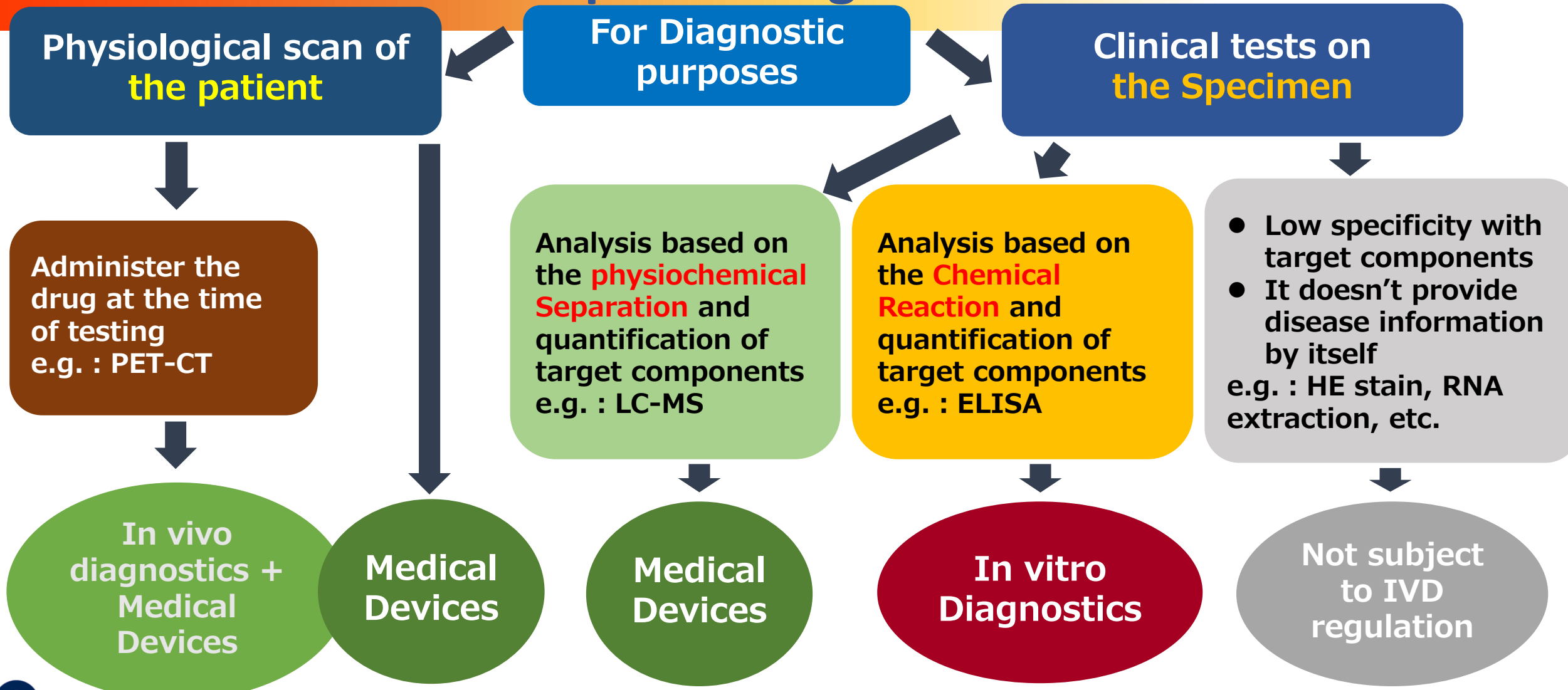
Interpretation under the Medical Care Act

- Due to the revision of the Medical Care Act, the standards for the accuracy control of the specimen tests have been clarified
- It can be interpreted as a medical technology implemented under the direction and management of a doctor.
- It can be interpreted that the use of research reagents and equipment is also possible.
- Quality and accuracy must be ensured by the laboratory that performs the test.

