Development and Regulation of Biopharmaceuticals in Japan

Teruhide YAMAGUCHI
Pharmaceuticals and Medical Devices Agency
National Institute of Health Sciences

2012.12.3.
Contents

1. Update in Japanese Regulation of Biologics
2. Guidance for Monoclonal Antibody Products
3. Update in Japanese Regulation of Follow-on Biologics (Biosimilar)
4. Future Issues of Biopharmaceuticals in Japan
# Category of Review Section (Past)

<table>
<thead>
<tr>
<th>Office</th>
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<tr>
<td><strong>Office of New Drug I</strong></td>
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# Category of Review Section (Current)

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Yamanaka, Gurdon win Nobel Prize for work on iPS cells

STOCKHOLM (Kyodo) -- Japan's Shinya Yamanaka and John Gurdon of Britain have jointly won this year's Nobel Prize in Physiology or Medicine for the discovery that mature cells can be reprogrammed to become pluripotent, the award-giving body said Monday.

Gurdon found in the 1960s that the specialization of cells is reversible, research that led to Yamanaka's development more than 40 years later of the induced pluripotent stem cell, or iPS cell, which has the potential to grow into any type of body tissue.

Yamanaka, 50, and Gurdon, 79, discovered that mature and specialized cells "can be reprogrammed to become immature cells capable of developing into all tissues of the body," the Nobel Assembly at Sweden's Karolinska Institute said.

Yamanaka is seen in a photo published by the Daily Mainichi.
Approved biotechnology products in Japan

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Review Process of MAA for New Molecular Entities in Japan

- **Applicant**
  - Manufacturing site
  - Application
  - F2F meeting
  - Inquiry/Response

- **PMDA**
  - GMP audit
  - Review report
  - Consultation

- **External experts**
  - Expert discussion

- **Minister of Health, Labour and Welfare**

- **Pharmaceutical Affairs and Food Sanitation Council**
  - Advisory (Positive or Negative opinion)
Review Process of MAA for Biosimilars in Japan

Applicant

Application

F2F meeting

Inquiry/Response

Manufacturing site

PMDA

GMP audit

Review report

External experts

Expert discussion

Report

Minister of Health, Labour and Welfare

Approval

Pharmaceutical Affairs and Food Sanitation Council

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## Approved monoclonal antibody products

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Current Technology of Monoclonal Antibody Products from Japan

- **Guidance for Monoclonal Antibody Products**
  The draft was published on April/2012 to collect the comments.
Competitive PCR analysis and ADCC assay of FUT8 expression in YB2/0 cells and CHO/DG44 cells.

A

B

Shinkawa T et al. J. Biol. Chem. 2003;278:3466-3473
Control of defucosylated Fc N-glycan enhances the affinity of monoclonal antibody to FcγIIIa.

Glycoengineered therapeutic antibodies lacking core fucose residue from the Fc N-glycans exhibit strong ADCC at lower concentrations with much higher efficacy compared to fucosylated counterparts.
Antibody recycling by engineered pH-dependent antigen binding improves the duration of antigen neutralization.

Tomoyuki Igawa, Shinya Ishii, Tatsuhiko Tachibana, Atsuhiko Maeda, Yoshinobu Higuchi, Shin Shimaoka, Chifumi Moriyama, Tomoyuki Watanabe, Ryoko Takubo, Yoshiaki Doi, Tetsuya Wakabayashi, Akira Hayasaka, Shoujiro Kadono, Takuya Miyazaki, Kenta Haraya, Yasuo Sekimori, Tetsuo Kojima, Yoshiaki Nabuchi, Yoshinori Aso, Yoshiki Kawabe, Kunihiro Hattori

*Nature Biotechnology, 28, 1203-1207 (2010)*
Engineering pH dependency into the interactions of therapeutic antibodies with their targets may enable them to be delivered less frequently or at lower doses.

