# Overview of the Regulation of In Vitro Diagnostics products in Japan

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

# Outline

1. Regulations of IVD in Japan
2. Submission Data and Timeline for Regulatory Review
3. Consultation

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# Regulatory approach to clinical laboratory products 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

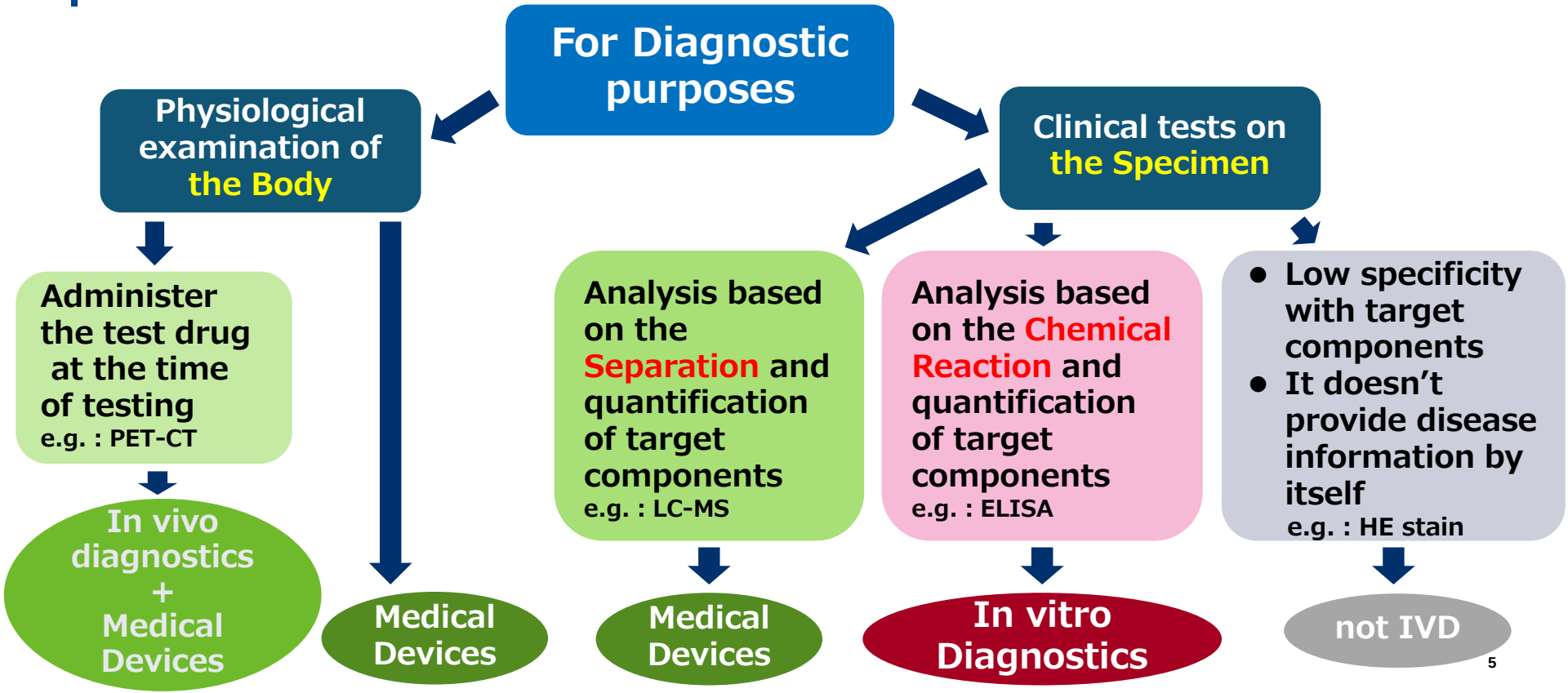
Interpretation under the Medical Care Act

- 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.

