PMDA Perspective: Recent Trends in the Regulation of Biopharmaceuticals

Jun SAKAMOTO
Director
Office of Cellular and Tissue-based Products
Pharmaceuticals and Medical Devices Agency (PMDA)
Disclaimer

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.
Japanese Regulatory Authorities for Pharmaceuticals and Medical Devices

■ MHLW
Planning basic policy, enforcement of administrative measures based on the law
➢ Marketing authorization of pharmaceuticals and medical devices
➢ Issue emergency safety information and direct product withdrawal
➢ Safety measures for emergent and significant cases

■ PMDA
Review, examination and data analysis
➢ Scientific review, GMP/GLP/GCP inspection and consultation on the development of pharmaceuticals and medical devices for marketing authorization
➢ Collection, analysis and dissemination of information relating to quality, efficacy and safety of pharmaceuticals and medical devices
# Review Categories of New Drugs

<table>
<thead>
<tr>
<th>Office</th>
<th>Review Category</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Office of New Drug I</td>
<td>Team 1</td>
<td>Gastrointestinal drugs, Dermatologic drugs</td>
</tr>
<tr>
<td></td>
<td>Team 6-2</td>
<td>Hormone drugs, Drugs for metabolic disorders</td>
</tr>
<tr>
<td>Office of New Drug II</td>
<td>Team 2</td>
<td>Cardiovascular drugs, Antiparkinsonian drugs, Antithrombotics, Anti-Alzheimer’s drugs</td>
</tr>
<tr>
<td></td>
<td>Team 5</td>
<td>Reproductive system drugs, Drugs for urogenital system, combination drugs</td>
</tr>
<tr>
<td></td>
<td>Radiopharmaceuticals</td>
<td>Radiopharmaceuticals</td>
</tr>
<tr>
<td></td>
<td>In vivo diagnostics</td>
<td>Contrast media</td>
</tr>
<tr>
<td>Office of New Drug III</td>
<td>Team 3-1</td>
<td>Central/peripheral Nervous system drugs (excluding anesthetic drugs)</td>
</tr>
<tr>
<td></td>
<td>Team 3-2</td>
<td>Anesthetic drugs, Sensory organ drugs (excluding drugs for inflammatory diseases), Narcotics</td>
</tr>
<tr>
<td>Office of New Drug VI</td>
<td>Team 4</td>
<td>Antibacterial drugs, vermifuge, Antifungal drugs, Antiviral drugs (excluding AIDS drugs)</td>
</tr>
<tr>
<td></td>
<td>Anti-AIDS drugs</td>
<td>Anti-HIV agents</td>
</tr>
<tr>
<td></td>
<td>Team 6-1</td>
<td>Respiratory tract drugs, Anti-allergy drugs (excluding dermatologic drugs), Sensory organ drugs for inflammatory diseases</td>
</tr>
<tr>
<td>Office of New Drug V</td>
<td>Oncology drugs</td>
<td>Antineoplastic drugs</td>
</tr>
<tr>
<td>Office of Cellular and Tissue-based Products</td>
<td>Bio-CMC</td>
<td>Quality of biologics, Biosimilars</td>
</tr>
<tr>
<td></td>
<td>Cellular and tissue-based products</td>
<td>Cellular and tissue-based products</td>
</tr>
<tr>
<td></td>
<td>Gene therapy products</td>
<td>Quality and safety of gene therapy products,</td>
</tr>
<tr>
<td>Office of Vaccines and Blood Products</td>
<td>Vaccines</td>
<td>Vaccines, Antitoxic serum</td>
</tr>
<tr>
<td></td>
<td>Blood products</td>
<td>Globulin, Blood coagulation factor products</td>
</tr>
</tbody>
</table>
Review Team of the Office of CTBP

CTBP: Cellular & Tissue-based Products
Recent Approaches for Innovative Medicines

Seeds originated in Japan

Quality Study | Non-Clinical Trial | Clinical Trial | Review | Approval | Post-marketing

Innovative Drugs and Medical Devices

Recent Approaches for Innovative Medicines

correspond better to the characteristics of innovative new medicines in all phases from seeds to practical use

(1) The Science Board
(2) Pharmaceutical Affairs Consultation on R&D Strategy
(3) Personnel exchange with academia
(4) Program of Collaborative Graduate Schools
(5) Regulations for Biosimilars in Japan
(6) QbD Assessment Project in PMDA
PMDA established the Science Board on May 14th 2012, as a high-level consultative body* to advance regulatory science and support PMDA to evaluate products with advanced science and technology.

* Members are external experts from medical, dental, pharmaceutical, engineering and other fields.