_Nature Biotechnology, 28, 1203-1207 (2010)_
A humanized bispecific antibody to factor IXa (FIXa) and factor X (FX), termed hBS23, that places these two factors into spatially appropriate positions and mimics the cofactor function of FVIII. hBS23 exerted coagulation activity in FVIII-deficient plasma, even in the presence of inhibitors, and showed in vivo hemostatic activity in a nonhuman primate model of acquired hemophilia A.

Action model of bispecific antibody products.
Guidance for the quality evaluation and control of monoclonal antibody products

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      3.2.2. Generation of cell substrate
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         3.2.4.1. Evaluation of viral safety of cell banks
         3.2.4.2. Viral clearance evaluation and characterization of manufacturing process
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      3.2.5. Process control
      3.2.6. Manufacturing process changes
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         3.3.1.1. Amino acid composition and amino acid sequencing
         3.3.1.1.1 Analysis of amino acid composition and amino acid sequencing
         3.3.1.1.2. N- and C-terminal amino acid and N- and C-terminal sequencing,
         3.3.1.1.3. Peptide mapping
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         3.3.1.3. Carbohydrate structure
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Guidance for the quality evaluation and control of monoclonal antibody products
Content (2)

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   3.3.2.2. Electrophoretic patterns
   3.3.2.3. Liquid chromatographic patterns
      3.3.2.3.1. size exclusion chromatography
      3.3.2.3.2. Ion-exchange chromatography
      3.3.2.3.3. Hydrophobic chromatography
3.3.3. Biological property
   3.3.3.1. Binding activity
   3.3.3.2. Functional property
3.3.4. Impurity
   3.4. Specification and test procedures
      3.4.1. Identification
      3.4.2. Purity and impurities
      3.4.3. Potency
      3.4.4. Protein content (mass)
3.5. Standard
3.6. Drug product
4. Platform technology for development of monoclonal antibody products
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A.1 Consideration for establishment of manufacturing process
A.2 Consideration issues for establishment of manufacturing process
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   A.2.2 Low pH treatment
   A.2.3 Anionic exchange chromatography
   A.2.4 Other chromatography
   A.2.5 Nanofiltration by virus removal filters
A.3. Characterization
   A.3.1 N- and C-terminal amino acid and N- and C-terminal sequencing
   A.3.2 Artificial modification of monoclonal antibody with radioisotope
A.4. General tests of Japanese pharmacopeia for specifications of monoclonal antibody
Manufacturing process for monoclonal antibody

Production of monoclonal antibody

Propagation process

Production process

Cell Bank

Medium

With serum-free, protein-free, chemically-defined media

Bulk harvest contains pure monoclonal antibody (e.g. 70-90%)

Bulk Harvest

Similar process can apply the manufacturing of monoclonal antibodies.

Purification process

Drug substrate

Drug product

Protein A

Column A

Column B

Nano filtration

Acid treatment

Virus inactivation

Virus removal

Production of monoclonal antibody
Focus

Objective: Monoclonal antibodies have the basic nature of immunoglobulins.

- Out-of Scope
- Non-recombinant hybridoma-derived monoclonal antibody
- Monoclonal antibody
- Fab
- F(ab’)2
- scFv
- Diabody
- The concept of guidance could be applied.
Viral safety evaluation in early phase of development

- The sponsor should conduct viral safety studies to submit the monoclonal antibody product for approval of new drug according to ICH Q5A.

- Since for development of monoclonal antibodies, same host cells are often utilized in same company, experiences about the viral safety of cell substrate which are already evaluated may apply the viral safety of clinical product in early clinical phase using same host cells.
  - Viral analysis of cell bank using information obtained from previous products
  - Rational virus design using experiences obtained from previous products

- When the sponsor develop monoclonal antibody product using new cell substrate, the viral safety about new substrate should be fully evaluated.
Biological property

• **variety of biological activity**
  – monoclonal antibody inhibit or enhance the biological reaction through the binding to target antigen: **Binding activity**
  – monoclonal antibody possess not only binding to target antigen but also ADCC or CDC activities: Functional activity
  – antibody conjugated with pharmacological chemical compound

• **Binding activity**: Enzyme-Linked Immunosorbent Assay Surface Plasmon Resonance: SPR
  – Analysis of monoclonal antibody to human cells/tissue will provide useful information about undesired pharmacological effects or potential of adverse effects, it is useful to evaluate the binding specificity or cross-reactivity of human cells/tissue using immunohistochemical staining methods.