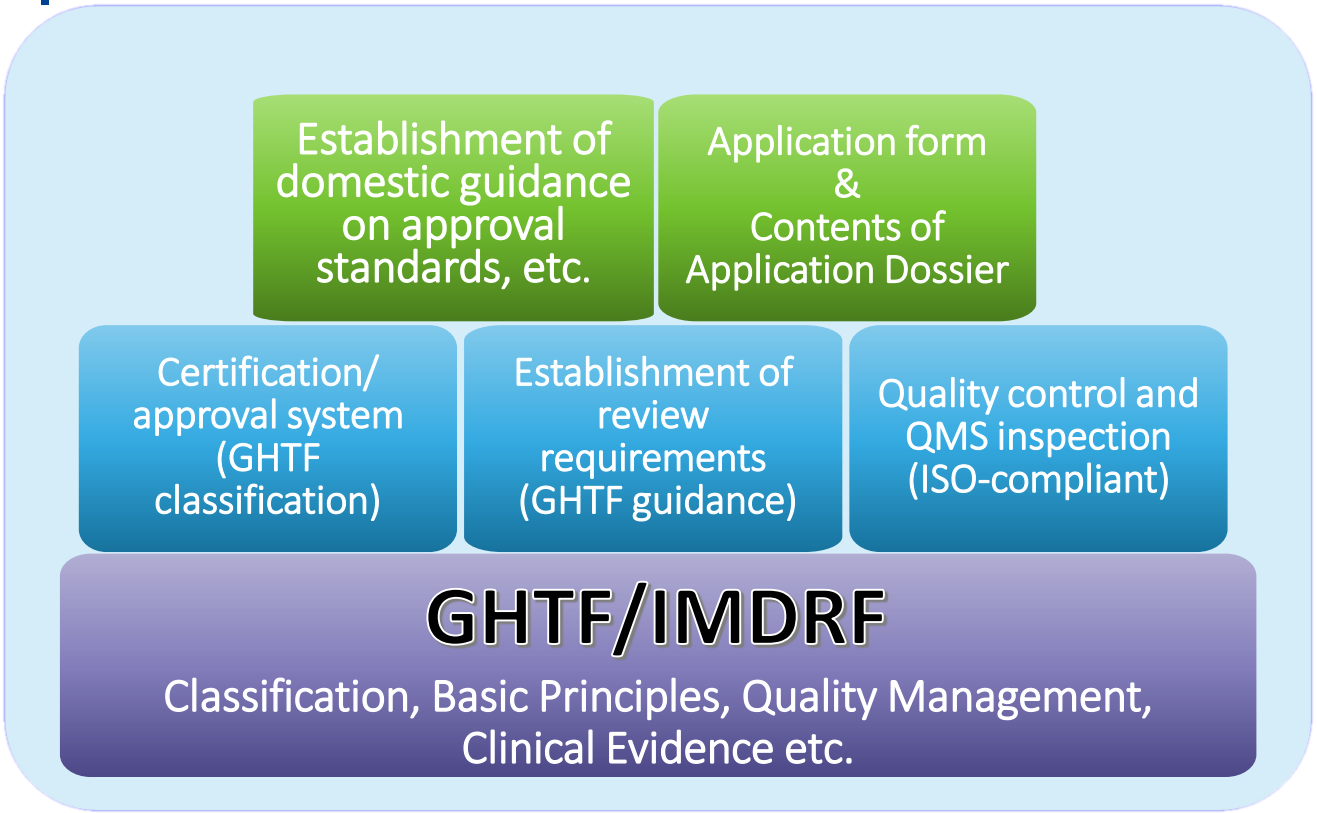
There is no system to ensure the quality, accuracy and performance of the test by the third-party.

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



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# Classification and Regulation of IVD

Minor ← (Risk) → Major

| | Class I | | Class II | | Class III |
|---|---|---|---|---|---|
| Concrete examples | ◆ Relatively Low diagnostic information risk<br>◆ Have minor impacts<br>◆ Have calibration standards<br>◆ Easy self-checking<br>(Examples)<br>Amino acids, hormones, enzyme activities, minerals, etc. | | ◆ Relatively Low diagnostic information risk<br>◆ Have minor impacts<br>◆ OTC test agents<br>(Examples)<br>(1) Hormones, enzyme activities, allergy-related substances (IgE), autoantibody assays, etc.<br>(2) Ovulation test kits, pregnancy test kits, etc. | | ◆ Relatively High diagnostic information risk<br>◆ Have major impacts<br>(Examples)<br>Bacterial/viral antigens, DNA・RNA, antibody titers associated with microbial infection, immunostaining, human genetic tests, cancer-related biomarkers, companion diagnostics, etc. |
| PMD Act | Conform to notified standards | Non-conforming | Conform to notified standards | Novel products, Non-conforming | Novel products, products with/without notified standards, Non-conforming |
| Regula-tion | Self-certification | Ministerial approval (reviewed by PMDA) | Third-party certification | Ministerial approval (reviewed by PMDA) | Ministerial approval (reviewed by PMDA) |

