Further Advancement for Early Patient Access

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Pharmaceuticals and Medical Devices Agency (PMDA)
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Today’s topics

- Introduction
- SAKIGAKE Designation System
- Conditional and Time-limited Approval for Regenerative Medical Products
- New Consultation Categories
- Actions for COVID-19
My Career

— Executive Director & Director of Center for Product Evaluation, PMDA (2020.4 - )
— Director of Center for Product Evaluation & Director of Center for Regulatory Science, PMDA (2018.4 - 2020.3)
— Professor of Department of Health Chemistry, Graduate School of Pharmaceutical Sciences at University of Tokyo (2000-2019)
  ➢ Dean (2016-2018)
— Overseas experiences at
  ➢ Tufts University, Medical School (1986-1988).
  ➢ University of Illinois (1984-1986)
— Graduated from the University of Tokyo in 1984.
  ➢ PhD in Biochemistry
New Technologies with Unknown Safety/Efficacy

Innovative Product Candidates arising from Japan

• Nobel prize awarded to many Japanese researchers
• Strong research capacity especially in regenerative medicine
(1) Early patient access by expedited approval process

- Legislation of
  - SAKIGAKE Designation System
  - Conditional Early Approval System
  - New Approval System for Medical Devices considering innovative technologies; Big Data, AI etc.

- Clarification of clinical trials process and ensuring safety of subjects

(2) Introduction of new Quality Management System

(3) Strengthen Safety Measures
Today’s topics

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**SAKIGAKE Designation System**

Established the “SAKIGAKE-designation system” to apply innovative drugs/medical devices/regenerative medicines in practical use in Japan sooner than other countries, aiming at early practical application with various supports (granting approval in 6 months, i.e., half the usual time).

### Designating criteria
1. Breakthrough treatment/diagnostic method: novel medical device in principle
2. Firstly developed and planed to submit application for approval in Japan (concurrent submission allowed)
3. Expected significant efficacy for a target disease, such as much improvement from existing treatment considering non-clinical data (mechanism of action, etc.) and early phase clinical data.

### Details of designation system

<table>
<thead>
<tr>
<th>Priority consultation</th>
<th>Enhanced pre-consultation</th>
<th>Priority review</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 months → 1 month</td>
<td>Substantive accelerated review</td>
<td>12 months → 6 months</td>
</tr>
<tr>
<td>Communicating with consulter swiftly to shorten the time from submission to a clinical trial consultation</td>
<td>Enhanced pre-consultation meeting allowing English materials</td>
<td>The goal of total review period is 6 months</td>
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<td></td>
<td></td>
<td>Submission of the Phase 3 study results after the application may be permitted to shorten the time from development to granting approval</td>
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- **①Priority consultation**
  - 2 months → 1 month
  - Communicating with consulter swiftly to shorten the time from submission to a clinical trial consultation

- **②Enhanced pre-consultation**
  - Substantive accelerated review
  - Enhanced pre-consultation meeting allowing English materials

- **③Priority review**
  - 12 months → 6 months
  - The goal of total review period is 6 months
  - Submission of the Phase 3 study results after the application may be permitted to shorten the time from development to granting approval

- **④Review partner**
  - PMDA concierge
  - Offering a concierge who supervises a necessary process including review, safety measure, quality management and quality assurance

- **⑤Enhanced post-marketing safety measure**
  - Prolongation of reexamination period
  - Improving post-marketing safety measure including expanding reexamination period, transmission of information overseas and collaboration with academic societies
New SAKIGAKE Designation

Press Release

New SAKIGAKE products: designated in April 2019 (4th term)

*Drugs*

15 +5 20

*Medical Devices and IVDs*

7 +4 11

*Regenerative Medical Products*

9 +2 11

Adds up to 42

13 products were approved (As of 2020.03.25)
### Name of product (Applicant) | Summary of Product
---|---
① BNCT System NeuCure (Sumitomo Heavy Industries, Ltd) | A neutron irradiation system used for BNCT (Boron Neutron Capture Therapy)
② BNCT dose calculation program NeuCure Dose Engine (Sumitomo Heavy Industries, Ltd) | A program used for dose distribution calculation of BNCT based on contour information and irradiation conditions to support the BNCT treatment planning
③ Steboronine® intravenous drip bag 9000mg/300mL (STELLA PHARMA Co) | A drug consists of increased abundance of Boron-10 (stable isotope) included in 4-borono-L-phenylalanine, a phenylalanine (essential amino acid) derivative