• **Functional activity**: cell growth assay, neutralized activity of virus, ADCC, CDC
Platform Technology

- Since structure of monoclonal antibody are highly similar, platform technology may be applied to evaluate the quality attributes of monoclonal antibodies and to design the manufacturing process.
  - Characterization cell bank; of which host cells have been already used for other monoclonal antibody products
  - Specification; validation of test methods
  - Design of manufacturing process including cell culture or purification process.
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Regulatory Topics on Follow-on Biologics in Japan

• "Guidelines for the Quality, Safety and Efficacy Assurance of Follow-on Biologics“ (Yakushoku shinsahatu 0304007 by MHLW / March 4, 2009)

• “Revision of marketing approval application” (Yakushoku shinsahatu 0331015 by MHLW / March 4, 2009)

• “Nonproprietary name and brand name of Follow-on Biologics“ (Yakushoku shinsahatu 0304011 by MHLW / March 4, 2009)
# Development of Follow-on biologics (Biosimilar Products) in Japan  
(Dec. 2012)

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Biotechnological Products Have Complex Structure

- aspirin

- primary / secondary / tertiary / quaternary structure
- heterogeneity
- molecular size, charge
- posttranslational modification such as glycosylation
- heterogeneity in bioengineered structure such as pegylation
- biological activity
- immunogenicity
Some Biotechnological Products Have Multiple Domains

Each domain has its own function.

A set of relevant functional assays are required.

- FN domain
- EGF domain
- Kringle domain
- Kringle domain
- Active center
- Plasminogen binding domain
- Serine protease domain
- tissue Plasminogen Activator (t-PA)
Dossiers of Follow-on Biologics to be Submitted

Dossiers of the innovator product

- Manufacturing Process
- Characterization of Quality Attributes
- Non-clinical study
- Clinical study

Dossiers of the biosimilar product

- Manufacturing Process
- Characterization of Quality Attributes
- Non-clinical study
- Clinical study

Comparability study
  + Individual study
  + Information

To establish stable and robust manufacturing process
To analyze the quality attributes individually
Follow-on Biologics Guideline: Contents

1. Introduction
2. Scope (Well-characterized recombinant protein products)
3. General principles for the development of follow-on biologics
4. Manufacturing process and quality characterization
5. Comparability studies on quality attributes
6. Specifications
7. Non-clinical studies
8. Clinical studies
9. Post-marketing surveillance
10. Glossary
## Scope of the guideline

The guideline applies to recombinant proteins and polypeptides

<table>
<thead>
<tr>
<th>Decision</th>
<th>Products</th>
<th>Reasons</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Recombinant plasma proteins</td>
<td>There is no reason to exclude recombinant plasma proteins from the scope, even though some proteins have highly complicated structure.</td>
<td>Some patients might prefer non-recombinant products. Blood product supply might be affected, even though overlapped product development ensures the consistent supply.</td>
</tr>
<tr>
<td></td>
<td>Recombinant vaccines</td>
<td>Well characterized recombinant vaccine can be possibly developed as follow-on biologics.</td>
<td>Vaccine is administrated to healthy humans. Lot-to-lot variation of adjuvant activity is relatively large.</td>
</tr>
<tr>
<td></td>
<td>PEGylated recombinant proteins</td>
<td>Conjugates are in the scope as is in ICH Q6B.</td>
<td>Development of PEGylated protein as follow-on biologics might be difficult due to the structural complexity.</td>
</tr>
<tr>
<td>No</td>
<td>Synthetic peptides</td>
<td>Impurity profile is different from that of recombinant proteins.</td>
<td>Synthetic peptides can be generic drugs, because desired product can be easily defined by structural analyses.</td>
</tr>
<tr>
<td></td>
<td>Polyglycans</td>
<td>Characterization is difficult.</td>
<td>Several polyglycan products have been approved as generic drugs in Japan.*</td>
</tr>
<tr>
<td>Case by case</td>
<td>Non-recombinant proteins*</td>
<td>Proteins that are highly purified and characterized could be developed as follow-on biologics.</td>
<td>Several urine-derived protein products have been approved as generic drugs in Japan.</td>
</tr>
</tbody>
</table>

* e.g. proteins such as isolated from tissues or body fluids
General Principles for the Development of Follow-on Biologics (1)

- As with new biotechnological products, establishment of the well-defined manufacturing process, and extensive characterization studies to reveal the molecular and quality attributes of the follow-on biologics are required.