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# List of user fees for reviews

(revised on May 5, 2022)

| Category | | | User fees (Yen) |
|---|---|---|---|
| Novel products | Non-CDx | | 2,534,000 |
| | CDx | | 4,295,000 |
| Out of scope of approval standards | With clinical study | Non-CDx | 2,534,000 |
| | | CDx | 4,295,000 |
| | Without clinical study | | 2,362,200 |
| Nonconformity with approval standards | With clinical study | Non-CDx | 2,534,000 |
| | | CDx | 4,295,000 |
| | Without clinical study | | 1,318,600 |
| Conformity with approval standards | Without clinical study | | 454,800 |

## Notification of Approval and Certification Standards

To make rules in advance to whether the correlation with existing products is good or poor, we set forth the criteria for correlation.

1. At least two products are approved for the novel clinical test item.
2. From the data of the two approved products, it can be judged that there is no obstacle in providing the product of same intended use to medical practice, based on the good correlation of products.

MHLW will issue a notification that the IVD products intended for the test item is subject to approval or certification standards.

# Correlation Study Criteria for Approval Standards

| | Qualitative Assay | Quantitative Assay |
|---|---|---|
| Samples | > **100** Clinical Samples | |
| | ・Both positive and negative samples are included at least **50**.<br>・Samples around cutoff value should be included. | ・Samples should be distributed throughout the measuring range.<br>・Samples around clinical cutoff value should be included. |
| Comparison Method | ・At least **2** IVD should be applied.<br>(or standardized methods can be selected)<br>・Two different principles should be selected. | |
| Criteria | Concordance rate: > **90%** | Correlation coefficient: >**0.9**<br>Slope of regression line:**0.9~1.1** |

If the product conforms to the standard, it is possible that the product is judged as Non-conforming products because of a difference from approved products.

# Correlation Study Criteria for Certification Standards

| | Qualitative Assay | Quantitative Assay |
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| Samples | > **50** Clinical Samples | |
| | ・Both positive and negative samples are included at least **25**.<br>・Samples around cutoff value should be included. | ・Samples should be distributed throughout the measuring range.<br>・Samples around clinical cutoff value should be included. |
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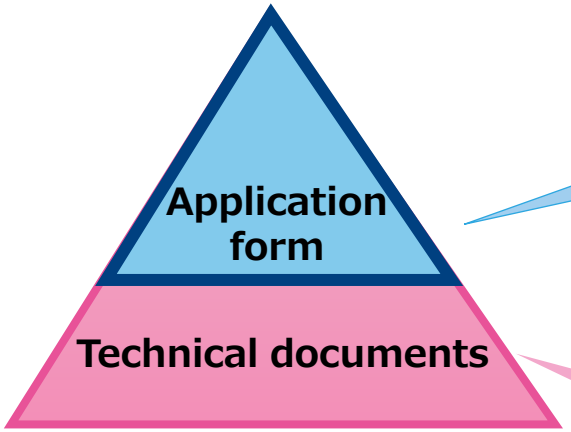
# Structure of Application Dossier




- Brand name
- Intended use
- Shape, structure and principle
- Active ingredients
- Specifications
- Assay procedure
- Manufacturing process
- Storage conditions and shelf life
- Manufacturing site

- History of development and status of use in foreign countries
- Product specifications
- Stability
- Conformity assessment in PMD Act, Article 41, Clause 3
- Performance
- Risk management
- Manufacturing method
- Clinical performance study

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Supporting documents
(literature references,
supplementary data, etc.)