The Board will make recommendations on review policy for innovative products, development of guidelines, regulatory science research, improvements in the scientific aspects of review.
Establishment of the Science Board

The Science Board was established in May 2012 to discuss how PMDA can better cope with products with advanced science & technology, in each developmental stage such as basic research, development support, product review, and post market safety measures.
The subcommittee has held multiple discussions from the scientific point of view on “tumorigenicity” that is the major safety concern of iPSCs for cellular and tissue-based products.

Main concerns on iPSCs

1. “Genetic abnormality that induces persistent cell proliferation”
   - Detection of residual exogenous pluripotency-inducing transgenes
   - Confirmation of karyotype and abnormality in DNA sequences of all exons

2. “Genomic instability”
   - Confirmation of the genomic mutation rate when iPSCs are subcultured

(NOTE) Provisional translation as of September 30, 2013. This report presents a summary on the development of cellular and tissue-based products from a scientific point of view, and not the requirements for regulatory approval of cellular and tissue-based products.
Examples of Cancer Related Genes in Gene Symbol

<table>
<thead>
<tr>
<th>ABL1</th>
<th>CBFA2T3</th>
<th>ERCC4</th>
<th>GATA1</th>
<th>MEN1</th>
<th>NUP214</th>
<th>SH3GL1</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABL2</td>
<td>CBLB</td>
<td>ERCC5</td>
<td>GATA3</td>
<td>MET</td>
<td>NUP96</td>
<td>SMAD4</td>
</tr>
<tr>
<td>ACVR1B</td>
<td>CBLC</td>
<td>ERCC6</td>
<td>GNA11</td>
<td>MITF</td>
<td>PALB2</td>
<td>SMARCA4</td>
</tr>
<tr>
<td>AFF3</td>
<td>CCND1</td>
<td>ETV4</td>
<td>GNAQ</td>
<td>MLH1</td>
<td>PAX8</td>
<td>SMARC1</td>
</tr>
<tr>
<td>AKAP9</td>
<td>CCND2</td>
<td>ETV6</td>
<td>GNAs</td>
<td>MLH3</td>
<td>PBRM1</td>
<td>SMO</td>
</tr>
<tr>
<td>AKT1</td>
<td>CCND3</td>
<td>EVI1</td>
<td>GOLGA5</td>
<td>MLL</td>
<td>PDE4DIP</td>
<td>SOCS1</td>
</tr>
<tr>
<td>AKT2</td>
<td>CDC73</td>
<td>EWSR1</td>
<td>GOPC</td>
<td>MLL2</td>
<td>PDGFB</td>
<td>SRGAP3</td>
</tr>
<tr>
<td>ALK</td>
<td>CDH1</td>
<td>EXT1</td>
<td>GPC3</td>
<td>MLL3</td>
<td>PDGFRA</td>
<td>SRSF2</td>
</tr>
<tr>
<td>APC</td>
<td>CDH11</td>
<td>EXT2</td>
<td>H3F3A</td>
<td>MLLT3</td>
<td>PDGFRB</td>
<td>SS18</td>
</tr>
<tr>
<td>ARHGEF12</td>
<td>CDK6</td>
<td>EZH2</td>
<td>HMG1A</td>
<td>MPL</td>
<td>PIK3CA</td>
<td>STAT3</td>
</tr>
<tr>
<td>ARID1A</td>
<td>CDKN2A</td>
<td>FAM123B</td>
<td>HMG2</td>
<td>MSH2</td>
<td>PIK3R1</td>
<td>STK11</td>
</tr>
<tr>
<td>ARID2</td>
<td>CDKN2C</td>
<td>FANCA</td>
<td>HNF1A</td>
<td>MSH6</td>
<td>PIM1</td>
<td>SUFU</td>
</tr>
<tr>
<td>ASXL1</td>
<td>CDX2</td>
<td>FANCB</td>
<td>HRAS</td>
<td>MUTYH</td>
<td>PLAG1</td>
<td>SUZ12</td>
</tr>
<tr>
<td>ATF1</td>
<td>CEBPA</td>
<td>FANCC</td>
<td>IDH1</td>
<td>MYB</td>
<td>PML</td>
<td>SYK</td>
</tr>
<tr>
<td>ATM</td>
<td>CHEK1</td>
<td>FANCD2</td>
<td>IDH2</td>
<td>MYC</td>
<td>PMS2</td>
<td>TCF3</td>
</tr>
<tr>
<td>ATR</td>
<td>CHEK2</td>
<td>FANCE</td>
<td>IKZF1</td>
<td>MYCL1</td>