- Demonstration of the high similarity in quality attributes with the reference medicinal product is also required.

- Comparability between the follow-on biologics and reference medicinal product should be evaluated based on the data from non-clinical and clinical studies in addition to the data of quality characteristics.
Development of Manufacturing Process

- It is necessary to establish the highly consistent and robust manufacturing process.

- If the host cell line used for the production of reference medicinal product is disclosed, it is desired to use the same cell line.

- For the establishment and characterization of the cell banks, ICH Q5A, Q5B, Q5D guidelines should be referred.

- It is recommended to adopt the manufacturing processes potentially improve the safety of the product insofar as these do not affect efficacy.
Optimization of manufacturing process according to the comparability studies (1)

Profile of sugar chain

It is possible that there is some difference of quality attributes, such as glycosylation, between candidate of follow-on biologics and the reference product.
Optimization of manufacturing process according to the comparability studies (2)

Characterization of eluted fractions

Alteration of the purification process could provide the similarity of both products. Optimization of manufacturing processes (MP) will be conducted in development of (MP).
Comparability Studies on Quality Attributes

In addition to elucidating the quality attributes of the follow-on biologics, comparability exercises about quality attributes between the follow-on biologics and the reference medicinal product should be conducted.

For example, comparability exercises are conducted to examine the following aspects:

1. Structural characterization and physicochemical properties
2. Biological activities
3. Others
Variations of the quality attributes of innovator products

It is not always feasible to analyze the variation of quality attributes of innovator products, because of the limitation of accessibility to various lot of innovator products.
Non-clinical Studies

- Non-clinical studies that can ensure the safety for administration to humans should be performed and completed prior to initiation of the clinical studies.

- Both “comparability assessment” and “individual assessment” are applicable, depending the purpose of the study. For example, comparability assessment may be conducted for pharmacological activity studies, whereas individual assessment is made to address the safety issues on impurities.

Graph showing the relationship between specific activity (10^4 x IU/mg) in vivo and sialic acid (mol/mol erythropoietin) for different samples:

- **C1**: Intact erythropoietin
- **NG(0)**: De-N-glycosylated erythropoietins
- **NG(1)**: De-N-glycosylated erythropoietins
- **NG(2)**: De-N-glycosylated erythropoietins
- **A1~A7**: Desialylated erythropoietins

The graph indicates a positive correlation between the specific activity and the decrease in sialic acid content.
Tissue Distribution of Radioactivity After a Single Intravenous Administration of Radioiodinated Control EPO or EPO-bi in Male Rats

Plasma  Bone  Marrow  Kidney  Spleen  Liver  Lung  Adrenal  Heart

Concentration of radioactivity (ng eq. /mL or g)

■ EPO  ■ EPO-bi

Non-clinical Studies - impurities

- For product- and process-related impurities, it may be more rational to assess safety on the basis of an established manufacturing process per se and characteristics of impurities than simply to compare impurities of follow-on biologics with reference medicinal products.

- It may be acceptable to compare the toxicity profiles between follow-on biologics with reference medicinal products in spite of difference of impurities.
Clinical Studies

- In general, clinical studies are required in development of follow-on biologics since the data from characterization of quality attributes and non-clinical studies will be insufficient to evaluate the comparability with reference product.

- Clinical studies should be designed based on not only the data of quality attributes characterizations, non-clinical studies and comparability studies but also relevant information about reference product.
Conclusion of FOB

1. Follow-on biologics can be developed through the abbreviated pathway by utilizing the expertise of the innovator products as a reference.