※ combination ①+② (medical device) and ③ (drug) for treatment

### Timeline
- Feb. 2017: **Designated for SAKIGAKE** (①②)
- Apr. 2017: **Designated for SAKIGAKE** (③)
- Oct. 2019: Submission for marketing approval (①-③)
- Mar. 2020: **Approval**

###【INDICATION】
Unresectable Locally Advanced or Locally Recurrent Head and Neck Carcinoma

### 【Novel mechanism】
Damaging cancer cells by α particles (helium nuclei) and Li recoil nuclei (lithium nuclei) released by nuclear reaction of a boron and a thermal neutron

![Figure 1. Principle of BNCT](image1.png)

![Figure 2. Schematic of neutron irradiation system used for BNCT](image2.png)
### Name of product (Applicant)

<table>
<thead>
<tr>
<th>Name of product (Applicant)</th>
<th>Summary of product</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEPMETKO® 250mg (Merck BioPharma CO., Ltd)</td>
<td>This is a low molecular weight compound that inhibits MET tyrosine kinase, which is designed to have inhibition of tumor cell proliferation against NSCLC with METex14 skipping alterations, by inhibiting MET phosphorylation and downstream signaling.</td>
<td>unresectable, advanced or recurrent non-small cell lung cancer (NSCLC) with MET exon 14 (METex14) skipping alterations</td>
</tr>
</tbody>
</table>

### Timeline

- **Mar. 2018:** Designated for SAKIGAKE
- **Nov. 2019:** Submission for marketing approval
- **4 months**
- **Mar. 2020:** Approval
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Conditional and Time-limited Approval for Regenerative Medical Products

Conventional Regulatory Approval Process

Clinical research

Clinical trial (Confirmation of efficacy and safety)

Approval

Marketing

Re-Application (or Expiration) within max. 7yrs

Clinical research

Clinical trial (likely to predict efficacy, confirmation of safety)

Conditional and time-limited approval

Marketing further confirmation of efficacy and Safety

Marketing Authorization or Revocation of the conditional approval

Continued marketing

Regulatory System that Facilitate Early Patient Access
Conditional and Time-limited Approval for Regenerative Medical Products

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Applicant Company</th>
<th>Indication</th>
<th>Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>HeartSheet</td>
<td>Terumo Corporation</td>
<td>serious heart failure caused by ischemic heart disease</td>
<td>Sep. 18, 2015</td>
</tr>
<tr>
<td>STEMIRAC Inj.</td>
<td>Nipro Corporation</td>
<td>neurological symptoms and functional disorders associated with spinal cord injury (only for use in patients with traumatic spinal cord injury and ASIA Impairment Scale A, B, or C)</td>
<td>Dec. 28, 2018</td>
</tr>
<tr>
<td>Collategene</td>
<td>AnGes, Inc.</td>
<td>ulcers in patients with chronic arterial occlusion (arteriosclerosis obliterans and Burger’s disease) who have not responded sufficiently to the standard drug therapy and are unable to undergo revascularization</td>
<td>Mar. 26, 2019</td>
</tr>
</tbody>
</table>
## Early Patient Access to Innovative Product

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<th>Name of product (Applicant)</th>
<th>Summary of product</th>
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</thead>
<tbody>
<tr>
<td>Collategene® Intramuscular injection 4mg (AnGes, Inc.)</td>
<td>The product is an injection of plasmid vector composed of 5,181 base pair including cDNA which encodes human hepatocyte growth factor. It is administered intramuscularly to an ischemic site of the lower limb.</td>
<td>Ulcers in patients with chronic arterial occlusion (arteriosclerosis obliterans and Burger’s disease) who have not responded sufficiently to the standard drug therapy and are unable to undergo revascularization.</td>
</tr>
</tbody>
</table>

### < Timeline >

**Jan. 2018:** Submission for marketing approval

**Mar. 2019:** **Conditional and Time-limited Approval**
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New Consultation Categories

Development Pipeline Meeting (Drugs)

➢ For product developer
   ◆ Advice on the multiple categories such as characteristic, new disease/treatment, evaluation method, phase, and timeline throughout the development
     https://www.pmda.go.jp/review-services/f2f-pre/consultations/0111.html (only in Japanese)

Consultation with/without site visit for Innovative Manufacturing (Drugs)

