PMDA Perspective:
Recent Trends in the Regulation of Biopharmaceuticals

Yasushi JOTATSU
Office Director
Office of Cellular and Tissue-based Products
Pharmaceuticals and Medical Devices Agency (PMDA)

The views and opinions expressed in this presentation are those of the presenter and should not necessarily represent the views and opinions of the PMDA.
Outline

- Revision of Pharmaceuticals and Medical Devices Act
- Accelerated Programs in Japan
- Update on Approved Regenerative medical products
- Gene Therapy and Cartagena Act
- Pilot Program for Post-Approval CMC Changes (in line with ICH Q12)
- Biosimilars
Outline

- Revision of Pharmaceuticals and Medical Devices Act
- Accelerated Programs in Japan
- Update on Approved Regenerative medical products
- Gene Therapy and Cartagena Act
- Pilot Program for Post-Approval CMC Changes (in line with ICH Q12)
- Biosimilars
To provide better medical products safely, promptly and efficiently.
To improve a pharmaceuticals provision system for patient's secure access in familiar community

<table>
<thead>
<tr>
<th>Modernizing Regulatory System</th>
<th>Value of Community Pharmacies/Pharmacists</th>
<th>Prevention of Illegality</th>
</tr>
</thead>
<tbody>
<tr>
<td>➢ Good performance in review process</td>
<td>➢ Expectation of patients for improving their service</td>
<td>➢ Unfavorable events</td>
</tr>
<tr>
<td>➢ Surrounded change</td>
<td>➢ Increasing importance of appropriate treatment with medicines</td>
<td>- Manufacturing through unapproved process</td>
</tr>
<tr>
<td>Advanced technology</td>
<td>- More concern about polypharmacy along with aging</td>
<td>- False/puffery advertising</td>
</tr>
<tr>
<td>– Needs for innovative products</td>
<td>- More outpatients suffering from cancer</td>
<td>- Distribution of a falsified product</td>
</tr>
<tr>
<td>Globalization</td>
<td>➢ Unmet medical needs</td>
<td>- Fraudulent procurement of a certification to import a product</td>
</tr>
<tr>
<td>➢ Unmet medical needs</td>
<td>➢ To facilitate patient access</td>
<td>➢ To set countermeasures</td>
</tr>
<tr>
<td>➢ To recommend some of services</td>
<td>➢ To help patients choose his/her pharmacy</td>
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Current Status

Issues

Proposed Measures

Revision of Pharmaceuticals and Medical Devices Act

《Basic Policy》

<table>
<thead>
<tr>
<th>Year</th>
<th>Current Status</th>
<th>Issues</th>
<th>Proposed Measures</th>
</tr>
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<tr>
<td>2016</td>
<td>➢ To facilitate patient access</td>
<td>➢ Introduction of new approval schemes into the Act</td>
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<td>➢ Recommendation of additional services</td>
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<tr>
<td></td>
<td>➢ To enhance safety measure</td>
<td>➢ Safety measure</td>
<td>➢ Following up adherence and condition of a patient</td>
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<td>➢ Information sharing with other healthcare professionals</td>
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Evaluation Lag

Deference of total review time btw. Japan and EU/US (median)

Estimated by PMDA

Current Status

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Accelerated Programs in Japan

**Priority Review (9-month-Review)**
- Orphan Drugs, Innovative Pharmaceuticals targeting Serious Diseases

**Sakigake Designation System (6-month-Review)**
- Medical Products for Diseases *in Dire Need of Innovative Therapy*
- Development & NDA *in Japan being World’s First* or Simultaneous with Other Countries
- **Prominent effectiveness** can be expected

**Conditional Early Approval System (9-month-Review)**
- Targeting *Serious and Life-Threatening Disease*
- **Clinical Superiority on Unmet Needs** compared to Existing Therapy
- Difficulty in conducting Phase III Studies
- Validated Certain Efficacy and Safety (except Phase III Studies)
SAKIGAKE Designation System

【Standard Review】

① Priority Consultations
② Prior-review
③ Priority Review
④ Review Partner System
⑤ Strengthening Post-Marketing Safety

Consultation
Non clinical studies, Clinical studies
Clinical trials I/II
Consultation on Clinical trials
phase III study
Review
Reimbursement
Post-Marketing

