Regulatory Updates and a Perspective on Biopharmaceuticals in Japan

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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.
Wisdom

(Explicit) Knowledge

“Ba”

Nonaka & Konno (1998)
Outline

• Recent trends of Biopharmaceuticals in Japan

• On-going ICH-Quality Topics

• Lessons Learned from COVID-19 Pandemic
Trend of New Active Ingredients (NAIs) and Biosimilars

<table>
<thead>
<tr>
<th>Fiscal year</th>
<th>2017</th>
<th>2018</th>
<th>2019</th>
<th>2020</th>
<th>2021</th>
<th>2022*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of NAIs</td>
<td>20</td>
<td>25</td>
<td>30</td>
<td>35</td>
<td>40</td>
<td>35</td>
</tr>
<tr>
<td>% of NAIs (Biologics) + Biosimilars</td>
<td>45</td>
<td>50</td>
<td>55</td>
<td>60</td>
<td>65</td>
<td>60</td>
</tr>
</tbody>
</table>

* As of August 31

#: Therapeutic proteins, Blood products and Vaccines. Regenerative Medical Products are not included

List of Approved Products | Pharmaceuticals and Medical Devices Agency (pmda.go.jp)
Trend of Biopharmaceuticals

• mAbs are predominant among therapeutic proteins (e.g., mAbs, Fusion proteins, EPOs, Enzymes, Hormones, Interferons, Coagulation factors).

• A mock example of CTD Module 2.3 (2.3.S.2.2, 2.3.S.2.3 and 2.3.S.2.4) and Application Form (Module 1.2) of mAb developed by AMED* Research group (Oct. 2022)

  BIO_mockup.pdf (nihs.go.jp)

  Note: The mock example should not be used as a template or the sole basis for a regulatory submission

• Various types of mAbs (conjugate (radioisotopes, drug, near infrared dye), bispecific, nanobody)
Regulatory History and Status of Biosimilars

Application Category for biosimilars
Nomenclature rules
Guideline

Q&A

Revision of
Nomenclature rules

Q&A

Revision of
Guideline and Q&As

2009
Somatropin BS
Epoetin alfa BS

2010
Filgrastim BS

2011
Filgrastim BS

2012
Filgrastim BS

2013
Infliximab BS

2014
Insulin glargine BS

2015
Etanercept BS
Trastuzumab BS

2016
Infliximab BS

2017
Rituximab BS

2018
Agalsidase beta BS
Darbepoetin alfa BS
Darbepoetin alfa BS
Darbepoetin alfa BS

2019
Bevacizumab BS

2020
Insulin lispro BS

2021
Bevacizumab BS
Adalimumab BS
Ranibizumab BS

2022
Adalimumab BS

2023

Red: mAbs and Fusion proteins
Blue: Others
Consultation for Biosimilars

<table>
<thead>
<tr>
<th>Fiscal year</th>
<th>No. of Consultation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>2</td>
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<td>2015</td>
<td>21</td>
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<td>2016</td>
<td>28</td>
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<td>2017</td>
<td>23</td>
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<td>2018</td>
<td>20</td>
</tr>
<tr>
<td>2019</td>
<td>22</td>
</tr>
<tr>
<td>2020</td>
<td>21</td>
</tr>
<tr>
<td>2021</td>
<td>31</td>
</tr>
</tbody>
</table>

- : mAbs and Fusion proteins
- : Others
Question to be addressed

• To what extent can analytical (incl. in vitro assay) similarity ensure equivalent efficacy and similar safety profile to/as the reference product?
Outline

• Recent trends of Biopharmaceuticals in Japan

• On-going ICH-Quality Topics

• Lessons Learned from COVID-19 Pandemic
On-going ICH-Quality Topics

- Q12 EWG: Step 4
- Q13 EWG
- Q2(R2)/Q14 EWG
- Q5A(R2) EWG: Step 2
- Q3E EWG: Step 2
- Q9(R1) EWG: Step 2
- M4Q(R2) EWG
- Q1/Q5C EWG: pending
ICH Q12 Implementation in Japan

ICH Q12 EWG/IWG

Step 2
Public consultation in Japan
31 Jan. 2018 to 30 Jul. 2018
15, 29 Mar. 2018
Q12 Briefing in Japan

Step 4
Revision of PMD. Act
Dec. 2019
Revision of Enforcement Reg. of the PMD. Act
Jan. 2021
Guideline for PACMP Implementation
Jun. 2021
Guideline & Q&A on PACMP
Aug. 2021
PACMP implementation

