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独立行政法人 医薬品医療機器総合機構
Pharmaceuticals and Medical Devices Agency

Current regulation on CMC of 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.

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Outline

1. Biosimilars in Japan
   - Approved Biosimilars
   - Regulatory Updates in Japan

2. CMC Consideration for New Modalities
   - ADC
   - Bispecific Antibodies

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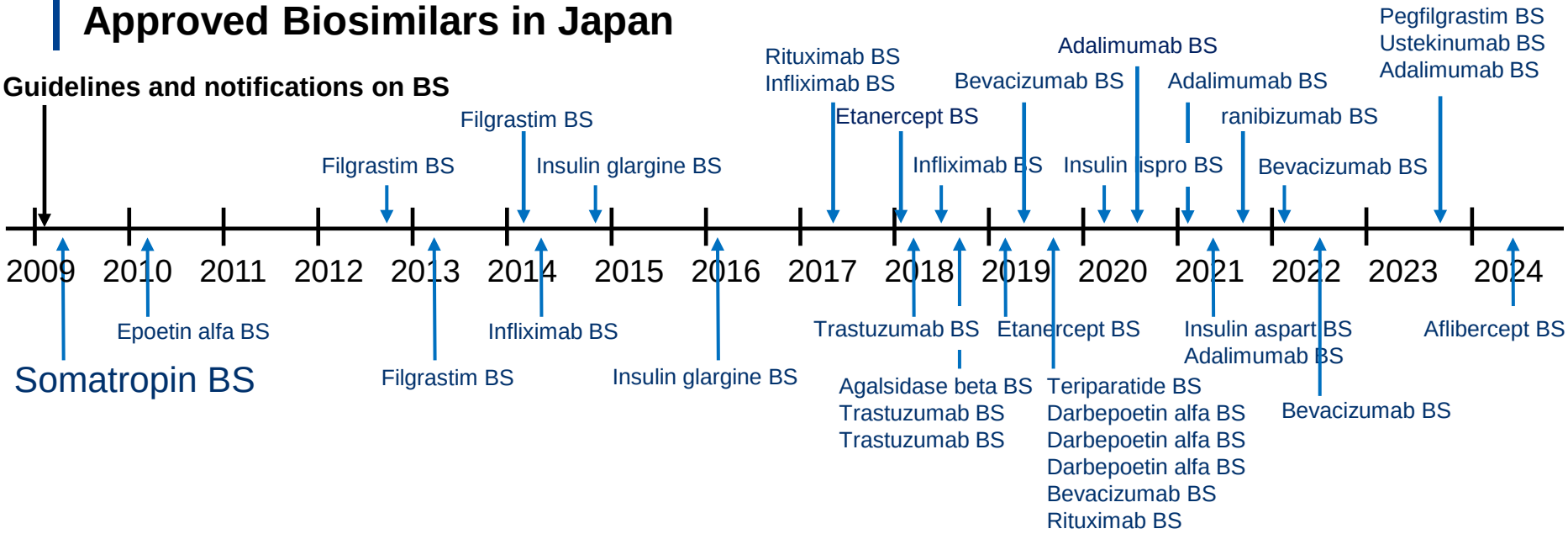
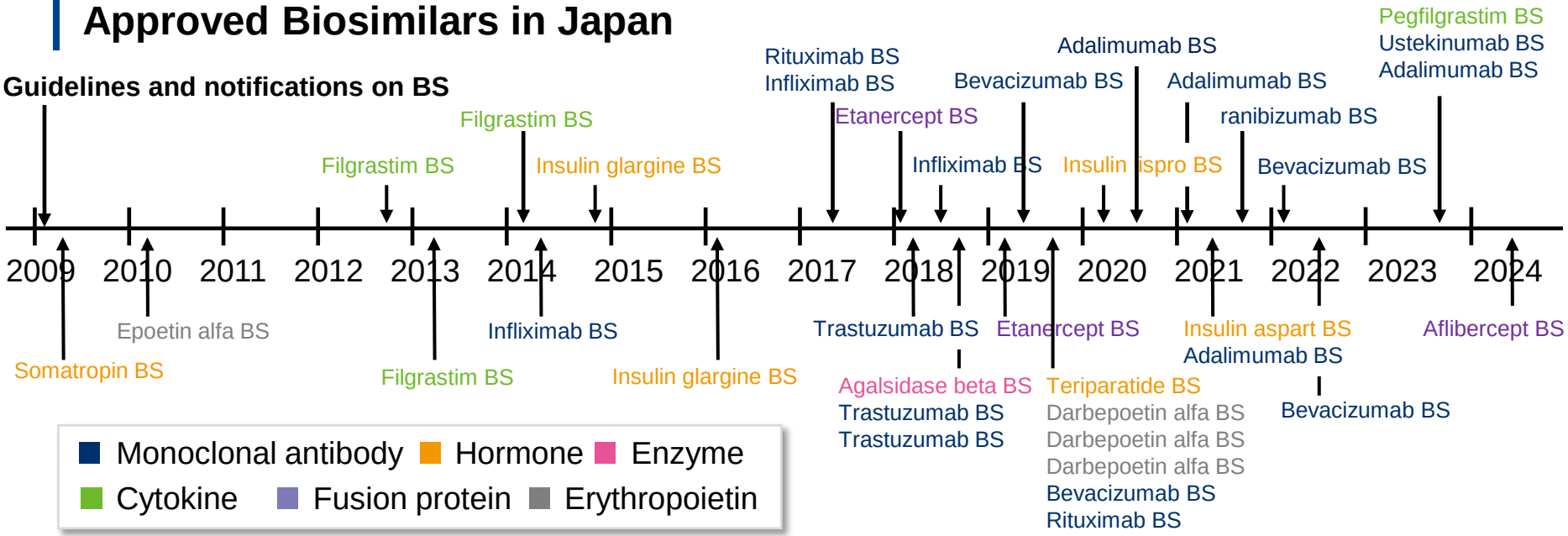
Approved Biosimilars in Japan