Consultation as SAKIGAKE
Designation as SAKIGAKE
Clinical trials I/II
Consultation on Clinical trials
phase III study
Review
Reimbursement
Post-Marketing

※ In some cases, may accept phase III data during review

Practical application of Innovative medical products
<table>
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<tr>
<th>Product Name</th>
<th>Applicant</th>
<th>Designated Date</th>
<th>Anticipated Indications</th>
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<tbody>
<tr>
<td>Valemetostat</td>
<td>Daiichi Sankyo</td>
<td>8, Apr. 2019</td>
<td>Relapsed or refractory peripheral T-cell lymphoma</td>
</tr>
<tr>
<td>Ixazomib Citrate</td>
<td>Takeda Pharma</td>
<td>8, Apr. 2019</td>
<td>AL amyloidosis</td>
</tr>
<tr>
<td>TAK-925</td>
<td>Takeda Pharma</td>
<td>8, Apr. 2019</td>
<td>Narcolepsy</td>
</tr>
<tr>
<td>ASP-1929</td>
<td>Rakuten Medical Japan</td>
<td>8, Apr. 2019</td>
<td>Head and neck cancer</td>
</tr>
<tr>
<td>E7090</td>
<td>Eisai</td>
<td>8, Apr. 2019</td>
<td>Unresectable cholangiocarcinoma with FGF2 fusion gene</td>
</tr>
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<td>Product Name</td>
<td>Applicant</td>
<td>Designated Date</td>
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<td>--------------------------------------------------------------</td>
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<tr>
<td>RTA402</td>
<td>Kyowa Hakko Kirin</td>
<td>27, Mar. 2018</td>
<td>Diabetic kidney disease</td>
</tr>
<tr>
<td>JR-141</td>
<td>JCR Pharma</td>
<td>27, Mar. 2018</td>
<td>Hunter Syndrome</td>
</tr>
<tr>
<td>Tafamidis Meglumine</td>
<td>Pfizer</td>
<td>27, Mar. 2018</td>
<td>Transthyretin Familial Amyloid Polyneuropathy</td>
</tr>
<tr>
<td>MSC2156119J</td>
<td>Merck</td>
<td>27, Mar. 2018</td>
<td>NSCLC (stage IIIB/IV) with MET Exon 14 Skipping Mutation</td>
</tr>
<tr>
<td>Trastuzumab Deruxtecan</td>
<td>Daiichi Sankyo</td>
<td>27, Mar. 2018</td>
<td>Metastatic HER2-overexpressing Gastric Cancer</td>
</tr>
<tr>
<td>Entrectinib</td>
<td>Chugai Pharma</td>
<td>27, Mar. 2018</td>
<td>NTRK Fusion Gene-Positive Solid Cancer</td>
</tr>
<tr>
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<td>Anticipated Indications</td>
</tr>
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</tr>
<tr>
<td>Olipudase Alfa</td>
<td>Sanofi</td>
<td>21, Apr. 2017</td>
<td>Acid Sphingomyelinase Deficiency</td>
</tr>
<tr>
<td>Aducanumab</td>
<td>Biogen Japan</td>
<td>21, Apr. 2017</td>
<td>Inhibiting the progression of Alzheimer's disease</td>
</tr>
<tr>
<td>DS-5141b</td>
<td>Daiichi Sankyo</td>
<td>21, Apr. 2017</td>
<td>Duchenne Muscular Dystrophy</td>
</tr>
</tbody>
</table>
| SPM-011       | Stella Pharma     | 21, Apr. 2017   | • Recurrent Malignant Gliomas  
• Head and Neck Cancer                                                               |
| Nivolumab     | Ono Pharm.        | 21, Apr. 2017   | Biliary Tract Cancer                                                                   |
| Sirolimus     | Nobel Pharma      | 27, Oct. 2015   | Vascular Fibrosis Associated with Tuberous Sclerosis                                   |
| NS-065/NCNP-01| Nippon Shinyaku   | 27, Oct. 2015   | Duchenne Muscular Dystrophy                                                            |
| S-033188      | Shionogi Pharm.   | 27, Oct. 2015   | Influenza Infection                                                                   |
| BCX7353       | Integrated Development Associates | 27, Oct. 2015 | Management of the Attacks of Angioedema for Hereditary Angioedema Patients |
| ASP2215       | Astellas Pharm.   | 27, Oct. 2015   | FLT3 mutated AML                                                                      |
SAKIGAKE Assignment 4th Round