29 Oct. 2021
Q12 Guideline (Step5)

[Abbreviations]
- PMD. Act: Pharmaceuticals and Medical Devices Act
- MCN: Minor Change Notification
- AF: Application Form

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Behind-the-scenes preparations

**PMDA ICH Q12 WG**
- **Dec. 2014**
  - Member: Sr. Mgmt., Reviewers (chemicals, biologicals, generics), GMP inspectors
  - Discuss regulatory, technical and practical issues within PMDA

**AMED Research Group**
- **Sep. 2016**
  - Member: Academia, Industry, PMDA
  - Discuss technical and practical issues, Report the outcome and proposal to the MHLW

**MHLW/PMDA-FPMAJ Task Force**
- **Members: MHLW, PMDA, FPMAJ (The Federation of Pharmaceutical Manufacturers’ Associations of JAPAN)**
- **Driven by “domestic problems” (not by ICH Q12)**
- **Streamline the regulatory procedures for post-approval CMC changes**
**PACMP: Guideline** (MHLW PSEHB/ELD Notification 0616-14, 16 Jun. 2021)

- **Applicant**
  - PACMP application
  - Confirmation of the pPACMP*
    - * proposed PACMP
  - Application for change in cPACMP*
    - * confirmed PACMP
  - Notification for minor change in cPACMP*
  - Application for change according to cPACMP
  - Notification for change in approved matters

- **PMDA & Prefectures**
  - Acceptance of application
  - Acceptance of the pPACMP*
    - * proposed PACMP
  - Acceptance of application
  - Acceptance of notification
  - Application for GMP compliance confirmation
  - Notification for minor change in cPACMP*

- **MHLW**
  - Confirmation of PACMP
  - [Confirmation Letter]
  - Change in Approved Matters
  - Implementation of normal Partial Change Application, Review of the cPACMP

- **Change in Approved Matters**
  - Acceptance of notification
  - Check of the notification

- **Data generation**
  - Application for GMP compliance confirmation

- **Notification for minor change in cPACMP**
  - Notification for minor change in cPACMP*

- **40 working days** (in particular case, 20 working days)

- E.g. in cases where the data generated does not meet the acceptance criteria/other conditions in cPACMP


Number of Consultations:
- PACMP Quality Consultation: 15
- PACMP GMP Consultation: 5

Products:
- Vast majority: therapeutic proteins
- Blood products, Chemicals

Scope:
- Addition of manufacture site with/without Manufacturing process change
- Extension of shelf-life

The number of PMDA Quality Consultation is limited for the time being.

- Share draft PACMP document and schedule b/t PMDA and MAH
- Determine the need for GMP consultation

* Confirm draft PACMP (incl. draft application Form)
* Agree PACMP b/w PMDA and MAH

If PACMP (incl. draft application Form) is changed, a follow-up meeting is used to confirm revised PACMP and agree b/w PMDA with MAH.

<Step 1>
- PACMP Quality Consultation
- PACMP GMP Consultation
- Follow-up meeting (optional)
- Pre-meeting

<Step 2>
- MCN
- PCA GMP inspection application*
- Approval
- PCA: Partial Change Application
- MCN: Minor Change Notification

*: Pre-approval GMP compliance inspection application

PACMP Quality Consultation: 4 mon.
PCA: 3mon. (median)

• Confirm GMP control at mfg. site
• Confirm process validation plan
Lessons learned from the Pilot Program and on-going pre-submission meetings

• Scope of one PACMP

  **ICH Q12**: If the protocol describes several changes for a particular product, a justification should be added showing how the changes are related and that inclusion in a single protocol is appropriate.

• Level of details of proposed changes/proposed acceptance criteria for each test/study at Step 1

  **ICH Q12**: A detailed description of the proposed change(s), including a rationale. The differences before and after the proposed change(s) should be clearly highlighted (e.g., in a tabular format).