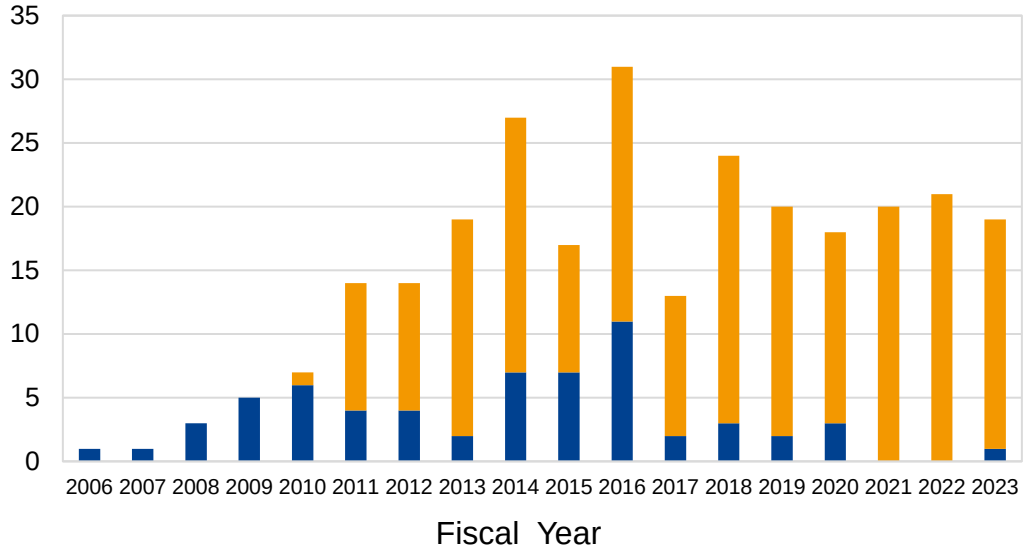
- The first approval of a biosimilar product in Japan was somatropin BS subcutaneous injection [Sandoz] in 2009.
- 36 biosimilar products were approved during the period 2009–2023.06.

Approved Biosimilars in Japan



- There are six types of biosimilars, namely mAb, hormone, erythropoietin, cytokine, fusion protein, and enzyme.
- In recent years, antibodies make up more than half of newly developed biosimilars.

Number of Consultation for Biosimilars



>250: Consultations
>75%: mAbs/Fusion proteins

- More than 250 consultations had been implemented by 2022.
- Interest in biosimilar development continued to remain high, and several biosimilars have been under review in Japan.

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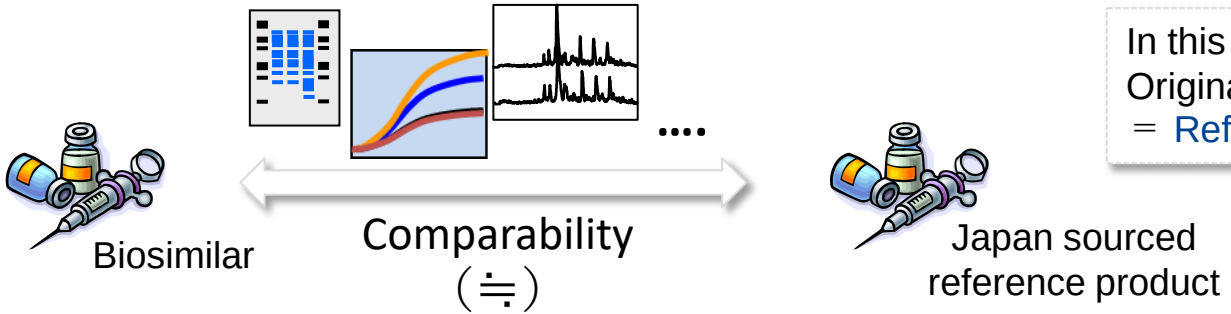
General Principles in the Development of Biosimilars (1)

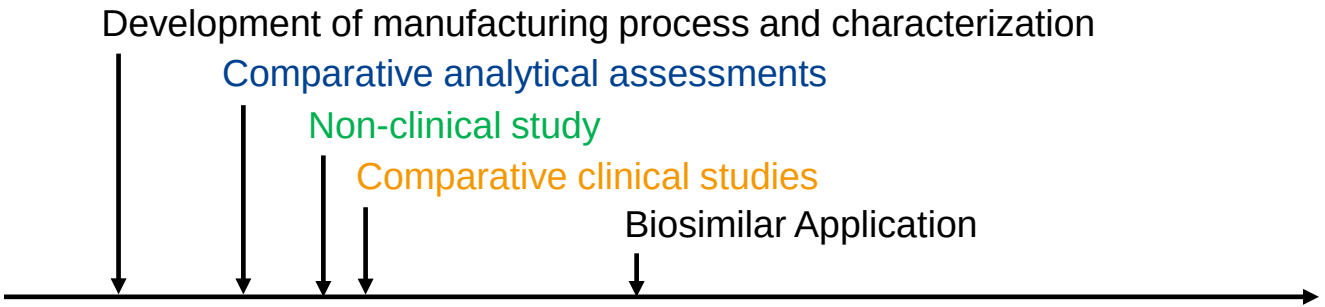


In this slide,
Original biopharmaceutical
＝ Reference product, or RP

- A biosimilar is a product comparable with regard to quality, safety, and efficacy to a original biopharmaceutical (a biotechnology-derived product already approved in Japan as a pharmaceutical with new active ingredients, which is developed by a different company).
- In the development of biosimilar products, “comparability” means that the quality attributes of a biosimilar are highly similar to those of its reference product and it can be scientifically justified that any differences in the quality attributes have no adverse impact on clinical safety or efficacy based on non-clinical and clinical trial results.