Regenerative medical products

Outline

Telomelysin is a gene-modified oncolytic adenovirus in which selectively replicate in cancer cells by introducing human telomerase reverse transcriptase (hTERT) promoter. Oncolytic adenovirus has much potential for cancer immunotherapy because its viral replication is highly immunogenic, and oncolysis induced by such virus releases tumor antigen and provides costimulatory danger signals. From the result of phase 1 clinical study in the US, OBP-301 showed abscopal effect, which non-injected tumor as well as injected tumor was regressed in melanoma patients after single injection into one single tumor and found that not only increasing infiltration of CD8 and antigen presenting cells but diminishing Treg cells in injected tumor site.

Oncolys has been conducting phase 1 clinical study of Telomelysin for hepatocellular carcinoma in Korea and Taiwan and phase 2 clinical study for melanoma in the US. We will also soon initiate phase 2 study for esophageal cancer in combination with radiation, and another study for esophageal cancer in combination with a check-point inhibitor in Japan.
SanBio announces SB623 regenerative cell therapy for traumatic brain injury has received Ministry of Health, Labour and Welfare (MHLW) Sakigake designation

Tokyo, Japan—Apr. 8, 2019—The SanBio Group (SanBio Co., Ltd. and SanBio, Inc.), a scientific leader in regenerative medicine for neurological disorders, announced today that SB623, a regenerative cell therapy that the Group is developing globally for the treatment of chronic motor deficit resulting from traumatic brain injury (TBI), has received the Sakigake Designation for innovative medical products from the Ministry of Health, Labour, and Welfare (MHLW) of Japan.

The Sakigake Designation System was unveiled in June 2014 as part of the “Strategy of SAKIGAKE” by an MHLW project team to lead the world in the practical application of innovative medical products. It is a scheme for rapid authorization of innovative pharmaceutical products initially developed in Japan for which exceptional effectiveness can be expected based on preclinical results and early-stage clinical trials. The Sakigake Designation System targets regenerative medicines that treat serious diseases which urgently require innovative therapies.

SanBio’s proprietary regenerative cell medicine SB623, which has been granted the Sakigake Designation, is made from modified and cultured adult bone marrow-derived mesenchymal stem cells that undergo temporary genetic modification. Implantation of SB623 cells into injured nerve tissue in the brain is expected to trigger the brain’s natural regenerative ability to recover lost motor functions.
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<tr>
<td>TBI-1301</td>
<td>Takara Bio</td>
<td>27, Mar. 2018</td>
<td>Synovial Sarcoma</td>
</tr>
<tr>
<td>CLBS12</td>
<td>Caladrius Biosciences</td>
<td>27, Mar. 2018</td>
<td>Sritical Limb Ischemia</td>
</tr>
<tr>
<td>AVXA-101</td>
<td>AveXis</td>
<td>27, Mar. 2018</td>
<td>Spinal Muscular Atrophy</td>
</tr>
<tr>
<td>CLS2702C/D</td>
<td>CellSeed</td>
<td>28, Feb. 2017</td>
<td>Extensive endoscopic submucosa dissection (ESD) in esophageal cancer</td>
</tr>
<tr>
<td>Dopamine neural precursor cell derived from allogenic iPS cell</td>
<td>Sumitomo Dainippon Pharma</td>
<td>28, Feb. 2017</td>
<td>Parkinson’s disease</td>
</tr>
<tr>
<td>HLCM051</td>
<td>Healis KK</td>
<td>28, Feb. 2017</td>
<td>Acute brain infarction</td>
</tr>
<tr>
<td>STR01</td>
<td>NIPRO</td>
<td>10, Feb. 2016</td>
<td>Patients with traumatic brain injury</td>
</tr>
<tr>
<td>G47Δ (DS-1647)</td>
<td>Daiichi Sankyo</td>
<td>10, Feb. 2016</td>
<td>Glioblastoma</td>
</tr>
<tr>
<td>JRM-001</td>
<td>Japan Regenerative Medicine</td>
<td>10, Feb. 2016</td>
<td>Pediatric congenital heart disease</td>
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New therapy for spinal cord injuries gets fast-tracked

By MASATOSHI TODA/Staff Writer
November 22, 2018 at 14:56 JST

The Asahi Shimbun

Treatment using stem cell regenerative medicine to restore damaged nerve connections in patients with spinal cord injuries, whose only course of treatment is rehabilitation, may be available by year-end.

http://www.asahi.com/ajw/articles/AJ201811220032.html
Japan’s approval of stem-cell treatment for spinal-cord injury concerns scientists

Chief among their worries is insufficient evidence that the therapy works.