2. The sponsor should evaluate high similarity of quality attributes between follow-on biologics and reference products, based on full-characterization of quality attribute as same as a new biologics.

3. In addition to quality data, sponsor should provide the enough data on comparability of follow-on biologics with reference product through the non-clinical and clinical studies necessarily.
Contents

1. Update in Japanese Regulation of Biologics
2. Guidance for Monoclonal Antibody Products
3. Update in Japanese Regulation of Follow-on Biologics (Biosimilar)
4. Future Issues of Biopharmaceuticals in Japan
   1. Cancer vaccine
   2. Rare disease
1. Cancer Vaccine (Cancer Immunotherapy)

Cancer Vaccine supported by Jpn. Gov. as SuperTokku

<table>
<thead>
<tr>
<th>Title</th>
<th>Institute</th>
<th>Nature</th>
</tr>
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<tbody>
<tr>
<td>Development of peptide vaccine</td>
<td>Tokyo univ + 55 labs</td>
<td>Tumor-specific peptide vaccine</td>
</tr>
<tr>
<td>Study for multiple vaccine therapy</td>
<td>Mie univ. + 8 univ./labs</td>
<td>Cell therapy/gene therapy/peptide</td>
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<tr>
<td>Advanced immunotherapy products; development of antibody and adjuvant</td>
<td>Osaka univ. Kyotouniv. Nibio</td>
<td>Regulation of Treg cell and adjuvant</td>
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Cancer Immunotherapy

<table>
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<tr>
<th>Title</th>
<th>Nature</th>
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<tr>
<td>Peptide vaccine</td>
<td>Tumor-specific 9-10mer peptide</td>
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<tr>
<td>Fusion protein</td>
<td>Tumor-specific peptide-protein conjugate</td>
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<tr>
<td>Cell therapy</td>
<td>Dendritic cells, Cancer-Ag-cells</td>
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<tr>
<td>Gene therapy</td>
<td>Virus vector, lasmid</td>
</tr>
</tbody>
</table>

Enroll of 1067 protocols in NIH web page

Current situation of cancer vaccines over sea


FDA: Guidance for Industry Clinical Considerations for Therapeutic Cancer Vaccines (2011)

Approve of Provenge (Sipleucel-T): Dendritic cell therapy for advanced prostate cancer treatment
Anti-tumor activity by immunotherapy

Tumor-specific antigen

Cancer

Peptide/protein

DCs

Combined therapy with peptide/protein, cell therapy/gene therapy

Antibody (Ab)

TCR

αβ TCR

αβ TCR

MHC Class 1

MHC Class 2

Cytotoxic T lymphocyte (CTL)

CD4+ cell

Naïve CD4+

Dendritic cell

Naïve CD4+

B cell

Antitumor activity by immunotherapy
Correlation between immune reaction and efficacy of cancer vaccine

- HLA tetramer assay (CD4/CTL)
- ELISPOT assay
- Cytokine assay (CD4+CTL)

+ Infusion of tumor-specific CD4/CTL into tumor
  + in vitro anti-tumor activity by CTL


Great progress has been made in the field of tumor immunology in the past decade, but optimism about the clinical application of currently available cancer vaccine approaches is based more on surrogate endpoints than on clinical tumor regression. In our cancer vaccine trials of 440 patients, the objective response rate was low (2.6%), and comparable to the results obtained by others. We consider here results in cancer vaccine trials and highlight alternate strategies that mediate cancer regression in preclinical and clinical models.
Could release from immune suppression overcome resistance of tumor against tumor immunotherapy?

Treg cells inhibit the anti-tumor function of tumor specific CD4+ T cells or CTL (Prof. Sakaguchi (Kyoto univ.))

Efficacy of ipilimumab

Ipilizumab: monoclonal antibody recognize CTLA-4 expressed by Treg cells.

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma through inhibition of Treg.

Clinicals with these antibody products showed promising results in anti-cancer immunotherapy

Weber published the data on anti PD-1 antibody BMS-936558, which caused considerable excitement at the American Society of Clinical Oncology (ASCO) annual meeting in June, can be an effective part of a treatment regimen that includes ipilimumab.