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# Notifications and Administrative Notices

https://www.pmda.go.jp/english/review-services/regulatory-info/0003.html

## *In Vitro* Diagnostics

| Issue Date | Document Type & No. | Title | Subject |
|---|---|---|---|
| Nov. 21, 2014 | PFSB/ELD/OMDE Notification No. 1121-16 | Points to Consider When Applying for Marketing Approval of *In Vitro* Diagnostics | Regulatory submission |
| | PFSB Notification No. 1121-15 | Applications for Marketing Approval of *In Vitro* Diagnostics | |

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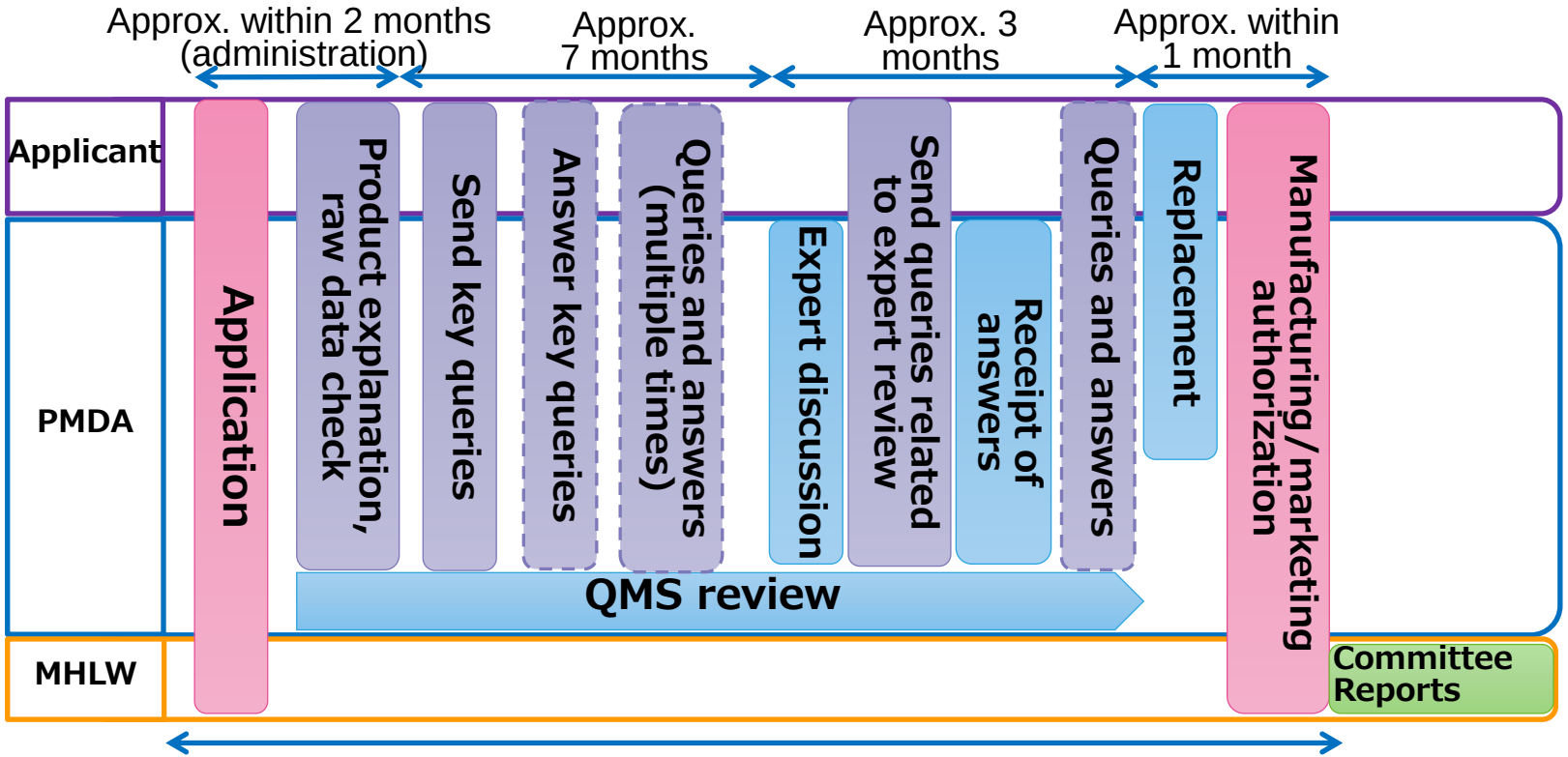
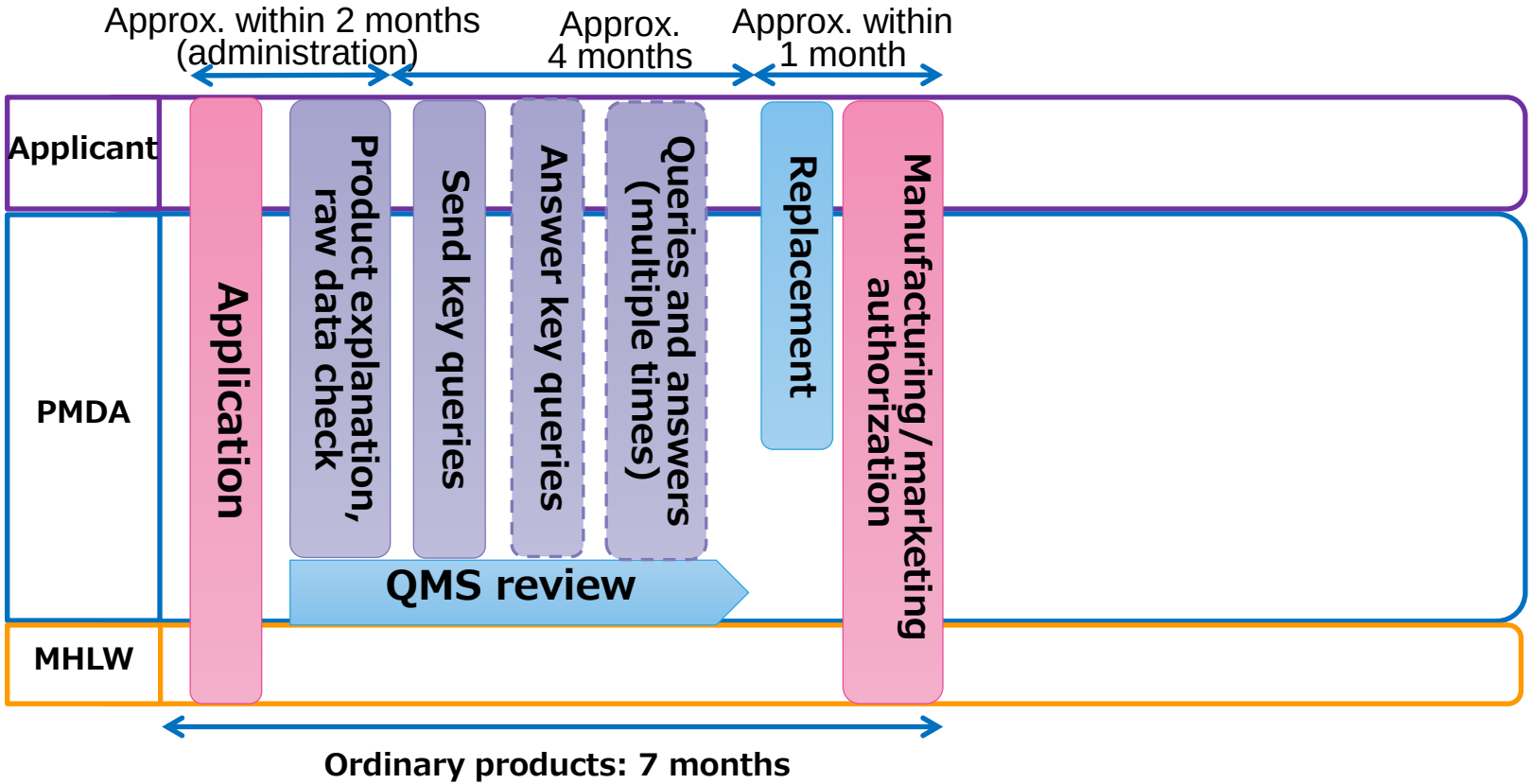
# Standard Process of Approval (12 months)




