PMDA Updates

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Reviewer
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.
Topics

- Pilot Program for Post-Approval CMC Changes (in line with ICH Q12)
- Biosimilars
- Accelerated Programs in Japan
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- Pilot Program for Post-Approval CMC Changes (in line with ICH Q12)
- Biosimilars
- Accelerated Programs in Japan

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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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
- PACMP CMC Consultation
- PACMP GMP Consultation
- Follow-up Meeting (Optional)
- MCNs
- PCA Applications
- Approval

PCA: Partial Change Approval
MCN: Minor Change Notification

<Step 1> 4 m.
<Step 2> 3 m. (Median Value)
PACMP (2)

<Scope>

- Already approved pharmaceuticals (chemicals and biologics)
  - ICH M4Q implementation (Regulatory dossier in either original MAA or last Partial Change Application; PCA is submitted as CTD-format)
  - whose Application Form are verified that there is no discrepancy from actual manufacturing situation

- Submission in parallel with the original MAA is excluded

- Changes in Maser File are excluded

- GMP compliance and effective PQS (ICH Q10) implementation

- Where pre-approval GMP compliance inspection is needed, GMP inspection authority is PMDA
  (Note: In Japan, depending on products and mfg. sites, local government (47 prefectures) is in charge of GMP inspection.)

- Changes which need non-clinical/clinical data are excluded

- Broader protocols are excluded
Pilot Program for Post-Approval CMC Changes*


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<table>
<thead>
<tr>
<th>Product Code</th>
<th>Applicant</th>
<th>Approved</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>JR-013sc</td>
<td>JCR Pharma</td>
<td>Jan. 2010</td>
<td>Espo (Epoetin alfa)</td>
</tr>
<tr>
<td>FSK0808</td>
<td>Fuji Pharma, Mochida Pharm.</td>
<td>Nov. 2012</td>
<td>Gran (Filgrastim)</td>
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<tr>
<td>TKN732</td>
<td>Nipponkayaku, Teva</td>
<td>Feb. 2013</td>
<td>Gran (Filgrastim)</td>
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<tr>
<td>EP2006</td>
<td>Sandoz</td>
<td>Mar. 2014</td>
<td>Gran (Filgrastim)</td>
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<tr>
<td>CT-P13</td>
<td>Nipponkayaku, Celltrion</td>
<td>Jul. 2014</td>
<td>Remicade (Infliximab)</td>
</tr>
<tr>
<td>LY2963016</td>
<td>Eli Lilly</td>
<td>Dec. 2014</td>
<td>Lantus (Insulin Glargine)</td>
</tr>
<tr>
<td>FFP-101</td>
<td>Fuji Film Pharma</td>
<td>Mar. 2016</td>
<td>Lantus (Insulin Glargine)</td>
</tr>
<tr>
<td>GP2013</td>
<td>Sandoz</td>
<td>Sep. 2017</td>
<td>Rituxan (Rituximab)</td>
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<tr>
<td>NI-071</td>
<td>Nichi-Iko</td>
<td>Sep. 2017</td>
<td>Remicade (Infliximab)</td>
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<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>
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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
- Advantages: Substantial Pre-application Consultation, Rolling Submission, Review Partner, Substantial Post-Marketing Measures

**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 (1)

【Standard Review】

1. Priority Consultations

【SAKIGAKE】

1. Priority Consultations
2. Prior-review
3. Priority Review
4. Review Partner System

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

Consultation as SAKIGAKE
Prior review (rolling submission)
Review
Reimbursement
Post-Marketing

Non clinical studies, Clinical studies
Clinical trials I/II
Consultation on Clinical trials
phase III study
※ In some cases, may accept phase III data during review

Practical application of Innovative medical products

Strengthening Post-Marketing Safety
<table>
<thead>
<tr>
<th>Product Name</th>
<th>Applicant</th>
<th>Designated Date</th>
<th>Anticipated Indications</th>
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<tbody>
<tr>
<td>Sirolimus</td>
<td>Nobel Pharma</td>
<td>27, Oct. 2015</td>
<td>Vascular Fibrosis Associated with Tuberous Sclerosis</td>
</tr>
<tr>
<td>NS-065/NCNP-01</td>
<td>Nippon Shinyaku</td>
<td>27, Oct. 2015</td>
<td>Duchenne Muscular Dystrophy</td>
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<tr>
<td>S-033188</td>
<td>Shionogi Pharm.</td>
<td>27, Oct. 2015</td>
<td>Influenza Infection</td>
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<tr>
<td>BCX7353</td>
<td>Integrated Development</td>
<td>27, Oct. 2015</td>
<td>Management of the Attacks of Angioedema for Hereditary Angioedema Patients</td>
</tr>
<tr>
<td></td>
<td>Associates</td>
<td></td>
<td></td>
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<tr>
<td>ASP2215</td>
<td>Astellas Pharm.</td>
<td>27, Oct. 2015</td>
<td>FLT3 mutated AML</td>
</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                      |
<p>| Nivolumab    | Ono Pharm.                 | 21, Apr. 2017   | Biliary Tract Cancer                                                                  |</p>
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<td>RTA402</td>
<td>Kyowa Hakko Kirin</td>
<td>27, Mar. 2018</td>
<td>Diabetic kidney disease</td>
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<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>Ignyta, Inc</td>
<td>27, Mar. 2018</td>
<td>NTRK Fusion Gene-Positive Solid Cancer</td>
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Conditional Early Approval System

【Standard Review】
Clinical trials I/II → phase III study → Review → Reimbursement, Post-Marketing

12 m.

【Conditional Early Approval System】
Clinical trials I/II → Consultation → Review → Reimbursement, Post-Marketing

9m.

Approval Conditions
- Revalidating Efficacy and Safety in Post-Marketing e.g.; Databases, Registry Studies
- Requirement for Institutions if it’s necessary for proper use

- Evaluation Report & certain Efficacy and Safety Data
- Priority Review
Sakigake vs CEAS

【SAKIGAKE】

Consultation → Designation as SAKIGAKE → Prior review (rolling submission) → Review

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

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

【Conditional Early Approval System】

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Thank you for your attention!

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