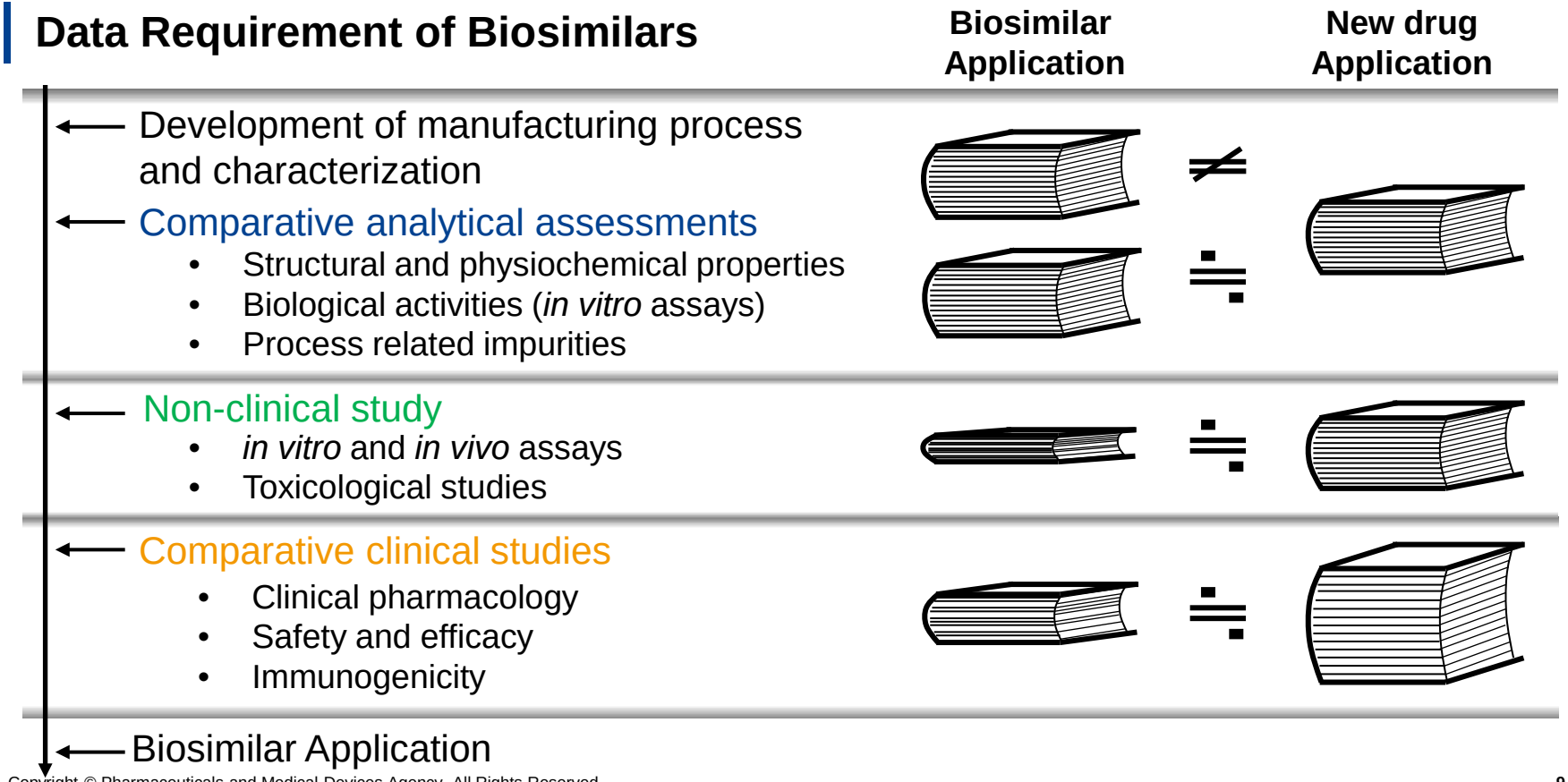
General Principles in the Development of Biosimilars (2)

Development flow of biosimilars



- The sponsor should demonstrate the comparability of the proposed product with its reference product through quality, non-clinical and clinical comparisons.
- The extent and necessity of non-clinical and clinical study data required for the demonstration of comparability will differ depending on the extent to which similarity of the biosimilar with its reference product has been demonstrated by a scientific and rational evaluation of the quality attributes in the comparative analytical assessment.

Data Requirement of Biosimilars



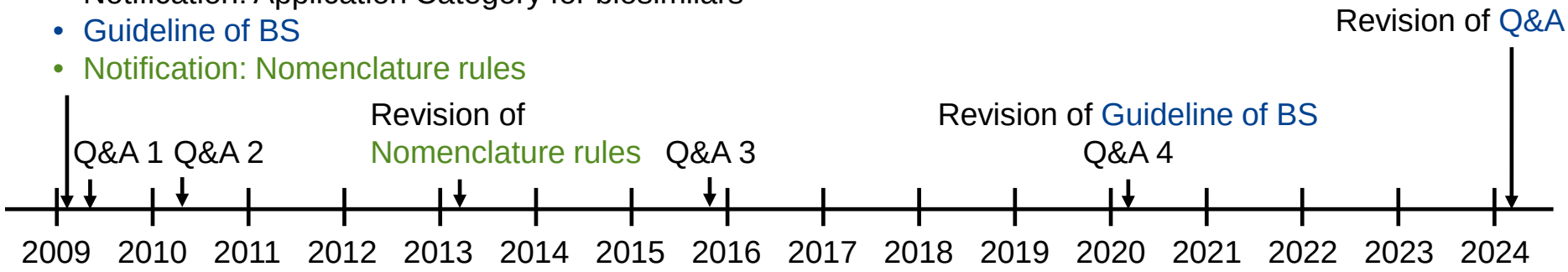
Guideline for Biosimilars in Japan

- Guideline for Ensuring Quality, Safety, and Efficacy of Biosimilars
  (*PSEHD/PED Notification No. 0204-1 / February 2020*)
- Questions & Answers regarding Guideline
  (*PSB/PED Administrative Notice / January 2024*)