• Practical procedures including administrative ones
Major Challenges toward Successful/Harmonized Implementation

- Effective Pharmaceutical Quality System (PQS) incl. Change Management
- Identification of Established Conditions (ECs) and Associated Reporting Categories (RCs)
  - Criticality assessment vs. Risk assessment
  - Risk Tolerance
  - Can PQS maturity reduce the details of ECs?
  - Feasibility of unified ECs/RCs across regions based on current RC systems in all regions
- PACMP
  - Need to accumulate experience for both regulators and the industry
- Product Lifecycle Management (PLCM) document
  - How a tabular format covers all elements of ECs?
Post-Approval CMC Changes in Japan

Where are we heading, in conjunction with ICH M4Q(R2)?
Outline

• Recent trends of Biopharmaceuticals in Japan

• On-going ICH-Quality Topics

• Lessons Learned from COVID-19 Pandemic
## COVID-19 Therapeutics and Vaccines in Japan

<table>
<thead>
<tr>
<th>Chemicals</th>
<th>Nonproprietary Name</th>
<th>Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veklury</td>
<td>Remdesivir</td>
<td>May 7, 2020</td>
</tr>
<tr>
<td>Lagevrio</td>
<td>Molnupiravir</td>
<td>December 24, 2021</td>
</tr>
<tr>
<td>paxlovid</td>
<td>Nirmatrelvir/Ritonavir</td>
<td>February 10, 2022</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Therapeutic proteins (mAbs)</th>
<th>Nonproprietary Name</th>
<th>Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ronapreve</td>
<td>Casirivimab/Imdevimab</td>
<td>July 19, 2021</td>
</tr>
<tr>
<td>Xevudy</td>
<td>Sotrovimab</td>
<td>September 27, 2021</td>
</tr>
<tr>
<td>Evusheld</td>
<td>Tixagevimab/Cilgavimab</td>
<td>August 30, 2022</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vaccines</th>
<th>Nonproprietary Name</th>
<th>Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comirnaty</td>
<td>Tozinameran</td>
<td>Feb 14, 2021</td>
</tr>
<tr>
<td>Spikevax</td>
<td>Elasomeran</td>
<td>May 21, 2021</td>
</tr>
<tr>
<td>Vaxzevria</td>
<td>COVID-19 (SARS-CoV-2) vaccine(recombinant chimpanzee adenovirus vector)</td>
<td>May 21, 2021</td>
</tr>
<tr>
<td>Nuvaxovid</td>
<td>Recombinant coronavirus (SARS-CoV-2) vaccine</td>
<td>April 19, 2022</td>
</tr>
<tr>
<td>Jcovden</td>
<td>COVID-19 (SARS-CoV-2) vaccine(recombinant chimpanzee adenovirus vector)</td>
<td>June 20, 2022</td>
</tr>
</tbody>
</table>

Information about extension of indication and adapted vaccines are not included.
Regulatory Flexibilities for COVID-19 mAbs

- **All products**
  - Early/frequent communication with applicants
  - Rolling review
  - Special Approval for Emergency (SAE)

- **Ronapreve (Casirivimab/Imdevimab)**
  - Number of model virus in viral clearance studies
  - Bioassay of DS/DP specification
  - Acceptance criteria of DS/DP specification
  - Shelf-life of DS/DP

- **Xevudy (Sotrovimab)**
  - Bioassay of DS/DP specification
  - Acceptance criteria of DS/DP specification
  - Storage condition and Shelf-life of DS/DP

- **Evusheld (Tixagevimab/Cilgavimab)**
  - Bioassay of DS/DP specification
  - Acceptance criteria of DS/DP specification
  - DP shelf-life extension of specific lots already released

**Note:** Based only on publicly available information (e.g., Review Reports: Drugs | Pharmaceuticals and Medical Devices Agency (pmda.go.jp) in English/Japanese)
ICMRA (International Coalition of Medicines Regulatory Authorities)

- A voluntary, executive-level, strategic coordinating, advocacy and leadership entity of regulatory authorities that work together to
  - address current and emerging human medicine regulatory and safety challenges globally, strategically and in an on-going, transparent, authoritative and institutional manner
  - provide direction for areas and activities common to many regulatory authorities' missions
  - identify areas for potential synergies
  - wherever possible, leverage existing initiatives/enablers and resources

- Provide a global architecture to support enhanced communication, information sharing, crisis response and address regulatory science issues
ICMRA-Industry Virtual Workshop on Enabling Manufacturing Capacity in the COVID-19 Pandemic (Jul. 7-8, 2021) (1)

- The overall aims were:
  - **enhance Regulators’ understanding of specific challenges** faced by manufacturers seeking to increase manufacturing capacity for COVID-19 therapeutics and vaccines
  - **improve Industry’s awareness of current regulatory approaches** that have been used to enable the rapid increase of manufacturing capacity for the production of COVID-19 therapeutics and vaccines
  - **identify opportunities for further collaboration, alignment, and/or harmonization** to enable more efficient and effective global regulatory response to the current and future public health emergencies

