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# Current Regulation on Biosimilar in Japan

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# Agenda



- Biosimilar in Japan
  - ➢ Approved biosimilar products
  - ➢ Consultation for biosimilar
- Regulation on Biosimilar in Japan
  - ➢ Guideline and QA on biosimilar
  - ➢ Revision of guideline and QA
- Future Challenge
  - ➢ Necessity of Comparative Efficacy Study



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# Definition of Biosimilar in Japan



## From Guideline

A biosimilar is a product comparable with regard to quality, safety, and efficacy to a biotechnology-derived product already approved in Japan as a pharmaceutical with new active ingredients (original biopharmaceutical), which is developed by a different marketing authorization holder.

This guideline covers recombinant proteins (including unmodified simple protein and glycoprotein), recombinant peptides, their derivatives, and products of which they are components (e.g., polyethylene glycol-conjugated proteins and antibody-drug conjugates). These proteins and peptides are produced from recombinant expression systems using microorganisms or animal cells and can be highly purified and well characterized using an appropriate set of analytical procedures.

Guideline for Ensuring Quality, Safety, and Efficacy of Biosimilars
(PSEHD/PED Notification No.0204-1, February 4, 2020)



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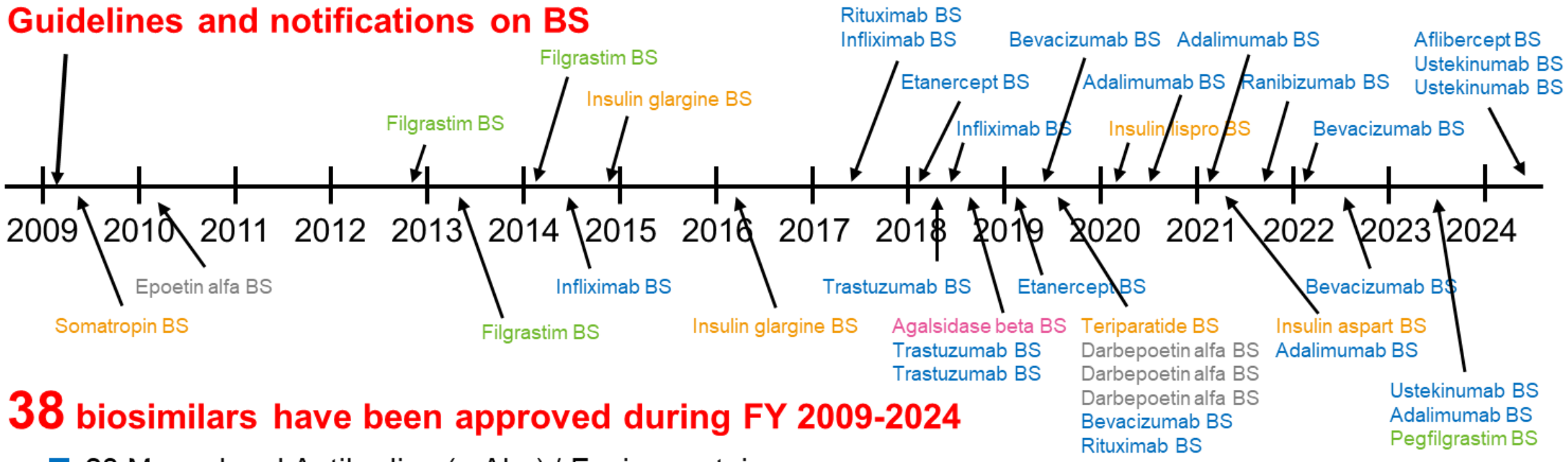
# Approved Biosimilar Products in Japan






**38 biosimilars have been approved during FY 2009-2024**

- 23 Monoclonal Antibodies (mAbs) / Fusion proteins
- 6 Hormones
- 4 Erythropoietins
- 4 Cytokines
- 1 Enzyme

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# Consultation for biosimilar in Japan



- Quality

  Strategies of comparative studies of quality attributes
  Results of comparative studies of quality attributes

- Safety

  Strategies of nonclinical studies

- Clinical

  Strategies of clinical studies (PK/PD, Efficacy)