- The guidelines and QA address the points to be considered during the development of biosimilars and clarify the data that should be submitted in biosimilar applications.
- The Q&A was revised in January 2024.

Guideline and Notifications for Biosimilars in Japan

- Notification: Application Category for biosimilars
- Guideline of BS
- Notification: Nomenclature rules



- Marketing Approval for Biosimilars
  (*PFSB Notification 0304004 / March 4, 2009*)
- Guideline for Ensuring Quality, Safety, and Efficacy of Biosimilars
  (*PSEHD/PED Notification No. 0204-1 / February 4, 2020*)
- Nonproprietary Name and Drug Name of Biosimilars
  (*PFSB/ELD Notification No. 0214-1, Administrative Notice / February 14, 2013*)

Revision of Guideline QA

<Q10> (partially revised)
Is it acceptable to use data from clinical trials conducted in non-Japanese subjects that confirm the equivalence of PK and efficacy (including PD) with original biopharmaceuticals for approval application?

<A10>
Clinical trials of biosimilars are intended to confirm the equivalence of PK and efficacy (including PD) to original biopharmaceuticals. Therefore, **if the ethnic factors of subjects do not affect the study results, data from clinical trials conducted overseas in non-Japanese subjects may be used, and it is acceptable not to conduct a clinical trial that includes Japanese subjects.**
If the sponsors conduct global clinical trials with Japanese subjects and the ethnic factors of subjects are considered to affect the study results, Method 1 and Method 2 as indicated in the "Basic Principles on Global Clinical Trials" (Notification No. 0928010 dated September 28, 2007, issued by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare) cannot be directly applied to the number of Japanese. However, the plan should be such that it can be explained that there is no discrepancy between the results of the Japanese population and those of the overall population with reference to the above notification.

Revision of Guideline QA

<Q11> (partially revised)
In Q&A10, it stated that if the ethnic factors of subjects are not expected to affect the clinical trial results, how do you evaluate this?

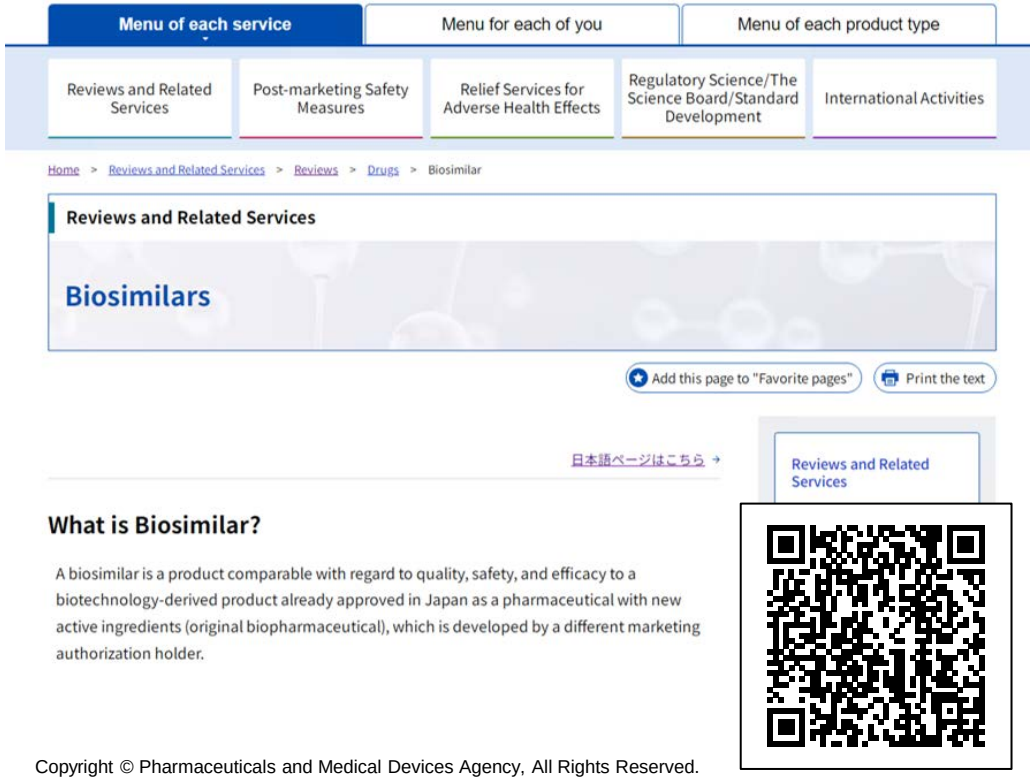
<A11>
For example, it is possible to identify ethnic factors and their impact based on the original biopharmaceuticals and to confirm the results of Japanese subgroup analysis of clinical trials from currently available evidence of original biopharmaceuticals.
Additionally, if some differences of quality attribute between a biosimilar and the original biopharmaceutical was observed, it is important to evaluate ethnic factors and their impact focusing on the differences.