By David Cyranoski

A stem-cell treatment for spinal-cord injuries will soon be available in Japan.

Japan

Stem-cell therapy raises concerns

Independent researchers warn that approval is premature.

By David Cyranoski

Japan has approved a stem-cell treatment for spinal-cord injuries — the first such therapy for this kind of injury to receive government approval for sale to patients.

"This is an unprecedented revolution of science and medicine, which will open a new era of health care," says oncologist Masanori Fukushima, head of the Translational Research Informatics Center, a Japanese government organization in Kobe that has been giving advice and support to the project for more than a decade.

They are proven to offer a benefit. "This approval is an unfortunate step away from everything researchers have learned over the past 70 years about how to conduct a valid clinical trial," says James Guest, a neurosurgeon at the Miami Project to Cure Paralysis at the University of Miami in Florida.

One inventor of the treatment, neurosurgeon Osamu Honmou of Sapporo Medical University in Japan, says he plans to publish a scientific paper that will discuss the clinical trial and safety issues. "I think it is very safe," he says. He did not do a double-blinded study because Japan's regulations do not require it.
AnGes Obtains Conditional Approval in Japan for HGF Gene Therapy to Treat Critical Limb Ischemia

AnGes, Inc., a biopharmaceutical company focused on developing innovative gene-based medicines for treating serious diseases, announced today that they have obtained conditional approval (“Approval with Conditions and Time Limit”) from the Japanese Ministry of Health, Labour and Welfare (MHLW) for HGF plasmid to treat patients with critical limb ischemia (CLI).

HGF plasmid is the first gene therapy product to be approved in Japan, for the improvement of ulcers in patients suffering from chronic arterial occlusion (arteriosclerosis obliterans and Buerger’s disease) who have had an inadequate response to standard pharmacotherapy and who experience difficulty in undergoing revascularization. AnGes applied for marketing approval to the MHLW in January 2018 based on positive results from the randomized, placebo-controlled phase three trial and investigator-led clinical study conducted in Japan. HGF plasmid is one of the first gene therapy products to be approved for a non-genetic disease with chronic and progressive symptoms.

Indication: Ulcer healing for CLI patient

https://www.anges.co.jp/en/project/proj_develop.html
Update on Approved Products

Regenerative medical products

Mar/2019

NOW APPROVED: The first and only CAR-T cell therapy approved in two indications for B-cell malignancies

KYMRIAH CAR-T

-CAR-T, chimeric antigen receptor T-cell.

THE TRANSFORMATION OF CANCER TREATMENT IS HERE

Explore how KYMRIAH is transforming the treatment of cancer by selecting an indication below.

[Images of people with text indicating indications: DLBCL and pALL]

INDICATION
KYMRIAH® (tisagenlecleucel) is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphomas (DLBCL) after two or more lines of systemic therapy.

INDICATION
KYMRIAH® (tisagenlecleucel) is indicated for the treatment of paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse.

https://www.novartis.co.jp/news/media-releases/prkk20180423-1
Press release in Japanese)
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Trend of Cell & Gene Therapy Development

No. Consultations

- Cell Therapy
  - 2015: 43
  - 2016: 68
  - 2017: 63
  - 2018: 44
  - 2019: 35

- Gene Therapy
  - 2015: 34
  - 2016: 35
  - 2017: 31
  - 2018: 48
  - 2019: 49

No. INDs

- Cell Therapy
  - 2015: 1
  - 2016: 10
  - 2017: 9
  - 2018: 8
  - 2019: 3

- Gene Therapy
  - 2015: 2
  - 2016: 9
  - 2017: 8
  - 2018: 6
  - 2019: 6
Guideline for Gene Therapy Clinical Research