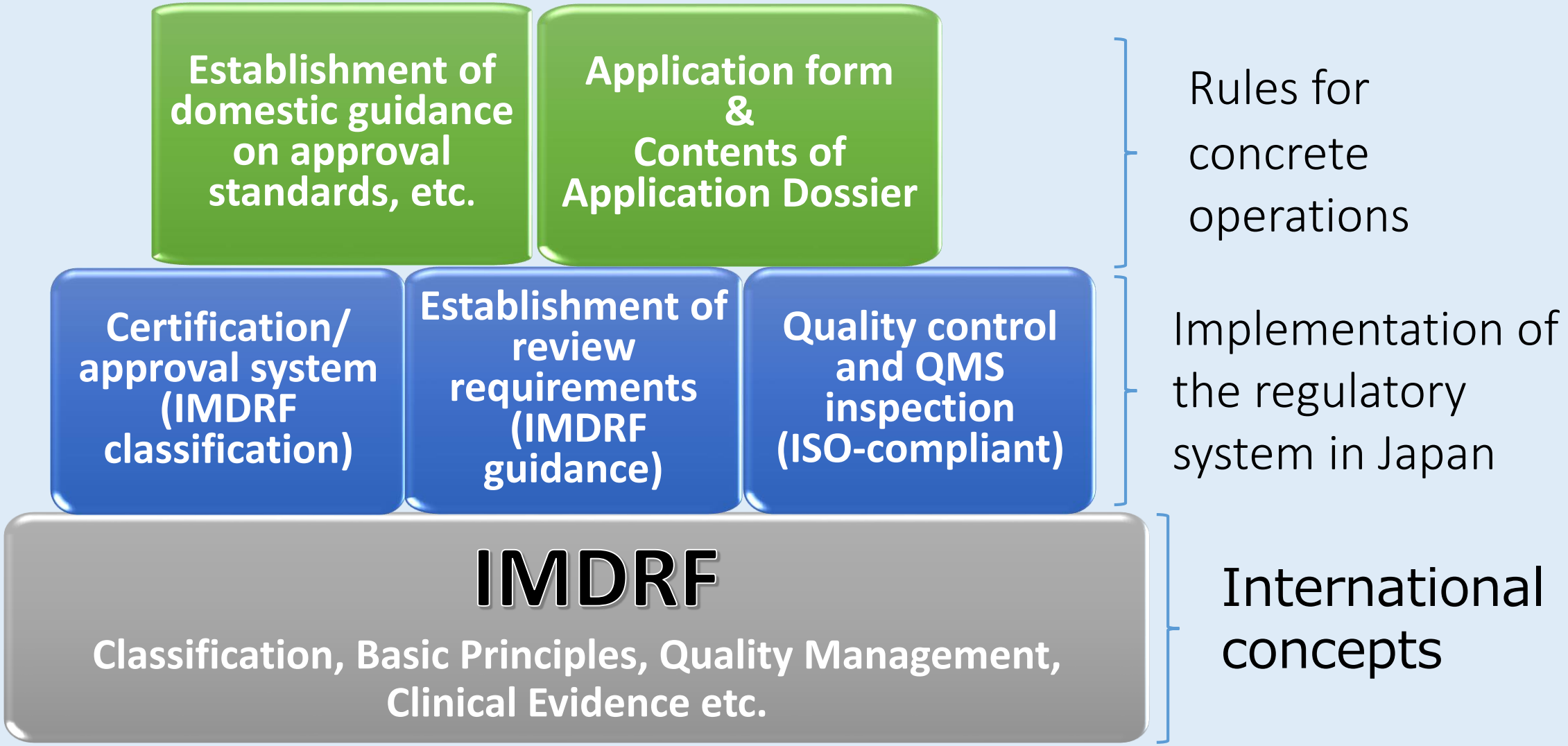
There is no system to ensure the quality, accuracy and performance of the test by the third-party.

Under the jurisdiction of the Health Policy Bureau of the MHLW

Category of Medical Device, IVD and non-IVD in Japanese regulation



Schematic Representation of Regulation of IVD in Japan



Classification and Regulation of IVD

<table>
<tr><th colspan="2">Class1</th><th colspan="2">Class2</th><th>Class3</th></tr>
<tr><td colspan="2">● Relatively low diagnostic risk
● Have minor impacts
● Have calibration standards
● Easy self-checking
(Examples) Amino acids, hormones, enzyme activities, minerals, etc.</td><td colspan="2">● Relatively low diagnostic risk
● Have minor impacts
● OTC test agents
(Examples)
(1) Hormones, enzyme activities, allergy-related substances (IgE), autoantibody assays, etc.
(2) Ovulation test kits, pregnancy test kits, etc.</td><td>● Relatively high diagnostic risk
● Have major impacts
(Examples)
Bacterial/viral antigens/DNA/RNA, antibody titers associated with microbial infection, immunostaining, human genetic tests, cancer-related biomarkers, companion diagnostics, etc.</td></tr>
<tr><td>Conform to notified standards</td><td>Non-conforming</td><td>Conform to notified standards</td><td>Novel products, Non-conforming</td><td>Novel products, Products with/without notified standards, Non-conforming</td></tr>
<tr><td>Self-certification</td><td>Approval by MHLW (reviewed by PMDA)</td><td>Third-party certification</td><td>Approval by MHLW (reviewed by PMDA)</td><td>Approval by MHLW (reviewed by PMDA)</td></tr>
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Products to be reviewed by the PMDA

	Type of application	Representative Products	Required studies	TC
1	Products to be tested that have not been previously approved or certified in Japan (Class3, Class2, Class1) and/or claiming novel clinical utility	CDx, genetic testing products, diagnostic markers for orphan diseases, diagnostics of new infectious diseases (e.g. COVID-19), new BMs for risk diagnosis	Clinical performance study	12 months
2	All products classified as Class 3		Concordance study to predicates	
a	without notified standards	new products with few approvals, nucleic acid test products for infectious diseases		
b	with notified standards	antigen test products, antibody test products for infectious diseases, BMs for tumor diagnosis		7 months
3	Products classified as Class 2 and Class 1 for which there are existing products for same target already launched, but which do not correlate well with existing products.	Various products	In some case clinical performance study is required	

Challenges against COVID-19

How MHLW and PMDA responded to Emergency Regulation

In principle, the approval review and QMS inspection of the COVID-19 test product will be completed 2-3 month (the normal standard period is specified as 12 months).