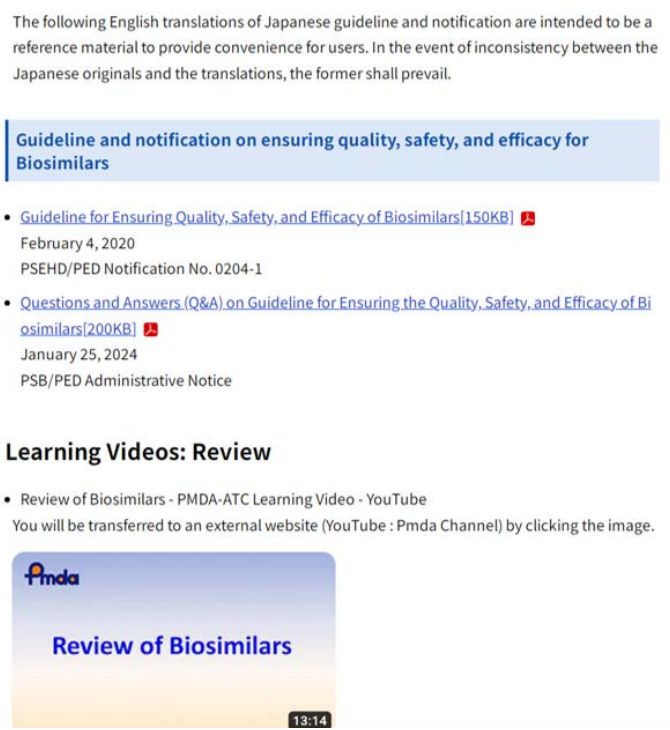
Revision of Guideline QA

- Previously the sponsors must conduct the clinical trial with Japanese subjects, but now if the ethnic factors of subjects do not affect the study results, data from clinical trials conducted overseas in non-Japanese subjects may be used, and it is acceptable not to conduct a clinical trial that includes Japanese subjects.

- If Japanese subjects are not included, it is recommended to consult with PMDA.

Introduction of Website





https://www.pmda.go.jp/english/review-services/reviews/0005.html

Recent Publication

- Kuribayashi R, Goto K, Hariu A, Kishioka Y. Revisions to the Requirement of the Japanese Clinical Study Data for Biosimilar Developments in Japan. Expert Opinion on Biological Therapy. 2024; 24(7): 637-645.
  https://doi.org/10.1080/14712598.2024.2377300
- Kuribayashi R, Hariu A, Nakano A, Kishioka Y. Survey of Data Package and Sample Size of Comparative Clinical Studies for Biosimilar Developments from PMDA Assessments. Pharmaceut Med. 2024; 38: 225-239.
  https://doi.org/10.1007/s40290-024-00525-y
- Kuribayashi R, Nakano A, Hariu A, Kishioka Y, Honda F. Historical Overview of Regulatory Approvals and PMDA Assessments for Biosimilar Products in Japan During 2009-2022. BioDrugs. 2023; 37(4): 443-451.
  https://doi.org/10.1007/s40259-023-00605-6

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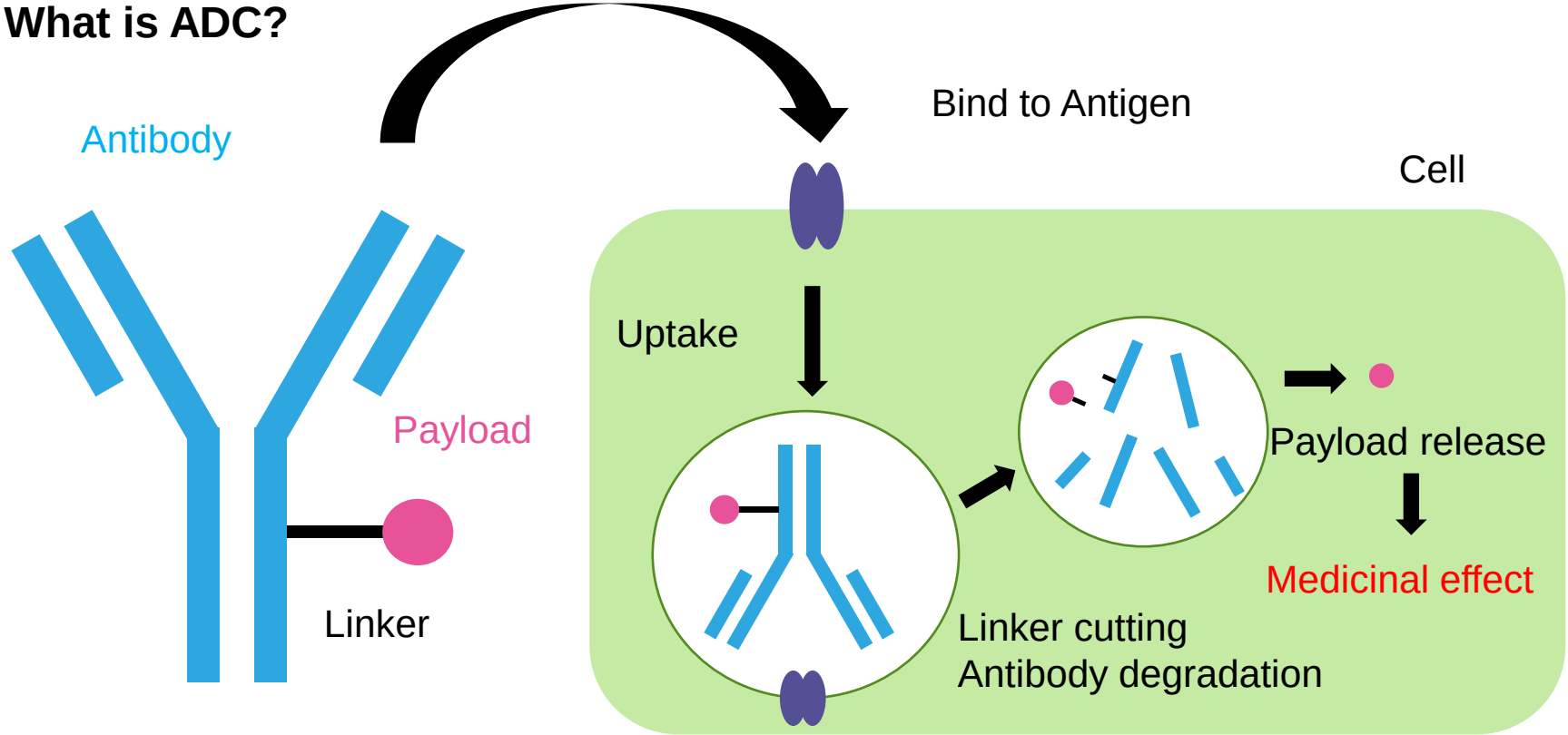
What is ADC?