- Established Oct 1st 2015
  - MHLW Ministerial Ordinance, 2015 No.344
  - For ensuring the medical utility and ethics of clinical research of gene therapy including \textit{in vivo} and \textit{ex vivo}

- Rev. February 28 2019
  - Appropriate implementation of clinical research using genome editing
Guidelines for Gene Therapy

Guideline for Assuring the Quality and Safety of Gene Therapy Products

- Established in July 2013
  - MHLW Notification, July 1st 2013 Yakushokushinsahatu 0701-4
  - Basic technical matters necessary for ensuring the quality and safety of regenerative medicine products such as gene products and transgenic cells

- Rev. July 9 2019
  - Incorporating the latest scientific knowledge and international trends
Significance of Cartagena Act’s Scheme

Use of Living Modified Organisms

Procedure of Type 1 Use
The Use of LMO without preventive measures against their dispersal into environment

- Biological Diversity Risk Assessment
- Environmental Risk Assessment
- Risk Assessment for third party

Use Genetically modified Virus Vector for human

Approval

Procedure of Type 2 Use
The use of LMO while taking preventive measures against their dispersal into environment

- Flexible system according to risks for using of LMO (GLISP)
- Use Genetically modified Virus Vector for manufacturing process of gene modified cells

Confirmation

On April 2019, new consultation menu start on the appropriateness of application dossier for procedure of Type I or Type II use.
Published on Oct 21 2019 as results of the AMED research

- Mockup of Type 1 use application form for adenovirus, herpes simplex virus and adeno-associated virus
- Point to consider for Biological Diversity Risk Assessment report

http://nrichd.ncchd.go.jp/genetics/shiryou_koukai.html#amed_cartagena_koukai
Regulatory framework of Cartagena Act

International framework

Convention on Biological Diversity

Cartagena Protocol

Domestic framework

Cartagena Domestic Act

Cabinet Order

Ministerial Ordinance (Enforcement of the Cartagena Act)

Ministerial Ordinance (Type 2 Use for research)

Ministerial Ordinance (Type 2 Use for industry)

Ministerial Notification (Basic Matters)

Ministerial Notification ( Applicant of Type 1 Use)

Ministerial Notification (host-vector system )

Ministerial Notification GLISP (MHLW, METI)

Pharmaceuticals and Medical Devices Agency
Purpose of Act

➢ For the conservation and sustainable use of biological diversity in cooperation with other nations, the Act aims to secure precise and smooth implementation of the Protocol by taking measures to regulate the use of living modified organisms.

Scope

➢ Living modified organism (LMO)

Technology used in order to obtain living modified organism

• Processing nucleic acid extracellularly for the purpose of introducing the nucleic acid into cells, viruses or viroids to transfer or replicate the nucleic acid

• Fusing cells of living organisms belonging to different taxonomic families
Definition of living organism

- single cells or cell colonies having the capacity to transfer or replicate nucleic acid, and viruses and viroids.

- Excluding the followings:
  - Human cells
  - Single cell or cell colonies (excluding individuals and gametes) which are capable of differentiating or have differentiated and which do not grow to individuals under natural conditions.
Examples of LMO

Within the scope of the Act

• Genetically modified micrograms
• Genetically modified animals
• Genetically modified viruses (including vaccine)

Beyond the scope of the Act

• Attenuated virus/vaccines
• Genetically modified animal cells (CHO cells, etc.)
For More Reasonable and Efficient Review

◆ “Biological Diversity Risk Assessment Report”  (use of background knowledge and prior knowledge)

◆ “Type I Use Regulations”  (consideration for virus shedding and mitigation for risk of transmission)

◆ Early PMDA consultation
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Pilot Program for Post-Approval CMC Changes*

PSEHB/PED Notification No. 0309-1,
PSEHB/CND Notification No. 0309-1,
March 9, 2018
Pilot Program for Post-Approval CMC Changes*


2. Rationalizing Descriptions on Specification in the Application Form

3. Procedures after being discovered Discrepancy between Application Form and Actual Manufacturing

4. How to describe Information on Application Form in the Case of Flexible-Disc-Applications

5. Approved Matters which is allowable to apply on the same Timing as other Partial Change Approval Applications

6. Procedure for extending Shelf Lives of Biologics

*PSEHB/PED Notification No. 0309-1, PSEHB/CND Notification No. 0309-1, March 9, 2018
Pilot Program for Post-Approval CMC Changes*


