Current status of Japanese Regulation and Development on Biologics

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Pharmaceuticals and Medical Devices Agency (PMDA)
Introduction of PMDA

- **NAME:** Pharmaceuticals and Medical Devices Agency
- **Establishment:**
  
  Established as an Incorporated Administrative Agency (IAA) in April, 2004 by integrating 3 review-related organizations.

- **Effective operation under “Medium Term Plan” for 5 years’ activities (1st 04’-08’) (2nd 09’-13’)**

- **PMDA submits performance report to MHLW annually, and that is evaluated by the “IAA Evaluation Committee” for necessary improvement.**
3 major work areas of PMDA

Review and Audit for Drugs/ Medical Devices
- Clinical Trial Consultation
- Review of Efficacy and Safety
- Conformity Audit for Application Materials of GLP, GCP and GMP

Post-marketing Safety Operations for Drugs/ Medical Devices
- Reinforced Safety Information (Database)
- Scientific Review and Research for Safety Information
- Provision of Information (via the Internet), Telephone Consultation Services for Consumers

Relief Service for ADR and Other Infectious Disease
- Provision of Medical Expenses, Disability Pensions etc.
- Relief Service for SMON, HIV-positive and AIDS patients, and HCV-positive and HC patients
Work flow of Review

Collection and evaluation of ADR information
ADR relief system
Order
Report

Approval
Ministry of Health, Labour and Welfare

Pharmaceutical Affairs and Food Sanitation Council (PAFSC)

GLP=Good Laboratory Practice
GCP=Good Clinical Practice
GMP=Good Manufacturing Practice
GPSP=Good Post-Marketing Study Practice
GVP=Good Vigilance Practice
GQP=Good Quality Practice
The work duty of Office of Biologics

1. Office of Biologics I
   - Blood Products
   - CMC for the Biologics (Pharmaceuticals)
   - Advanced therapy products (Gene therapy products)

2. Office of Biologics II
   - Biological Products (Vaccines etc.)
   - CMC for the Biologics (Medical devices)
   - Advanced therapy products (Cell/Tissue based products, Regenerative medicine)
## Consolidation of Safety Measures for Biological Products

### For higher risk products

<table>
<thead>
<tr>
<th>Source materials</th>
<th>Manufacturing</th>
<th>Post-marketing</th>
</tr>
</thead>
<tbody>
<tr>
<td>“ADD-ON” for Biological Products</td>
<td>Safety measures for source materials incl. donor deferral criteria</td>
<td>Preventing spread of infection</td>
</tr>
<tr>
<td>Chemical drug / normal devices</td>
<td>GMP/GQP (Good Manufacturing Practice/Good Quality Practice): manufacturing / quality control to keep consistent quality of products</td>
<td>Proper labeling/use information provision</td>
</tr>
<tr>
<td>Starting materials selection criteria</td>
<td>e.g. sterilized condition for aseptic products</td>
<td>Look back/traceability</td>
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<tr>
<td></td>
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<td>Periodic infectious disease surveillance report</td>
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<tr>
<td></td>
<td></td>
<td>GSP/GVP: Good Post-Marketing Study Practice/Good Vigilance Practice e.g. safety management of companies to deal with vigilance information</td>
</tr>
</tbody>
</table>

- **Information review and corrective actions**
  - Prevention of contamination
  - Establishment requirements
  - Record retention
  - Periodic infectious disease surveillance report
  - Proper labeling/use information provision
  - Look back/traceability
The Requirements for Biological Source Materials

1. General Notices and Requirements
2. Requirements for human Blood
   i. Source for blood products for transfusion
   ii. Source for plasma-derived products
3. Requirements for human-derived materials
   i. Cell and Tissue-derived materials
   ii. Urine-derived materials
   iii. Other human-derived materials
4. Requirements for animal-derived source materials
   i. Ruminant-derived materials
   ii. Cell and Tissue-derived materials
   iii. Other animal-derived materials
Development Process of Gene-therapy Products and Cell / Tissue-based products in Japan under the PAL.

1. Application for Confirmation “Kakunin-Shinsei”
   ADD-ON for Gene-therapy and Cell/Tissue-based products

2. Confirmation “Kakunin”

3. Review of Clinical trial protocol (30days-IND)

4. Clinical Trial

5. NDA

6. Approval

Kakunin-Shinsei: pre-IND
Evaluation with respect to the quality and safety of Gene therapy & Cell/Tissue-based products intended for clinical use
Number of new biologics approved from 2001 to 2008 in Japan

The review reports of these products prepared by the PMDA are publicly available on the Web site. [http://www.info.pmda.go.jp/shinyaku/shinyaku_index.html](http://www.info.pmda.go.jp/shinyaku/shinyaku_index.html)
New Approved Biologics (1)