Advantage of ADCs

Conventional chemotherapy

- Due to safety concerns, the dose cannot increase and the therapeutic area is narrow.

ADC

- ADC can directly deliver the cytotoxic small molecule drug to target cells or tissues , and are expected to have high therapeutic effects and a wide therapeutic range.

ADCs Approved in Japan

Brand Name	INN	Approval Dates
Mylotarg	Gemtuzumab Ozogamicin	2005/7/25
ZEVALIN yttrium	Ibritumomab tiuxetan	2008/1/25
ZEVALIN indium	Ibritumomab tiuxetan	2008/1/25
Kadcyla	Trastuzumab Emtansine	2013/9/20
Adcetris	Brentuximab vedotin	2014/1/17
Besponsa	Inotuzumab ozogamicin	2018/1/19
Enhertu	Trastuzumab deruxtecan	2020/3/25
Akalux	Cetuximab sarotalocan sodium	2020/9/25
Polivy	Polatuzumab vedotin	2021/3/23
Padcev	Enfortumab vedotin	2021/9/27

- All are anticancer pharmaceuticals

Antibodies and Payloads of ADCs Approved in Japan

Brand Name	INN	Target of Antibodies	Payloads
Mylotarg	Gemtuzumab Ozogamicin	CD33	*N*-acetyl calicheamicin
ZEVALIN yttrium	Ibritumomab tiuxetan	CD20	MX-DTPA
ZEVALIN indium	Ibritumomab tiuxetan	CD20	MX-DTPA
Kadcyla	Trastuzumab Emtansine	HER2	Maytansine
Adcetris	Brentuximab vedotin	CD30	MMAE
Besponsa	Inotuzumab ozogamicin	CD22	*N*-acetyl calicheamicin
Enhertu	Trastuzumab deruxtecan	HER2	Derivative of exatecan
Akalux	Cetuximab sarotalocan sodium	EGFR	Derivative of phthalocyanin
Polivy	Polatuzumab vedotin	CD79b	MMAE
Padcev	Enfortumab vedotin	nectin4	MMAE

N-acetyl calicheamicin: DNA cutting effect, Maytansine and MMAE: Microtubule inhibition effect
Exatecan: Topoisomerase inhibition effect, Phthalocyanin: Photochemical reaction caused by laser light irradiation

Current Status of Guidelines in the Development of ADC

- There are no specific guidelines for ADC in Japan.

- For non-clinical development, refer the following two guidelines:
  - Nonclinical evaluation for anticancer pharmaceuticals（ICH S9、ICH S9 Q&A）
  - Preclinical safety evaluation of biotechnology-derived pharmaceuticals （ICH S6（R1））

Current Status of Guidelines in the Development of ADC

➢ For quality, refer the following guidelines:

- Stability testing（ICH Q1A（R2）～ICH Q1E）
- Impurities（ICH Q3A（R2）～ICH Q3D（R2））
- Test procedures and acceptance criteria（ICH Q6A）
- Quality of biotechnological products（ICH Q5A (R1)～ICH Q5E、ICH Q6B）
- Guidance for quality evaluation of antibodies (PFSB/ELD Notification No. 1214-1 / December 14, 2012)

Guidance for Quality Evaluation of Antibodies

Antibodies

- Chimeric antibodies, humanized antibodies, human antibodies・・・
- Subclass（IgG1～4）
- Presence or absence of effector functions such as ADCC activity

Linkers

- Cutting linkers, non-cutting linkers

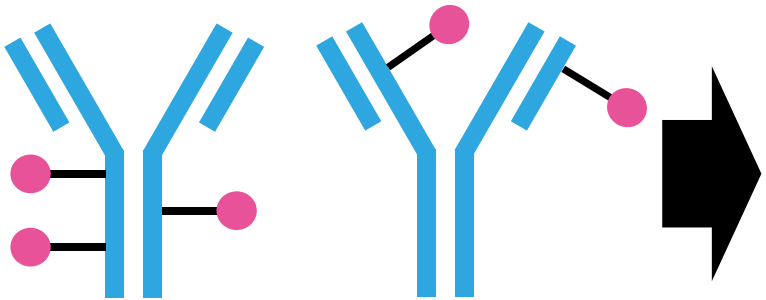
Payloads

- DNA inhibition effect、microtubule inhibition effect ・・・

Binding of Antibodies and Payloads

- In the case of using free cysteine residues generated by dissociating disulfide bonds between antibody molecules with a reducing agents

Heterogeneity of binding numbers and binding sites



Managing heterogeneity is important

Affects;

- Pharmacological effects
- Conformational structure of antibodies
- Antigen binding activity
- Effector functions such as ADCC activity etc

Binding of Antibodies and Payloads

➢ In the case of using lysine residues of antibodies

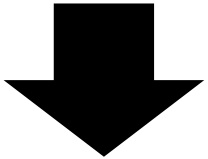
- It is possible that payloads bind to CDR surrounding sequences involved in antigen binding, Fcγ receptors involved in effector functions, and complement C1q binding sites.
- A complex mixture is formed when the payload binds to the many lysine residues in antibody.