➢ For product developer
   ◆ Advice on the
     1. Development strategy for future production
     2. Formulation of strategy for product quality control and its verification method
     https://www.pmda.go.jp/review-services/f2f-pre/consultations/0109.html (only in Japanese)

Consultation for Database Utilization (Drugs)

➢ For database provider
   ◆ Advice on the
     1. Planning for utilization registry data into regulatory submission or post approval review
     2. Improving data quality
     3. Ensuring data reliability
     https://www.pmda.go.jp/review-services/f2f-pre/consultations/0110.html (only in Japanese)

For the time being, “Continuous Production” is the subject for this consultation.
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For COVID-19 Products

- Approved Drugs for COVID-19
- Approved IVDs for COVID-19
- Close interaction with sponsors
- Clinical trials starting without waiting for 30 days

For non-COVID-19 Products

- Providing information on how to manage clinical trials

https://www.pmda.go.jp/english/about-pmda/0002.html
Special Approval for Emergency of Remdesivir

May 2nd  Cabinet Order was amended to expand the scope of Special Approval for Emergency to include the drugs for novel coronavirus

Novel Influenza  COVID-19

May 4th  Regulatory Submission by Gilead Sciences

May 7th  Discussed by Pharmaceutical Affairs and Food Sanitation Council of the MHLW

Special Approval for Emergency of Remdesivir

Under article 14-3 of the PMD Act, a certain medical product may be approved under when

1. an emergency situation requires an unapproved medical product to be used to prevent damage to the public health caused by the spread of diseases
2. such emergency situation cannot be managed appropriately by any means other than the use of the unapproved product, and
3. such product is legally available in a country with a regulatory system for medical products that is equivalent to Japan

## Seven In Vitro Diagnostics received marketing authorization

As of May 31

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Applicant Company</th>
<th>Approval Date</th>
</tr>
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<tbody>
<tr>
<td>2019-nCoV Fluorescence Detection Real-time RT-PCR Kit</td>
<td>Sysmex Corporation</td>
<td>Mar. 27, 2020</td>
</tr>
<tr>
<td>Loopamp Novel Coronavirus 2019 (SARS-CoV-2) Detection Kit</td>
<td>Eiken Chemical Co., Ltd.</td>
<td>Mar. 31, 2020</td>
</tr>
<tr>
<td>cobas SARS-CoV-2</td>
<td>Roche Diagnostics K.K.</td>
<td>April 7, 2020</td>
</tr>
<tr>
<td>TaqPath Real Time PCR Reagent Kit for SARS-CoV-2</td>
<td>Life Technologies Japan Ltd.</td>
<td>April 20, 2020</td>
</tr>
<tr>
<td>ESPLINE SARS-CoV-2</td>
<td>Fujirebio Inc.</td>
<td>May 13, 2020</td>
</tr>
<tr>
<td>MEBRIGHT SARS-CoV-2 Kit</td>
<td>Medical &amp; Biological Laboratories Co., Ltd.</td>
<td>May 21, 2020</td>
</tr>
</tbody>
</table>

Loopamp 2019-nCoV Testing Reagent Kit

Product Overview
- This product is used for amplification/detection of SARS-CoV-2 using the advantages of the RT-LAMP※ method.
- Using Loopamp Realtime Turbidimeter LoopampEXIA®, it enable all processes from amplification to detection to be completed in a single step (35min).

※“LAMP” stands for “loop-mediated isothermal amplification”

Nasopharyngeal swab or sputum

Specimen → Amplification → Detection

Mar 19th, 2020: Submission for marketing approval within 2 weeks
Mar 31th 2020: Approval

35min
Close interaction with sponsors

- To further streamline the development of products for COVID-19
- Countless meetings on specific products were held

Ensure the efficient development

Clinical trials start without waiting for 30 days

Submission of Initial Clinical Trial Notification

Start Clinical Trial

Normal candidate product

30 days are required

COVID-19 candidate product

<30 days are allowed

Early Patient Access

Administrative Notice issued by the Pharmaceutical Evaluation Division and the Medical Device Evaluation Division of the Pharmaceutical Safety and Environmental Health Bureau of the MHLW on 19th March, 2020,

Q&A on how to manage clinical trials during the COVID-19 pandemic

alternative measures that can be taken by the sponsor and/or clinical trial site when the process predetermined in the study protocol is not deemed feasible due to the COVID-19 situation.

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Thank You
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