In all cases, companies wishing to launch COVID-19 test products will be able to consult PMDA promptly and free of charge before submitting an application (a total of approximately 600 consultations have been held by the end of November 2021).

PMDA as a whole issued a notification on priority reviews for products related to COVID-19.

https://www.pmda.go.jp/files/000234904.pdf

https://www.pmda.go.jp/files/000235010.pdf

Basic concept for review of IVDs for COVID-19

Challenges

- The time within which to conduct clinical performance studies is very limited.
- Since the epidemic in Japan is limited, it is difficult to obtain clinical samples.
- It is difficult to conduct long-term storage tests based on the actual storage period to guarantee the product quality.

Conditions for approval

- Post-marketing studies with adequate sample size should be conducted to evaluate the clinical performance.
- Post-marketing stability studies should be conducted under actual storage conditions.

EUA has not been established in the Japanese regulation under Pharmaceutical and Medical Device Act. COVID-19 IVD products are approved in ordinary regulatory scheme.

Acceptance criteria of nucleic acid test kits

Reverse transcription and gene amplification time	Detection limit
≥1 hr	≤ 50 viral genome copies/reaction
15 min ~ < 1 hr	≤ 100 viral genome copies/reaction
< 15 min	≤ 200 viral genome copies/reaction

Based on the performance evaluation recommended by NIID as of March 2020, the evaluation is required with 10 or more positive samples in the range of approximately 10 to 200,000 copies (incl. 2 or more of 10-20 copies and 1 or more of 100-200 copies) and 15 or more negative samples.

Clinical Performance of the first rapid antigen test product approved in Japan

Clinical Performance Study1

- Negative agreement rate 98% (44/45 subjects)
- Positive agreement rate 37% (10/27 subjects)
- Positive agreement rate with RT-PCR at ≥100 copies/test or higher: 83% (5/6 cases)

Clinical Performance Study2

- Negative agreement rate 100% (100/100 cases)
- Positive agreement rate 66.7% (16/24 subjects)
- ≥ 1,600 copies/test, positive agreement rate 100% (12/12 cases), ≥ 400 copies/test, 93% (14/15 cases), ≥ 100 copies/test, 83% (15/18 cases)

For follow-on products, detection sensitivity equal to or higher than that of the preceding product is required.

Guidance on COVID-19 Pathogen Test in Japan

- Kits for quantitative assessment of viral RNA of SARS-CoV-2. The following 2 types are available.
- **In vitro diagnostics:** Products having been assured as to quality by QMS and having undergone review and approval by PMDA pursuant to the Drug and Medical Device Act.
- **Laboratory Developd Test:** Products not covered by QMS or the Drug and Medical Device Act but verified as to performance at the National Institute of Infectious Diseases (NIID).

- Used for measuring viral antigen of SARS-CoV-2, allowing more sensitive quantitation if used in combination with a device, and variety of products are developed.

- For follow-on products, detection sensitivity equal to or higher than that of the preceding product (i.e. ESPLINE) is required.

Test subjects		Nucleic acid detection kit			Antigen test (quantitative)			Antigen test (rapid detection kit)		
		Naso-pharynx	Nasal cavity	Saliva	Naso-pharynx	Nasal cavity	Saliva	Naso-pharynx	Nasal cavity	Saliva
Individuals with symptoms (including individuals after disappearance of symptoms)	Within 9 days after symptom onset	⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙	×
	10 or more days after symptom onset	⊙	⊙	–	⊙	⊙	–	△	△	×
Individuals without symptoms		⊙	–	⊙	⊙	–	⊙	–	–	×

Positioning of antibody test in Japan

Approval for intended use of diagnosis

- Clarification of examination scheme in addition to antigen test and nucleic acid test: What kind of subject should be examined?
- Clinical significance of antibody titer: Does the obtained antibody titer reflect the severity of COVID-19? Antibody titers differ between products, but how standardize them? How to utilize qualitative test?

Approval for intended use of vaccine efficacy or infection history

- Information on the cut-off value of antibody titers related to reinfection and onset is insufficient.
- It is necessary to consider the optimal way of testing including unaffected persons nationwide.

Distribution as RUO products

- It is possible to distribute them as an RUO product and accumulate evidence.

Summary

- In Japan, in vitro diagnostic products are classified into classes based on risk, and the PMDA mainly reviews the approval of products with new biomarkers and products in Class 3. In principle, clinical performance study is required for new biomarkers and for advocacy of new clinical utility.
- Non-targeting reagents that could be used universally in clinical laboratories are not subject to in vitro diagnostic product regulations.
- The COVID-19 test product was approved with the condition of approval for post-marketing issues based on limited data because of limited outbreak in Japan. The application data package for COVID-19 IVD will be developed through prior consultation with MAH.