**Products requiring expert review (including companion diagnostics): 12 months**

# Standard Process of Approval (7 months)



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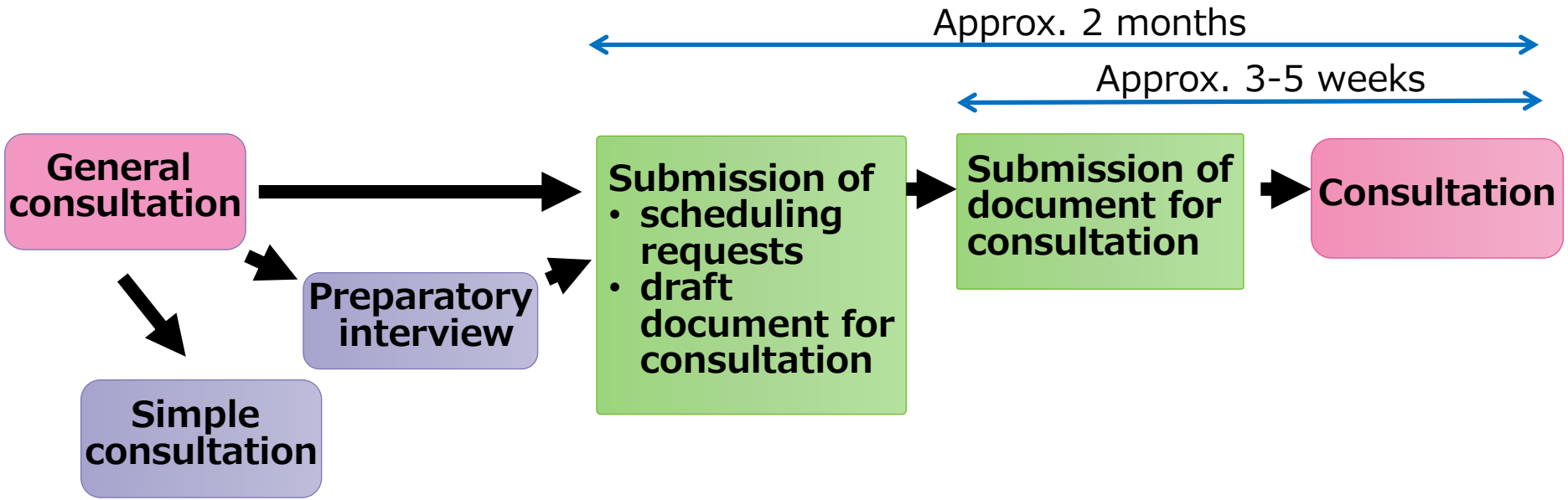
# Standard Procedure of consultation (1)



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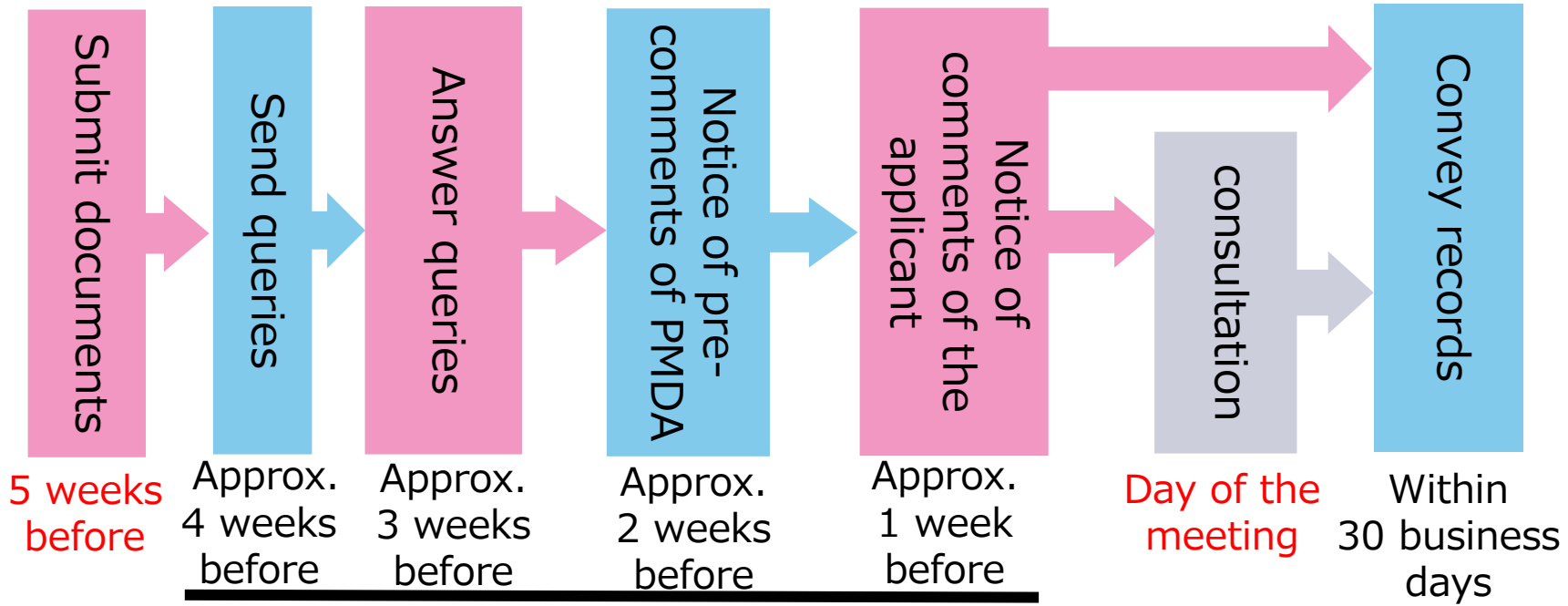
# Menu of consultation

