Current Status and Challenges of Development for Orphan Drugs in Japan

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Designation Criteria of Orphan Drug in Japan

(1) Number of patients
- The number of patients who may use the drug should be less than 50,000 in Japan*.
  *less than 3.9 per 10,000 individuals approximately.

(2) Medical needs
- The drugs should be indicated for the treatment of serious diseases, including difficult-to-treat diseases. In addition, they must be drugs for which there are high medical needs satisfying one of the following criteria.
  ✓ There is no appropriate alternative drug or treatment in Japan
  ✓ High efficacy or safety is expected compared with existing medical products in Japan

(3) Possibility of development
- There should be a theoretical rationale for the use of the product for the target disease, and the development plan should be appropriate.
### Main Players and Roles Related to Orphan Drug Development in Japan

<table>
<thead>
<tr>
<th>MHLW</th>
<th>Collaboration</th>
<th>PMDA</th>
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</thead>
<tbody>
<tr>
<td>- Designation and approval of orphan drugs</td>
<td>- Support MHLW’s conclusion for orphan designations by providing prior assessment reports</td>
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<tr>
<td>- Pre-designation consultation for orphan drugs</td>
<td>- Priority scientific consultation for marketing authorization</td>
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<tr>
<td>- Payment for the operational cost of NIBIO</td>
<td>- Priority review of orphan drugs</td>
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<tr>
<td>- Policy making related to designation and approval of orphan drugs</td>
<td>- Subsidy payment to the applicant</td>
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<tr>
<td>- Measures against intractable diseases, such as promotion of research and reduction of co-payment of medical fees</td>
<td>- Accreditation for research expenses to be used by the applicant</td>
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<tr>
<td></td>
<td>- Provision of guidance and consultation to the applicant</td>
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MHLW: Ministry of Health, Labor and Welfare  
PMDA: Pharmaceuticals and Medical Devices Agency  
NIBIO: National Institute of Biomedical Innovation
Orphan Drug Designation and Incentives for Development

Development of Orphan Drugs

Screening, Hits to Leads, Lead optimization
Pre-clinical study (non-GLP)
Pre-clinical Study (GLP)

Clinical Trial

Application for Orphan Designation (to MHLW)
Application for Grant (to NIBIO)

Incentives for Post-Orphan Designation

1. Administrative and Scientific Advice (NIBIO)
2. Grant-in-Aid for R&D Expenses (NIBIO)
3. Authorization for R&D Expenses for Tax Deduction (NIBIO)
4. Priority Consultation and Priority Review (PMDA)
5. Reduction of Application Fee and Consultation Fees (PMDA)
6. Extension of Re-examination Period (MHLW)
### Key Contents required for application of orphan designation

<table>
<thead>
<tr>
<th>Contents</th>
<th>Outline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of the active substance(s)</td>
<td><strong>Composition of investigational product</strong></td>
</tr>
<tr>
<td>Outline of manufacturing</td>
<td><strong>Expected dosage and administration</strong></td>
</tr>
<tr>
<td>Expected indication</td>
<td><strong>Justification of significant benefit in Japan</strong></td>
</tr>
<tr>
<td>Remarks</td>
<td><strong>Summary of current development status and plan of the product in Japan</strong></td>
</tr>
</tbody>
</table>

#### <From Application Form>

- **Following points should be given.**
  - **A) Description of the target disease**
    - Summary of the cause and symptom
    - Number of patients (prevalence of the condition)
    - Justification as to why existing methods are not satisfactory
  - **B) Medical Plausibility**
    - Mechanism of action
    - Clinical data
  - **C) Summary of current regulatory or development status, and marketing history, out of Japan.**
  - **D) Summary of current development status and plan of the product in Japan**

- **Applicants may explain above things on the separate sheet and attach it.**

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(Notes): 1. The size of this paper is A4 and should be submitted.
2. This application form is completed with black ink, and a clear signature is required.
3. In case of any corrections, please use a black pen and ensure the text is clear.
Incentives for Orphan Drug in Japan

(1) Grant-in-Aid for R&D Expenses
- Applicants can receive subsidies through NIBIO
(In FY2012, 21 items received grants totaling 880 million yen*.)
  *Approximately 8.98 million USD.