<td>POLE</td>
<td>TCL1A</td>
</tr>
<tr>
<td>ATRX</td>
<td>CIC</td>
<td>FANCF</td>
<td>IL2</td>
<td>MYCN</td>
<td>POLH</td>
<td>TET2</td>
</tr>
<tr>
<td>AXIN1</td>
<td>COL1A1</td>
<td>FANCG</td>
<td>IL7R</td>
<td>MYD88</td>
<td>PPARG</td>
<td>TFG</td>
</tr>
<tr>
<td>AXIN2</td>
<td>CREB1</td>
<td>FANCI</td>
<td>IRF4</td>
<td>MYST3</td>
<td>PPP2R1A</td>
<td>TLX1</td>
</tr>
<tr>
<td>BAP1</td>
<td>CREBBP</td>
<td>FANCJ</td>
<td>JAK2</td>
<td>NCOA2</td>
<td>PRKAR1A</td>
<td>TNFAIP3</td>
</tr>
<tr>
<td>BCL11A</td>
<td>CTNNB1</td>
<td>FANCL</td>
<td>JUN</td>
<td>NCOA4</td>
<td>PTCH1</td>
<td>TP53</td>
</tr>
<tr>
<td>BCL11B</td>
<td>CYLD</td>
<td>FANCN</td>
<td>KDM5C</td>
<td>NF1</td>
<td>PTEN</td>
<td>TPR</td>
</tr>
<tr>
<td>BCL2</td>
<td>DAXX</td>
<td>FANCP</td>
<td>KDM6A</td>
<td>NF2</td>
<td>PTPN11</td>
<td>TSC1</td>
</tr>
<tr>
<td>BCL3</td>
<td>DDB2</td>
<td>FBXW7</td>
<td>KDR</td>
<td>NFE2L2</td>
<td>RAD51C</td>
<td>TSC2</td>
</tr>
<tr>
<td>BCL6</td>
<td>DDIT3</td>
<td>FEV</td>
<td>KIT</td>
<td>NFkB2</td>
<td>RAF1</td>
<td>TSHR</td>
</tr>
<tr>
<td>BCOR</td>
<td>DDX5</td>
<td>FGFR1</td>
<td>KRAS</td>
<td>NIN</td>
<td>RB1</td>
<td>USP6</td>
</tr>
<tr>
<td>BCR</td>
<td>DDX6</td>
<td>FGFR1OP</td>
<td>LCK</td>
<td>NONO</td>
<td>REL</td>
<td>VHL</td>
</tr>
<tr>
<td>BHD</td>
<td>DEK</td>
<td>FGFR2</td>
<td>LMO2</td>
<td>NOTCH1</td>
<td>RET</td>
<td>WRN</td>
</tr>
<tr>
<td>BLM</td>
<td>DICER</td>
<td>FGFR3</td>
<td>MAF</td>
<td>NOTCH2</td>
<td>RNF213</td>
<td>WT1</td>
</tr>
<tr>
<td>BMPR1A</td>
<td>DNMT3A</td>
<td>FH</td>
<td>MAFB</td>
<td>NPM1</td>
<td>ROS1</td>
<td>XPA</td>
</tr>
<tr>
<td>BRAF</td>
<td>EGFR</td>
<td>FLCN</td>
<td>MAML2</td>
<td>NR4A3</td>
<td>RUNX1</td>
<td>XPC</td>
</tr>
<tr>
<td>BRCA1</td>
<td>ELK4</td>
<td>FLT3</td>
<td>MAP2K4</td>
<td>NRAS</td>
<td>SDHB</td>
<td>ZNF521</td>
</tr>
<tr>
<td>BRCA2</td>
<td>EP300</td>
<td>FOXL2</td>
<td>MDM2</td>
<td>NSD1</td>
<td>SDHD</td>
<td></td>
</tr>
<tr>
<td>CARD11</td>
<td>ERBB2</td>
<td>FOXP1</td>
<td>MDM4</td>
<td>NTRK1</td>
<td>SETD2</td>
<td></td>
</tr>
<tr>
<td>CARS</td>
<td>ERCC3</td>
<td>FUS</td>
<td>MED12</td>
<td>NTRK3</td>
<td>SF3B1</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: There are genes that have been reported to be related to carcinogenesis besides those listed in this table and knowledge/information on cancer-related genes is being renewed daily. Therefore, we note that the content of this table should be updated as necessary.
Valley of Death
- Insufficient knowledge on regulation and development strategy

(2) Pharmaceutical Affairs Consultation on R&D Strategy

Strategic Consultation

Basic Research
- Pharmaceuticals and Medical Devices candidates

Quality Study
- Consultation on quality or toxicity study of biologics, cellular therapy products

Non-Clinical Study

Clinical Trial
- Up to the level of POC studies
- Consultation on endpoints or sample size of early clinical trial

Practical Use
- Innovative Products

Pharmaceutical Affairs Consultation on R&D Strategy
Consultation and Review

Review of Clinical Trial Protocol (30 days-IND review)
* To prevent the occurrence or spread of hazard to the public.