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4. How to describe Information on Application Form in the Case of Flexible-Disc-Applications

5. Approved Matters which is allowable to apply on the same Timing as other Partial Change Approval Applications

6. Procedure for extending Shelf Lives of Biologics

*PSEHB/PED Notification No. 0309-1, PSEHB/CND Notification No. 0309-1, March 9, 2018
PACMP

➢ Post-Approval Change Management Protocol (PACMP)
  ● Regulation Tool for enabling to facilitate Transparency and Flexibility in terms of Post-Approval Process Changes
  ● Enabling smoother Procedure on changing Approval Matters by using PACMP compared to by not using that

➢ PACMP Consultation

Pre-meeting

<table>
<thead>
<tr>
<th>PACMP CMC Consultation</th>
<th>Follow-up Meeting (Optional)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 m.</td>
<td>3 m. (Median Value)</td>
</tr>
</tbody>
</table>

MCNs

PCA Applications

Approval

PCA: Partial Change Application
MCN: Minor Change Notification
11 submissions to the PACMP CMC consultation (-Nov. 2019)

10 biologics, 1 chemical

Change plans including:
- Site change
- Scale-up
- Extending shelf lives

2. Rationalizing Descriptions on Specification in the Application Form

3. Procedures after being discovered Discrepancy between Application Form and Actual Manufacturing

4. How to describe Information on Application Form in the Case of Flexible-Disc-Applications

5. Approved Matters which is allowable to apply on the same Timing as other Partial Change Approval Applications

6. Procedure for extending Shelf Lives of Biologics

*PSEHB/PED Notification No. 0309-1, PSEHB/CND Notification No. 0309-1, March 9, 2018
Dissolve 10mg of Ofloxacin in 50mL of a mixture of water and acetonitrile (6:1), and use this solution as the sample solution. Pipet 1mL of the sample solution, and add a mixture of water and acetonitrile (6:1) to make exactly 20mL. Pipet 1mL of this solution, add a mixture of water and acetonitrile (6:1) to make exactly 10mL, and use this solution as the standard solution.

Sample solution: 0.2mg/mL ofloxacin in the Diluent
Standard solution: Dilute the sample by the diluent in 200 fold
Diluent: Water/Acetonitrile (6:1)
Available to rationalize description on oligosaccharide profiling and potency (cell growth assay) according to the examples attached to the memorandum.
Outline

- Revision of Pharmaceuticals and Medical Device Act
- Accelerated Programs in Japan
- Update on Approved Regenerative medical products
- Gene Therapy and Cartagena Act
- Pilot Program for Post-Approval CMC Changes (in line with ICH Q12)
- Biosimilars
Consultation for Biosimilars

Fiscal year (from April 1 to March 31)

*until Nov.
## Regulatory Update on Biosimilars in Japan

### 2019 (-Oct.)

<table>
<thead>
<tr>
<th>Product Code</th>
<th>Applicant</th>
<th>Approved</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>YLB113</td>
<td>YL biologics / Kyowa Pharmaceutical Industry</td>
<td>Mar. 2019</td>
<td>Enbrel (etanercept)</td>
</tr>
<tr>
<td>PF-06439535</td>
<td>Pfizer</td>
<td>Jun. 2019</td>
<td>Avastin (Bevacizumab)</td>
</tr>
<tr>
<td>RGB-10</td>
<td>Mochida Pharmaceutical</td>
<td>Sep. 2019</td>
<td>Forteo (Teriparatide)</td>
</tr>
<tr>
<td>JR-131</td>
<td>JCR Pharmaceuticals</td>
<td>Sep. 2019</td>
<td>Nesp (darbepoetin alfa)</td>
</tr>
<tr>
<td>SK-1401</td>
<td>Sanwa Kagaku Kenkyusho co., ltd.</td>
<td>Sep. 2019</td>
<td>Nesp (darbepoetin alfa)</td>
</tr>
<tr>
<td>CKD-11101J</td>
<td>Mylan EPD G.K.</td>
<td>Sep. 2019</td>
<td>Nesp (darbepoetin alfa)</td>
</tr>
<tr>
<td>ABP 215</td>
<td>Daiichi Sankyo</td>
<td>Sep. 2019</td>
<td>Avastin (Bevacizumab)</td>
</tr>
<tr>
<td>PF-05280586</td>
<td>Pfizer</td>
<td>Sep. 2019</td>
<td>Rituxan(Rituximab)</td>
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# Biosimilars in Japan