(2) Administrative and Scientific Advices
- Pre-submission meeting/advices by MHLW on application for orphan drug designation(free of charge).
- Administrative advices by NIBIO on R&D after the designation(free of charge).
- Priority Consultation by PMDA(lower rate than normal drugs).

(3) Authorization of R&D Expenses for Tax Deduction
- 12 percent of total R&D expenses for orphan drug during the grant period is deductible
- NIBIO authorizes the R&D expenses for tax deduction.
(4) Priority Consultation and Priority Review
- Priority review for marketing authorization
- Lower user fees are applicable for review and scientific consultation

(5) Extension of re-examination period
- The re-examination period for the drugs will be extended up to 10 years for drugs (usually 8 years for NDA)

Marketing authorization Application for generic products is not accepted by MHLW and PMDA during the ‘Re-examination’ period of the reference product.
→ Re-examination period acts as “data exclusivity period”
Changes in Orphan Drug Development in Japan

As of 2013/4/4

Designated  Approved  In development  Revoked

<table>
<thead>
<tr>
<th>Year</th>
<th>Designated</th>
<th>Approved</th>
<th>In development</th>
<th>Revoked</th>
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</thead>
<tbody>
<tr>
<td>2004</td>
<td>11</td>
<td>8</td>
<td>2</td>
<td>0</td>
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<tr>
<td>2005</td>
<td>8</td>
<td>3</td>
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<td>2006</td>
<td>17</td>
<td>13</td>
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<tr>
<td>2012</td>
<td>28</td>
<td>28</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

As of 2013/4/4
MHLW Webpage of ‘Overview of Orphan Products Designation System’

NIBIO Webpage of ‘Orphan drug, Orphan medical device Development support program’


List of products designated as orphan drugs is provided in this site (http://www.nibio.go.jp/shinko/orphan/english/pdf/h2504kisyoiyaku-hyo1.pdf)
Recent Efforts for Promoting Orphan Drug Development in PMDA -1-

New Scientific Consultation: *Pharmaceutical Affairs Consultation on R&D Strategy*

- From July 1st, 2011
- For Accelerating the development for Japan-originated medial products
- Academia, Technology ventures can take advices at special rates

**Priority areas**

<table>
<thead>
<tr>
<th>☑ Regenerative medicine (cell- and tissue- based products)</th>
<th>☑ Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>☑ Difficult-to-cure diseases and rare diseases</td>
<td>☑ Pediatrics</td>
</tr>
<tr>
<td>☑ Other than the above, products utilizing particularly innovative technologies</td>
<td></td>
</tr>
</tbody>
</table>
Recent Efforts for Promoting Orphan Drug Development in PMDA -2-

New Project: *Orphan Drugs Working Group*

- From December, 2011, consists of members from each Office of New Drugs

**Our Task is...**

- To review and analyze the problems surrounding development of orphan drugs
- Encourage industries and investigators to develop medicinal products for Orphan diseases
- Standardize development of medicinal products
  - Necessary data for approval
  - Labeling description
  - Timing of development
- Strengthen collaboration with other regulatory agencies
Various Challenges Still Remain…

Let’s consider Global Drug Development

- To increase feasibility of clinical trials in the orphan diseases
- To establish more appropriate strategies to develop medicines for orphan diseases

*We will proactively push forward the orphan drug development!*
Thank you for your attention.

Information
– Email: nitta-akiko@pmda.go.jp
– PMDA Homepage (English)
– PMDA Orphan Drugs WG Webpage(English)
  http://www.pmda.go.jp/english/service/projects_am_e.html