(revised on August 1, 2021)

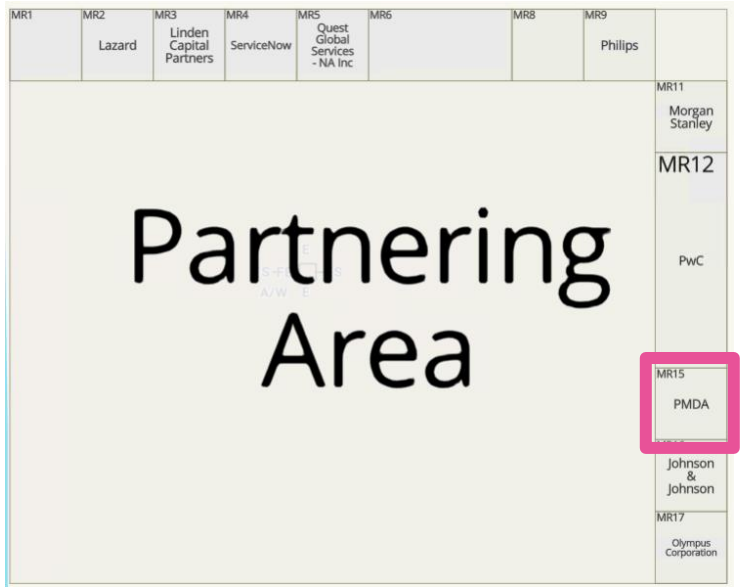
| Category | | User fees (Yen) |
|---|---|---|
| Pre-development consultation for IVD reagents | | 196,000 |
| Pre-development consultation for companion diagnostics (CDx) | | 293,800 |
| CDx Package development consultation | | 1,541,600 |
| Protocol consultation | Quality | 127,400 |
| | Performance (other than quality) | 127,400 |
| | Correlation | 254,800 |
| | Clinical performance study | 735,300 |
| | Clinical performance study for CDx | 2,353,100 |
| Evaluation consultation | Quality | 127,400 |
| | Performance (other than quality) | 127,400 |
| | Correlation | 254,800 |
| | Clinical performance study | 440,700 |
| | Clinical performance study for CDx | 1,470,700 |
| Application procedure | | 78,300 |
| Simple consultation | | 39,400 |

## Standard Procedure of consultation (2)




The process can be ahead of/behind schedule by a few days.
Please contact consultation staff directly for a concrete schedule.
Additional queries may also be required if necessary.

## Information about 30-minute free regulatory consultation at meeting room




**#MR15**

**PMDA**

Please send your meeting request to **pmda-md-intl@pmda.go.jp** or via medtech app with specific questions and a preferred day/time if you are interested in having a private meeting with us.