Medical Devices Topic 3:

RA's support to COVID-19 related IVDs development

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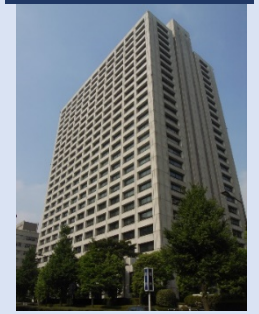
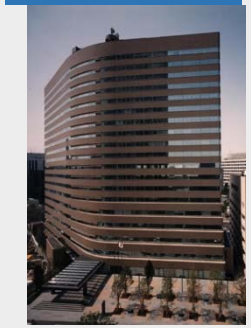
The role of agencies against COVID-19

MHLW



- Decides the policy for clinical tests of COVID-19
- Supports logistics of COVID-19 clinical tests scheme
- Promotes new IVD development

PMDA



- Evaluates dossiers for IVD approval
- Holds consultation for rapid development of IVDs
- Post market surveillance

National Institute of Infectious Diseases

- Establishment of standard RT-PCR method
- Promotion of development of new IVDs also supported by AMED

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 in 1-2 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 300 consultations have been held by the end of December).

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

Nucleic Acid Test Kits

Representative approved product in Japan

Loopamp novel coronavirus 2019 (SARS-CoV-2) detection reagent kit

By Eiken Chemical Co., Ltd.

http://loopamp.eiken.co.jp/products/turbidimeters/index.html
http://loopamp.eiken.co.jp/products/sars-cov-2/index.html

Basic concept for development and review of nucleic acid test kits

Difficulty of clinical performance studies

Equivalence to the gold standard established by NIID explain the clinical utilities.

Difficulty of obtaining clinical samples

Limited number of contrived samples are acceptable.

Setting the shelf life of the product

Based on the stability test and accelerated test using the same or similar components.

Conditions for approval

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

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.

Antigen Detection Test Kits

Representative approved product in Japan
ESPLINE SARS-CoV-2
By FUJIREBIO Inc.

https://www.fujirebio.co.jp/products/espline/sars-cov-2/index.html

Basic concept for development and review of antigen detection test kits

Direct comparison with PCR is essential.

Clinical performance study is mandatory.

Lower sensitivity than nucleic acid test

The precautions on label are discussed with our medical expert panel.

Setting the shelf life of the product

Based on the stability test and accelerated test using the same or similar components.

Conditions for approval (Same as nucleic acid test kits)

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

Antigen Quantification Test Kits

Representative approved product in Japan
Lumipulse SARS-CoV-2 Ag
By FUJIREBIO Inc.

https://www.fujirebio.co.jp/products/lumipulse.html#item01

Basic concept for development and review of antigen quantification test kits

Is it possible to confirm infection by the antigen test around the cut-off value?

Discussed with our medical expert panel.

Is investigation using contrived saliva samples acceptable?

Acceptable considering the research result on studies using saliva supported by MHLW

Setting the shelf life of the product

Based on the stability test and accelerated test using the same or similar components.

[Important precautions] (at initial approval)
" The results of measurements between 1.00 pg/mL and less than 10.00 pg/mL could not be used to confirm infection or non-infection, and additional test such as the nucleic acid test should be considered if necessary. "

Conditions for approval: Post-marketing clinical performance studies using saliva and stability studies under actual storage conditions should be conducted.

Guidance on COVID-19 Pathogen Test in Japan (released on Oct.2)

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 Developed 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		✔	–	✔	✔	–	✔	–	–	×

*In case of a negative result, it's recommended to retest using other methods.

Antibody Test Kits

No product has been approved in Japan

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?
- Optimal use of IgM and IgG antibody: How to distinguish past infection history from new infection?
- 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 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 view of the COVID-19 pandemic, a system of priority review for these tests has been established in Japan, and nucleic acid and antigen tests have been approved through this pathway.
- Although the data available at the time of approval are limited, these tests have been approved based on the rationale of evaluating a certain level of clinical performance and with post-approval conditions requiring follow-up data.
- To minimize healthcare worker's exposure during medical examination, additional specimen types for tests have been rapidly added in cooperation with the MHLW. For example, at present, many nucleic acid and antigen tests can be performed using saliva or nasal cavity specimen.