Application for Marketing Authorization

Consultation on Strategy
* To ensure safety and quality.

Consultation on Conducting Clinical Trials
(3) Personnel exchange with academia

- Develop standards and guidelines at early phase
- Facilitate practical application of innovative technologies
- Decrease drug/device lag

Acquisition of innovative technologies
Speed up and improve product review

Outcome of researches

Fostering of Regulatory Scientist
Promotion of appropriate R & D

Human resource development

Reviewers

Researchers

Universities and research institutions
Medical Institutions

NIHS
Pmda
(4) Program of Collaborative Graduate Schools

- **PMDA Staff members**
  - Visiting Professor (Lecture in regulatory science)
  - Graduate student (Ph.D. program); Research at Graduate schools

- **Graduate school students**
  - Graduate student (Ph.D. program); Research at PMDA

Agreement with 17 Universities (as of June, 2013)
(5) 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)

  with Overview of comments on Guideline

  *: “Follow-on Biologics” in this guideline is a synonym for “Biosimilars”.

- 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
  *(PFSB/ELD Administrative Notice / July 21, 2009, March 31, 2010)*
Regulatory History and Status of Biosimilars

- Guideline
- Application Category for biosimilars
- Nomenclature rules

Revision of Nomenclature rules

2005
2009
2010
2011
2012
2013

Somatropin BS

Epoetin alfa BS

Filgrastim BS [F], [MOCHIDA]
(Same active substance, different applicants)

Filgrastim BS [NK], [TEVA]
(Same active substance, different applicants)
# List of Approved Biosimilars in Japan

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Japanese Accepted Name (JAN)</th>
<th>Manufacturer (Country)</th>
<th>Reference product</th>
<th>Approved year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatropin BS s.c. Injection 5mg [SANDOZ] etc. *1</td>
<td>Somatropin (genetical recombination)</td>
<td>SANDOZ(Austria)</td>
<td>Genotropin (Somatropin) (Pfizer)</td>
<td>2009.5</td>
</tr>
<tr>
<td>Epoetin alfa BS Injection 750 syringe [JCR] etc. *1</td>
<td>Epoetin Kappa (genetical recombination) [Epoetin Alfa Biosimilar 1]</td>
<td>JCR Pharmaceuticals (Japan)</td>
<td>Espo (Epoetin alfa) (Kyowa Hakko Kirin)</td>
<td>2009.11</td>
</tr>
<tr>
<td>Filgrastim BS Injection 75µg syringe [F] etc. *1,2</td>
<td>Filgrastim (genetical recombination) [Filgrastim Biosimilar 1]</td>
<td>Fuji Pharma (Japan)</td>
<td>Gran (Filgrastim) (Kyowa Hakko Kirin)</td>
<td>2012.11</td>
</tr>
<tr>
<td>Filgrastim BS Injection 75µg syringe [MOCHIDA] etc. *1,2</td>
<td>Filgrastim (genetical recombination) [Filgrastim Biosimilar 1]</td>
<td>Mochida Pharmaceutical (Japan)</td>
<td>Gran (Filgrastim) (Kyowa Hakko Kirin)</td>
<td>2012.11</td>
</tr>
<tr>
<td>Filgrastim BS Injection 75µg syringe [NK] etc. *1,3</td>
<td>Filgrastim (genetical recombination) [Filgrastim Biosimilar 2]</td>
<td>NIPPON KAYAKU (Japan)</td>
<td>Gran (Filgrastim) (Kyowa Hakko Kirin)</td>
<td>2013.2</td>
</tr>
<tr>
<td>Filgrastim BS Injection 75µg syringe [TEVA] etc. *1,3</td>
<td>Filgrastim (genetical recombination) [Filgrastim Biosimilar 2]</td>
<td>Teva Pharma Japan (Japan)</td>
<td>Gran (Filgrastim) (Kyowa Hakko Kirin)</td>
<td>2013.2</td>
</tr>
</tbody>
</table>

*1: etc. means different presentations.
*2: Same active substance, different applicants
*3: Same active substance, different applicants
Number of Consultations for Biosimilar

Fiscal year

No. of consultations

2006 2007 2008 2009 2010 2011 2012 2013

As of October 23, 2013
Based on date of application
(6) QbD Assessment Project in PMDA

PMDA is participating as an observer in the EMA-FDA pilot program for Quality by Design (QbD) in March 2011. The European Medicine Agency (EMA) and the U.S. Food and Drug Administration (FDA) announced the EMA-FDA pilot program for parallel assessment of Quality by Design (QbD) applications, which aims at a parallel assessment by both agencies of certain Quality/CMC sections of a selected number of applications under the confidentiality arrangements.