Of those three types, the highest objective response rate—which included patients who achieved complete or partial responses—was observed in melanoma, with 26 of 94 patients (28%) responding to the treatment. Additionally, six of those melanoma patients (6%) achieved stable disease for at least 24 weeks.
From the current studies about cancer immunotherapy

- Usefulness of monoclonal antibodies which overcome immune-suppression by tumor cells.
- Open the new indications in monoclonal antibody products
- Novel PD marker to evaluate the tumor immune reaction.
2. Update on Development of Biologicals for Rare diseases

• Gene Therapy
  – EU approved first gene therapy products for LPL-deficiency (glybera)
  – Many rare disease gene therapy products are developing: β-thalathemia disease, adenoleukodystrophy, X-SCID, ADA-SCID

• Enzyme replacement therapy
  – Aldurazyme(laronidase), Cerezyme (imiglucerase), Fabrazyme (agalsidase beta), Lumizyme (alglucosidase alfa), Myozyme (alglucosidase alfa)

• Monoclonal antibody
  – eculizumab (paroxysmal nocturnal hemoglobinuria)
<table>
<thead>
<tr>
<th>Year</th>
<th>Product Name</th>
<th>Indication</th>
<th>Company</th>
<th>Appr. Year</th>
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<tbody>
<tr>
<td>1993</td>
<td>Interferon gamma-1a (genetical recombination)</td>
<td>chronic granulomatous disease</td>
<td>Shionogi</td>
<td>1998</td>
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<tr>
<td>1993</td>
<td>Anti-human Thymocyte Immunoglobulin, Rabbit</td>
<td>aplastic anemia</td>
<td>Genzyem JPN</td>
<td>2008</td>
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<tr>
<td>1993</td>
<td>Anti-human T-lymphocyte immunoglobulin, rabbit</td>
<td>aplastic anemia</td>
<td>Nippon Zoki</td>
<td>1995</td>
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<td>1993</td>
<td>Human activated protein C, freeze-dried concentrated</td>
<td>Protein C Deficiency</td>
<td>kaketsuken</td>
<td>2000</td>
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<tr>
<td>1994</td>
<td>Freeze-dried Human Blood Coagulation Factor VIII Concentrate</td>
<td>Congenital hemophilia and acquired hemophilia of Bleeding restraint</td>
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<td>–</td>
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<tr>
<td>1995</td>
<td>Anti-human CD11a mouse monoclonal antibody??</td>
<td>GVHD in transfusion of HSC forSCID</td>
<td>#VALUE!</td>
<td>–</td>
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<tr>
<td>1995</td>
<td>Nonacog alfa (genetical recombination)</td>
<td>hemophilia B</td>
<td>Pfizer</td>
<td>2009</td>
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<td>1998</td>
<td>Laronidase (genetical recombination)</td>
<td>mucopolysaccharidosis I</td>
<td>Genzyem JPN</td>
<td>2006</td>
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<td>1998</td>
<td>Agalsidase Beta (Genetical Recombination)</td>
<td>Fabry's disease, Fabry disease</td>
<td>Genzyem JPN</td>
<td>2004</td>
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<tr>
<td>2004</td>
<td>Alglucosidase Alfa (Genetical Recombination)</td>
<td>glycogen storage disease type II</td>
<td>Genzyem JPN</td>
<td>2007</td>
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<tr>
<td>2006</td>
<td>Idursulfase (genetical recombination)</td>
<td>mucopolysaccharidosis II</td>
<td>Genzyem JPN</td>
<td>2007</td>
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<tr>
<td>2007</td>
<td>Galsulfase (genetical recombination)</td>
<td>mucopolysaccharidosis VI</td>
<td>Aenges MG</td>
<td>2008</td>
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<tr>
<td>2008</td>
<td>Eculizumab (genetical recombination)</td>
<td>paroxysmal nocturnal hemoglobinuria</td>
<td>Alexion</td>
<td>2010</td>
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<td>2010</td>
<td>Canakinumab (genetical recombination)</td>
<td>cryopyrin-associated periodic syndrome, Familial chilly self-inflammatory syndrome, Muckle-Wells syndrome The newborn baby period onset many organs system inflammation-related disease</td>
<td>Novartis Pharma K.K.</td>
<td>2011</td>
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<td>2011</td>
<td>Velaglucerase alfa</td>
<td>Gaucher’s disease</td>
<td>Shire HGT</td>
<td></td>
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<td>2011</td>
<td>Dornase alfa (genetical recombination)</td>
<td>cystic fibrosis; mucoviscidosis</td>
<td>Chugai</td>
<td>2012</td>
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<tr>
<td>2011</td>
<td>GSK2402968</td>
<td>Duchenne-type dystrophy</td>
<td>GSK</td>
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<td>2011</td>
<td>Recombinant von Willebrand Factor</td>
<td>von Willebrand Factor Deficiency</td>
<td>Baxter</td>
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<td>2011</td>
<td>Rurioctocog alfa (genetical recombination)</td>
<td>von Willebrand Factor Deficiency</td>
<td>Baxter</td>
<td>–</td>
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</table>
**Current Status of Development of Intractable Rare Diseases in Japan, USA, and EU (1)**