➢ In the case of using free cysteine residues generated by dissociating disulfide bonds between antibody molecules under reducing conditions.

- It may affect the conformational structure of antibodies.
- Compared to the case of using lysine residues of antibodies, the number of free cysteine residues is small, and the binding numbers and binding sites can be easily managed.

Managing Heterogeneity

- It is important to develop a manufacturing process that can consistently produce homogeneous ADCs.
- Manufacturing conditions to consider;
  - Antibody to reducing agent ratio, pH of reduction reaction, temperature and time
  - Drug to antibody ratio (DAR), temperature and time of binding reaction



DAR, binding sites,
effect on biological activity, etc.

Identifying critical manufacturing conditions

Managing Heterogeneity

- It is important to understand the properties of ADCs.

- Examples of evaluation items for quality attribute analysis, specifications and test procedures.

- DAR
- Binding sites of payload
- Amount of antibody with no payload bound
- Amount of payload not bound to antibody
- Antigen binding activity
- Cytotoxicity assay, etc

ADC Evaluation Methods

➢ DAR
- UV/visible spectrophotometry
- Hydrophobic interaction chromatography, etc

➢ Binding sites of payload
- Peptide map, etc

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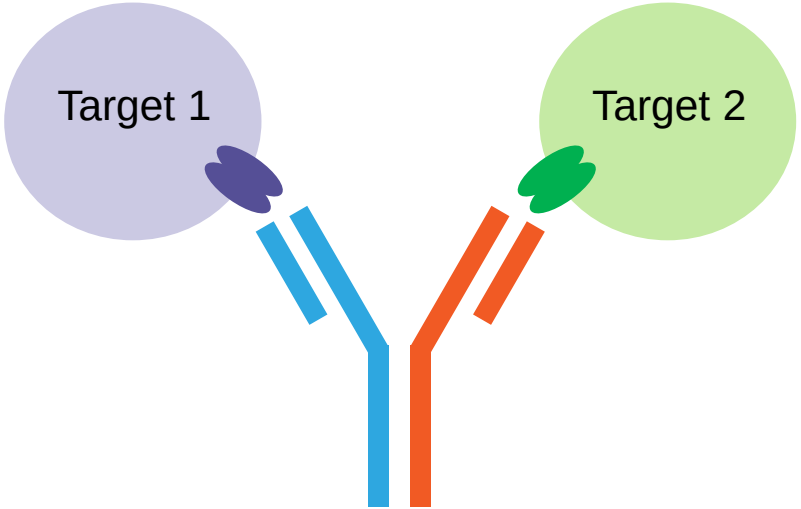
What is Bispecific Antibodies(BsAbs)?

- BsAbs bind two different epitopes.
- Dual specificity for antigens enables novel mechanisms of action.

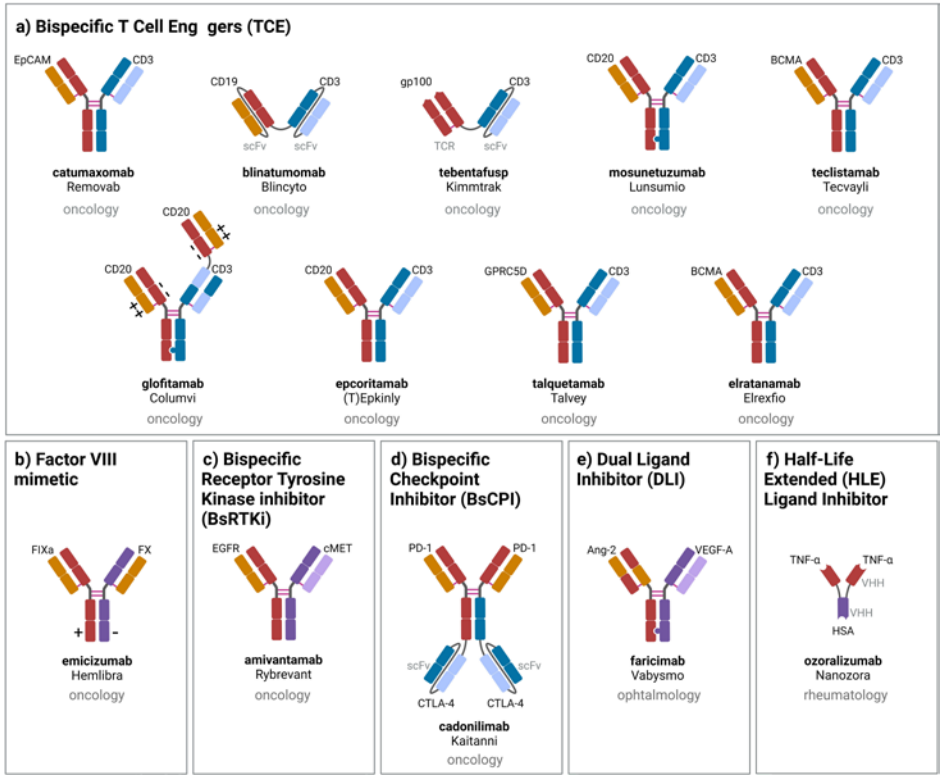
- For manufacturing heterodimeric molecules, correct assembly of the two different heavy chains is important.
  - knobs-into-hole technology
  - Fab-arm exchange



The MOAs of BsAbs

- The variety of BsAbs derived from antibody formats and the targets.