## 2017-2018

<table>
<thead>
<tr>
<th>Product Code</th>
<th>Applicant</th>
<th>Approved</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>LBEC0101</td>
<td>Mochida Pharm.</td>
<td>Jan. 2018</td>
<td>Enbrel (Etanercept)</td>
</tr>
<tr>
<td>CT-P6</td>
<td>Nipponkayaku, Celltrion</td>
<td>Mar. 2018</td>
<td>Herceptin (Trastuzumab)</td>
</tr>
<tr>
<td>PF-06438169</td>
<td>Pfizer</td>
<td>Jul. 2018</td>
<td>Remicade (Infliximab)</td>
</tr>
<tr>
<td>JR-051</td>
<td>JCR Pharma</td>
<td>Sep. 2018</td>
<td>Fabrazyme (Agalsidase β)</td>
</tr>
<tr>
<td>ABP980</td>
<td>Daiichi Sankyo</td>
<td>Sep. 2018</td>
<td>Herceptin (Trastuzumab)</td>
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<tr>
<td>PF-05280014</td>
<td>Pfizer</td>
<td>Sep. 2018</td>
<td>Herceptin (Trastuzumab)</td>
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<td>NI-071</td>
<td>Nichi-Iko</td>
<td>Sep. 2017</td>
<td>Remicade (Infliximab)</td>
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<tr>
<td>GP2013</td>
<td>Sandoz</td>
<td>Sep. 2017</td>
<td>Rituxan (Rituximab)</td>
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</tbody>
</table>
## Biosimilars in Japan

### 2009-2016

<table>
<thead>
<tr>
<th>Product Code</th>
<th>Applicant</th>
<th>Approved</th>
<th>Reference</th>
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<tbody>
<tr>
<td>FFP-101</td>
<td>Fuji Film Pharma</td>
<td>Mar. 2016</td>
<td>Lantus (Insulin Glargine)</td>
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<tr>
<td>LY2963016</td>
<td>Eli Lilly</td>
<td>Dec. 2014</td>
<td>Lantus (Insulin Glargine)</td>
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<tr>
<td>CT-P13</td>
<td>Nipponkayaku, Celltrion</td>
<td>Jul. 2014</td>
<td>Remicade (Infliximab)</td>
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<tr>
<td>EP2006</td>
<td>Sandoz</td>
<td>Mar. 2014</td>
<td>Gran (Filgrastim)</td>
</tr>
<tr>
<td>TKN732</td>
<td>Nipponkayaku, Teva</td>
<td>Feb. 2013</td>
<td>Gran (Filgrastim)</td>
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<td>FSK0808</td>
<td>Fuji Pharma, Mochida Pharm.</td>
<td>Nov. 2012</td>
<td>Gran (Filgrastim)</td>
</tr>
<tr>
<td>JR-013sc</td>
<td>JCR Pharma</td>
<td>Jan. 2010</td>
<td>Espo (Epoetin alfa)</td>
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</tbody>
</table>
Regulations for Biosimilars in Japan

• Guideline for the Quality, Safety and Efficacy Assurance of Follow-on Biologics (FOBs)*
  (PFSB/ELD Notification No. 0304007 / March 4, 2009)
  http://www.pmda.go.jp/english/service/pdf/notifications/PFSB-ELD-0304007.pdf (GL in English)

• Marketing Approval Application for FOBs
  (PFSB Notification 0304004 / March 4, 2009)

• Nonproprietary Name and Drug Name of FOBs
  (PFSB/ELD Notification No. 0214-1, Administrative Notice / February 14, 2013)

• Questions & Answers regarding Guideline

➢ We are working on revising our BS guideline published in 2009 to include the contents in the QA documents.
➢ Public consultation on the revised draft guideline (written in only Japanese) has recently finished.
Thank you for your attention!