**monoclonal antibodies**

- chimera
- humanized (Humira; 2008)
- Fab (Lucentis; 2009)
- conjugated (Zebarin; 2008)

**human serum albumin (genetical recombination)**

- Medway
  Manufacturer: Mitsubishi Tanabe Pharm

**Indications:**
Hypoalbuminaemia caused by loss of albumin and reduced albumin synthesis, and hemorrhagic shock

**Approved in:** 2007
New Approved Biologics (2)

Adsorbed Influenza Vaccines (H5N1)

- Adsorbed Influenza Vaccines (H5N1) “Kitasato”
  Manufacturer; The Kitasato Institute
- Adsorbed Influenza Vaccines (H5N1) “BIKEN”
  Manufacturer; Research Foundation for Microbial Diseases, Osaka University

Indications: Prophylaxis of influenza (H5N1)
Approved in 2007

Autologous cultured keratinocytes

- JACE
  Manufacturer; Japan Tissue Engineering Co., Ltd.

Indications: Serious large burns

Approved in 2007
Near Future Developments

Follow-on Biologics (Biosimilar)

Biotechnology Products

Gene Therapy Products

Vaccines, Therapeutic vaccines, Blood Products

Regenerative medicine Cell/Tissue based products
R&D of the “Biologics” in Japan

- **Biotechnology products**
  - cell substrate derived protein products (antibodies, protein, etc.)
  - animal (plant) factory (GE-animals, GE-plants)

- **Gene therapy products**

- **Cell / tissue-based products** (Regenerative medicine)
  - cells, tissue, stem-cells, ES cells, iPS cells

- **Vaccines, Antitoxins**

- **Therapeutic vaccines** (immunotherapy products, DNA etc.)

- **Blood Products**

- **Follow-on biologics (Biosimilar)**
### Special Districts for Development of Advanced Medical Care (Super Special Districts)

**2008 ~**

<table>
<thead>
<tr>
<th>5 Priority Areas</th>
<th>24 Districts</th>
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<tbody>
<tr>
<td>(1) Applications using iPS cells</td>
<td>- - - 2</td>
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<tr>
<td>(2) Regenerative medicines</td>
<td>- - - 5</td>
</tr>
<tr>
<td>(3) Development of innovative medical devices</td>
<td>- - - 8</td>
</tr>
<tr>
<td>(4) Development of innovative biotechnology-based pharmaceuticals</td>
<td>- - - 4</td>
</tr>
<tr>
<td>(5) R&amp;D of pharmaceuticals and medical devices crucial to public health</td>
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For Development of Biologics

Based on the cooperative interaction between Academia, Industries, Regulatory agency

- The **Consultation** from the early stage of the development
  - Full-fledged consultation services of the PMDA
  - Launching the consultations for PGx/Biomarker
    (Introduction of the new evaluation approaches)

- Establishment of the **Guidelines** to ensure quality, efficacy, and safety
Category of Consultation for pharmaceutical development

From non-clinical tests, IND to NDA

Non-clinical tests

IND Phase I trials

Phase II trials (First stage)

Phase II trials (Last stage)

Phase III trials

NDA (MHLW)

Category of Consultation

Administrative Procedures
Quality(bio-)
Safety
PGx / Biomarker
Bioequivalence
Document format on biologics etc.

Pre-Phase I
Pre-first period Phase II
Pre-latter period Phase II
Post-Phase II
Pre-NDA
Guidelines for Biologics (1)
-Cell / Tissue-based Products-

• General Principles for the Handling and Use of Cell/Tissue-based Products
  - Notification No.266 (28 Mar. 2001)
• Guidelines on Ensuring Quality and Safety of Autologous Human Cells/Tissue-based Products
  - Notification No.0208004 (8 Feb. 2008)
• Guidelines on Ensuring Quality and Safety of Allogeneic Human Cells/Tissue-based Products
  - Notification No.0912007 (12 Sep. 2008)
• Points to Consider on Manufacturing and Quality Control of Autologous Human Cells/Tissue-based Products
  - Notification No.0327025 (27 Mar. 2008)
Guidelines for Biologics (2)

- Assuring the Quality and Safety of Gene-therapy Products
  - Notification No.1062 (15 Nov. 1995)
    Rev1. 29 Mar. 2002
    Rev2. 28 Dec. 2004

- Other related guidelines:
  ICH Guidelines
  (Quality, Safety, Efficacy, Multidisciplinary)
Guidelines under Development

• Vaccines
  - for clinical study
  - for pre-clinical study
  - for adjuvants

• Regenerative medicine
  - Cardiac muscle, Cornea etc.

• Stem cells
  - iPS cells, ES cells

• Follow-on biologics (Biosimilar)
PMDA 3rd International Symposium on Biologics

The Theme of the Symposium

“Follow-on biologics” (Biosimilar)
Thank you for your attention

http://www.pmda.go.jp