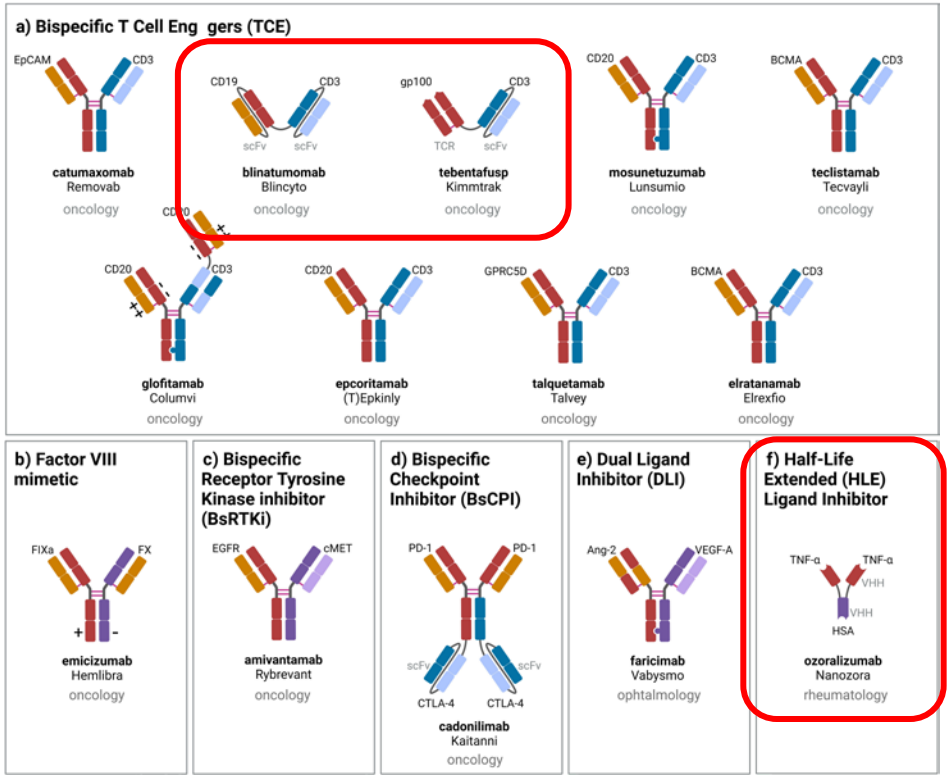
- T cell engagement
- factor VIII mimetic, dual signaling inhibition
- bispecific receptor tyrosine kinase inhibitor
- bispecific checkpoint inhibitor
- dual ligand inhibitor
- half-life extended ligand inhibitor



From Mabs. 2024;16(1):2321635

The MOAs of BsAbs

- The variety of BsAbs derived from antibody formats and the targets.
- In addition to BsAbs with Fc region, there are BsAbs fragments with no Fc region.
- These BsAbs fragments will lack Fc-mediated effector functions.



From Mabs. 2024;16(1):2321635

BsAbs Approved in Japan

Brand Name	INN	Approval Dates	Target
Hemlibra	Emisizumab	2018/3/23	F.IXa/anti-F.X
Blincyte	Brinatumomab	2018/9/21	CD19/CD3
Vabysmo	Fariscimab	2022/3/28	VEGF-A/Ang2
Nanozora	Ozolarizumab	2022/9/26	TNFα/albumin
Epkinly	Epcoritamab	2023/9/25	CD20/CD3
Elrexfio	Elranatamab	2024/3/26	BCMA/CD3

- In recent years, the approval of BsAb is increasing.

Current Status of Guidelines in the Development of BsAbs

- There are no specific guidelines for BsAbs in Japan.

- For non-clinical development, refer the following two guidelines:
  - Nonclinical evaluation for anticancer pharmaceuticals（ICH S9、ICH S9 Q&A）
  - Preclinical safety evaluation of biotechnology-derived pharmaceuticals （ICH S6（R1））

Current Status of Guidelines in the Development of BsAbs

➢ For quality, refer the following guidelines:

- Stability testing（ICH Q1A（R2）～ICH Q1E）
- Quality of biotechnological products（ICH Q5A (R1)～ICH Q5E、ICH Q6B）
- Guidance for quality evaluation of antibodies (PFSB/ELD Notification No. 1214-1 / December 14, 2012)

Guidance for Quality Evaluation of BsAbs

- Some BsAbs are manufactured from the assembly of two antibodies.
- For manufacturing heterodimeric molecules, correct assembly of the two different antibodies is important.
  - knobs-into-hole technology
  - Fab-arm exchange

Guidance for Quality Evaluation of BsAbs

Unique Impurities of BsAb

- Each different antibody used as an intermediate
- Homodimer

Control strategy

- In the case of using 2 antibodies,
  - It is important to consider which steps are included in viral clearance studies
  - It is possible to control the impurities such as each different antibody in appropriate step.

Summary

Biosimilars in Japan

- 36 biosimilar products were approved in Japan.
- Guideline for Biosimilars in Japan
  - Guideline for Ensuring Quality, Safety, and Efficacy of Biosimilars
  - Questions & Answers regarding Guideline
- The Q&A was revised in January 2024.

CMC Consideration for New Modalities

- There are no specific guidelines for ADCs and BsAbs in Japan.
- Guidance for Quality Evaluation
  - ADC : Antibody, Linker, Payload, Heterogeneity・・・
  - BsAbs : Unique impurities, Viral clearance study・・・

Thank you for your kind attention.

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Reviewer
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