This pilot program mainly focuses on consistent implementation between EU and US of ICH Q8, 9, 10 guidelines in the assessment process and to facilitate sharing of regulatory decisions on new regulatory concepts.

PMDA participation is under the EMA, FDA and PMDA confidentiality arrangements, in order to share information and points to consider relating to QbD review.

Pharmaceutical and Medical Devices Agency (PMDA) participates in the EMA-FDA pilot program of QbD as an observer under the EMA, FDA and PMDA confidentiality arrangements, in order to share information and points to consider relating to QbD review.

PMDA expects its participation can facilitate increased harmonization of QbD application assessment.

PMDA participation in this pilot program is under the sponsor/applicant agreement. However, this does not mean PMDA undertakes review of the QbD application of the product in the Japanese regulatory process. At this stage, PMDA participation is limited to one application and expansion to other applications will be decided based on the evaluation of this first attendance.

In November 2011, PMDA launched a new project team consisting of reviewers and inspectors to handle the participation in this pilot program and to share common understanding of QbD between offices in PMDA.

http://www.pmda.go.jp/english/service/qbd_e.html (in English)
QbD Assessment Project Team
The Pharmaceutical Affairs Law

Revision History:

- 1960
- 2002
- 2006

Past:
- HIV contaminated plasma derivatives
- Fibrinogen-transmitted Hepatitis C
- Iatrogenic CJD through transplantation of dura mater

Strengthening of safety measures for Biopharmaceuticals

Risk-based safety measures
Main Pillars for Revision of Pharmaceutical Affairs Law

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td><strong>To strengthen safety measures</strong> by stakeholders related to pharmaceuticals/medical devices</td>
</tr>
<tr>
<td>2.</td>
<td>To construct regulation considering <strong>unique characteristics of medical devices</strong></td>
</tr>
<tr>
<td>3.</td>
<td>To construct regulation considering <strong>unique characteristics of regenerative medical products</strong></td>
</tr>
<tr>
<td>4.</td>
<td><strong>To strengthen supervision</strong> of designated medical products</td>
</tr>
<tr>
<td>5.</td>
<td><strong>To rename Pharmaceutical Affairs Law</strong> to reflect its scope more precisely</td>
</tr>
</tbody>
</table>

*Draft (Tentative Translation) Under Consideration*
Definition of “Regenerative Medicinal Products”

<Chapter 1 Article 9>

The term “Regenerative Medicinal Products” (as “SAISEI-IRYOU-TOU-SEIHIN” in Japanese) used in this law refers to the articles (excluding quasi-drugs and cosmetics) specified in the following items which are specified by the government ordinance.

(1) These articles specified in the following items which are intended to use in the treatment of disease in humans or animals, and are **cultured and/or processed human or animal cells**.

A To reconstruct, restore or reproduce the structure or functions of human or animal body.

B To treat or prevent disease in humans or animals.

(2) The articles which are intended to use in the treatment of disease in humans or animals, and are **transgened to express in human or animal cells**.

The Term “Regenerative Medicinal Products” in this law includes “Gene Therapy” and “CTBPs.” This concept is similar to “Advanced Therapy Medicinal Products (ATMPs)” in EU.
New Approval System

【Current System】
Clinical Research → Clinical Trial (confirmation of efficacy and safety) → Approval → Marketing

【Proposed System】
Clinical Research → Clinical Trial (confirmation of probable benefit* and safety**) → Provisional Approval with condition → Marketing (further confirmation of efficacy and safety) → Application → Approval or Expiration of provisional approval

※Earlier Patient Access!

* Probable benefit: Confirmation of efficacy with small patient population.
** Safety: Earlier detection and evaluation of adverse events.
New Regenerative Medicine Law
To ensure safety of regenerative medicine by stipulating standards for medical facilities and processing/manipulation plants

Pharmaceutical Affairs Law
To ensure efficacy and safety of marketing products by stipulating manufacturing standards

Clinical Research/Medical Practice

Outsourcing of Processing

Company Plants (with permission)

Medical institutions (with notification)

Collection

Processing

Outsourcing

Transplant

Processing

cell/tissue

Company Plants (with permission)

New Law

PAL
Thank you for your attention!