- Video recording, presentation, transcript and workshop report are available at ICMRA website
ICMRA-Industry Virtual Workshop on Enabling Manufacturing Capacity in the COVID-19 Pandemic (Jul. 7-8, 2021) (2)

• the most effective regulatory flexibilities were identified as the following;

<table>
<thead>
<tr>
<th>Regulator Position</th>
<th>Industry Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Use of PACMPs, or similar, to expedite PACs</td>
<td>• Establishment of quick, frequent, and continuous communications/ engagement with regulators</td>
</tr>
<tr>
<td>• Remote inspections</td>
<td>• Specific reliance practices: Full or partial reliance on assessment reports of regulatory authorities from other regions</td>
</tr>
<tr>
<td>• Rolling review</td>
<td>• Process Qualification/Validation Data: leveraging of platform data and prior knowledge, concurrent validation, decoupling DS and DP validation, and/or continuous process verification</td>
</tr>
<tr>
<td>• Expedited timelines to meet public need</td>
<td>• Approval of PACs in the ‘absence of full data’ (with certain data provided at a later date)</td>
</tr>
<tr>
<td>• Labelling flexibilities</td>
<td></td>
</tr>
<tr>
<td>• Conditional marketing authorisation /emergency use authorisation / or similar regulatory mechanism to meet urgent public health need</td>
<td></td>
</tr>
<tr>
<td>• Use of risk-based, post-authorization obligations to collate CMC-data (e.g., what is the most/least critical data required for approval)</td>
<td></td>
</tr>
</tbody>
</table>
ICMRA Statement on Pre-Requisites for Regulatory Flexibility in Pharmaceutical Manufacturing Change Management (Oct. 12, 2021)

ICMRA calls on pharmaceutical companies and manufacturers to continually demonstrate their commitment to quality, including striving for better product and process knowledge, ensuring GMP compliance, and implementing an effective PQS. These collectively enable regulatory authorities to grant suitable flexibilities that can facilitate post-approval change management, enabling industry to expand their manufacturing capacities of essential vaccines and therapeutics to meet critical and global needs created by pandemics like COVID-19.
PQKMS (Pharmaceutical Quality Knowledge Management System)

Pharmaceutical Quality Knowledge Management System (PQKMS) | International Coalition of Medicines Regulatory Authorities (ICMRA)

• ICMRA Statement on Global Pharmaceutical Quality Knowledge Management: Enhancing Regulatory Reliance and Agility (Jun 11, 2021)

Global Pharmaceutical Quality Knowledge Management: Enhancing Regulatory Reliance and Agility | International Coalition of Medicines Regulatory Authorities (ICMRA)

• ICMRA-ICH-PIC/S-IPRP Joint Reflection Paper;
A Regulatory Pharmaceutical Quality Knowledge Management System (PQ KMS) to Enhance the Availability of Quality Medicines (Jul. 21, 2022)

A Regulatory Pharmaceutical Quality Knowledge Management System (PQ KMS) to Enhance the Availability of Quality Medicines | International Coalition of Medicines Regulatory Authorities (ICMRA)
ICMRA Pilot Programs

Pharmaceutical Quality – Regulatory Collaboration Pilots: Call for Industry Applications | International Coalition of Medicines Regulatory Authorities (ICMRA)

• Collaborative Assessment Pilot
• Collaborative Hybrid Inspection Pilot

• Aims;
  • Develop an initial common framework for collaborative assessment and hybrid inspections
  • Deliver a single list of questions to the sponsor or manufacturer wherever possible, and identify any misalignments, differences, and potential areas for alignment or harmonization across participating regulators’ regions
  • Share application sponsors’ or manufacturer responses between the participating quality assessors/inspectors who will work towards a common approach to assessment and decision making
  • **Identify best practices and standards** in the quality assessment of CMC post-approval changes and collaborative hybrid inspections to inform relevant quality assessments
  • Identify the conditions (products/cases) where cross-regional collaboration efforts in the collaborative assessment and hybrid inspection pilots should focus and make recommendations to ICMRA for a future cross-regional pathway(s)
Wisdom

(Explicit) Knowledge

“Ba”

Nonaka & Konno (1998)
Thank you for your attention!

KISHIOKA Yasuhiro
Office of Cellular and Tissue-based Products
Pharmaceuticals and Medical Devices Agency