<table>
<thead>
<tr>
<th>Developed in Jpn, USA, EU</th>
<th>24/139</th>
<th>myelodysplastic syndrome, paroxysmal nocturnal hemoglobinuria, Pulmonary hypertension, age-related macular degeneration, acromegalicgigantism, ulcerative colitis, Fabry’s disease (Fabry disease), Pompe’s disease (Pompe disease), mucopolysaccharidosis VI, polycystic renal disease, etc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developed in only Jpn</td>
<td>9/139</td>
<td>aplastic anemia, Central eating disorder, spinocerebellar ataxia, subacute sclerosing panencephalitis, refractory nephrotic syndrome etc.</td>
</tr>
<tr>
<td>Developed in only USA, EU</td>
<td>29/139</td>
<td>thrombotic thrombocytopenic purpura, amyloidoses, myelofibrosis, Niemann–Pick disease, Metachromatic Leukodystrophy, mitochondrial disease, juvenile emphysema, cystic fibrosis, epidermolysisbullosa etc.</td>
</tr>
<tr>
<td>Developed in neither Jpn nor USA/EU</td>
<td>77/139</td>
<td>autoimmune hemolytic anemia, Buerger’s disease (Buerger disease), Fatal Familial Insomnia, striatonigral degeneration, chorea–acanthocytosis, peroxisomal disorder, refractory optic neuropathy, Meniere’s disease (Meniere disease), hypertrophic cardiomyopathy pulmonar y, lymphangioleiomyomatosis, congenital ichthyosiformerythroderma, xerodermapigmentosum, IgA nephropathy etc.</td>
</tr>
</tbody>
</table>

Intractable Rare Diseases are thought to be more than 6,000. In Japan, 65 Intractable diseases (nanbyo) are designated as the Specified Disease Treatment Research Program; e.g. primary immunodeficiency syndromea, lysosomal storage diseases, mitochondrial disease, plastic anemia etc.
### Product Name | Indications | Approved Year
--- | --- | ---
Canakinumab | Cryopyrin-associated periodic syndrome | 2011
Dornase Alpha | Cystic fibrosis transmembrane conductance regulator (CFTR) | 2012
Natarizumab | Multiple sclerosis | 2012
Human immunoglobulin | Congenital immunodeficiency | off-label
Leuprolin | Central precocity | off-label

**Issues for development of rare disease drugs**
- Patient population
- Mechanism of Diseases
- Market Size
New approach to develop biopharmaceuticals for rare diseases

- Development of biopharmaceuticals for rare diseases using data from disease model cells
  - Establishment of iPS cells
  - Oct3/4, Sox2, Klf4, c-Myc
  - Disease model cells

clarification of disease mechanism
There are many patients with rare diseases and their families hoping development of drugs to treat their diseases.
Thank you for your attentions!