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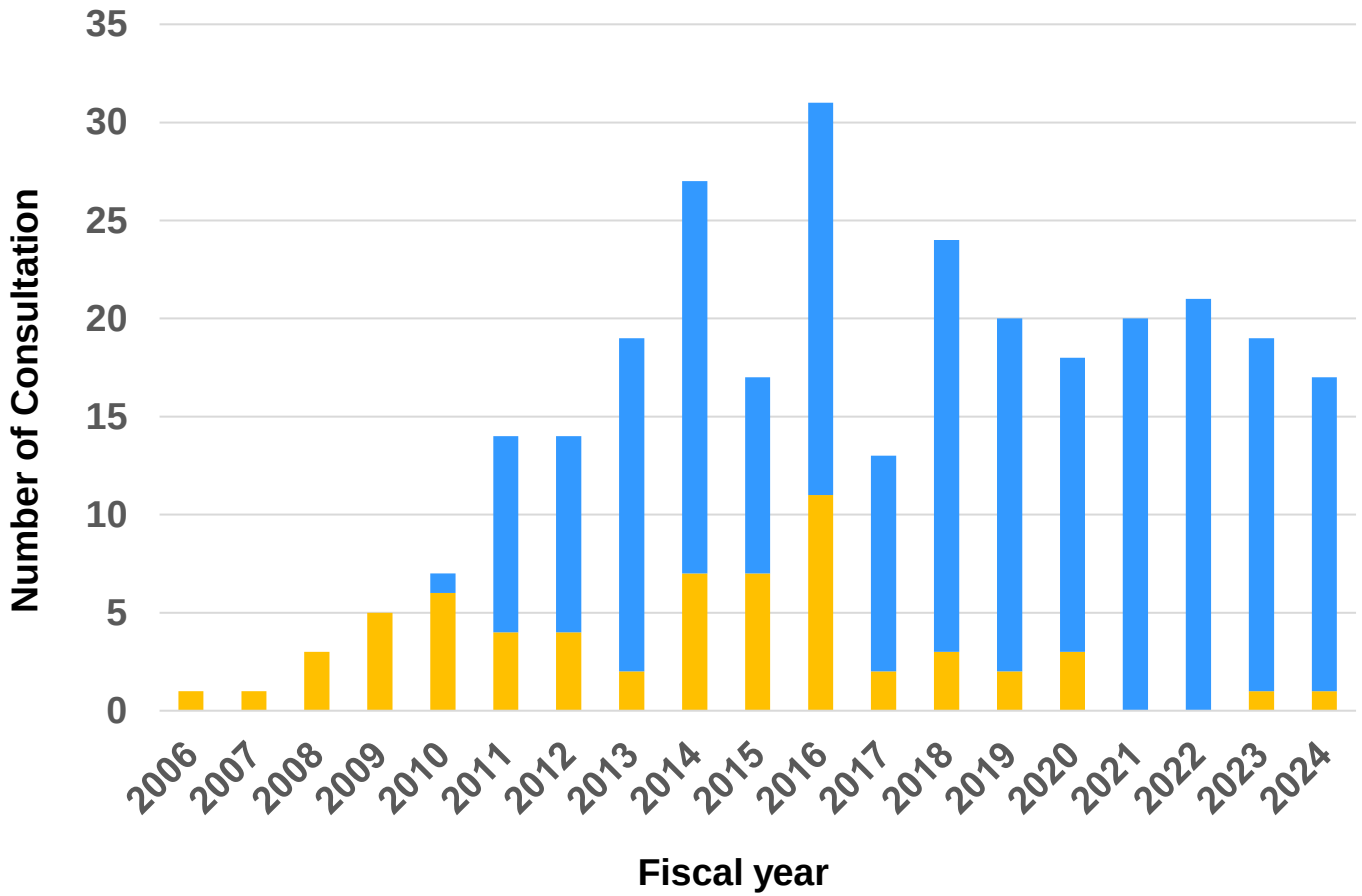
# Consultation for biosimilar in Japan






: mAbs/Fusion proteins

: Others

**>250**: Consultations

**>75%**: mAbs/Fusion proteins

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# Sales of Biologics



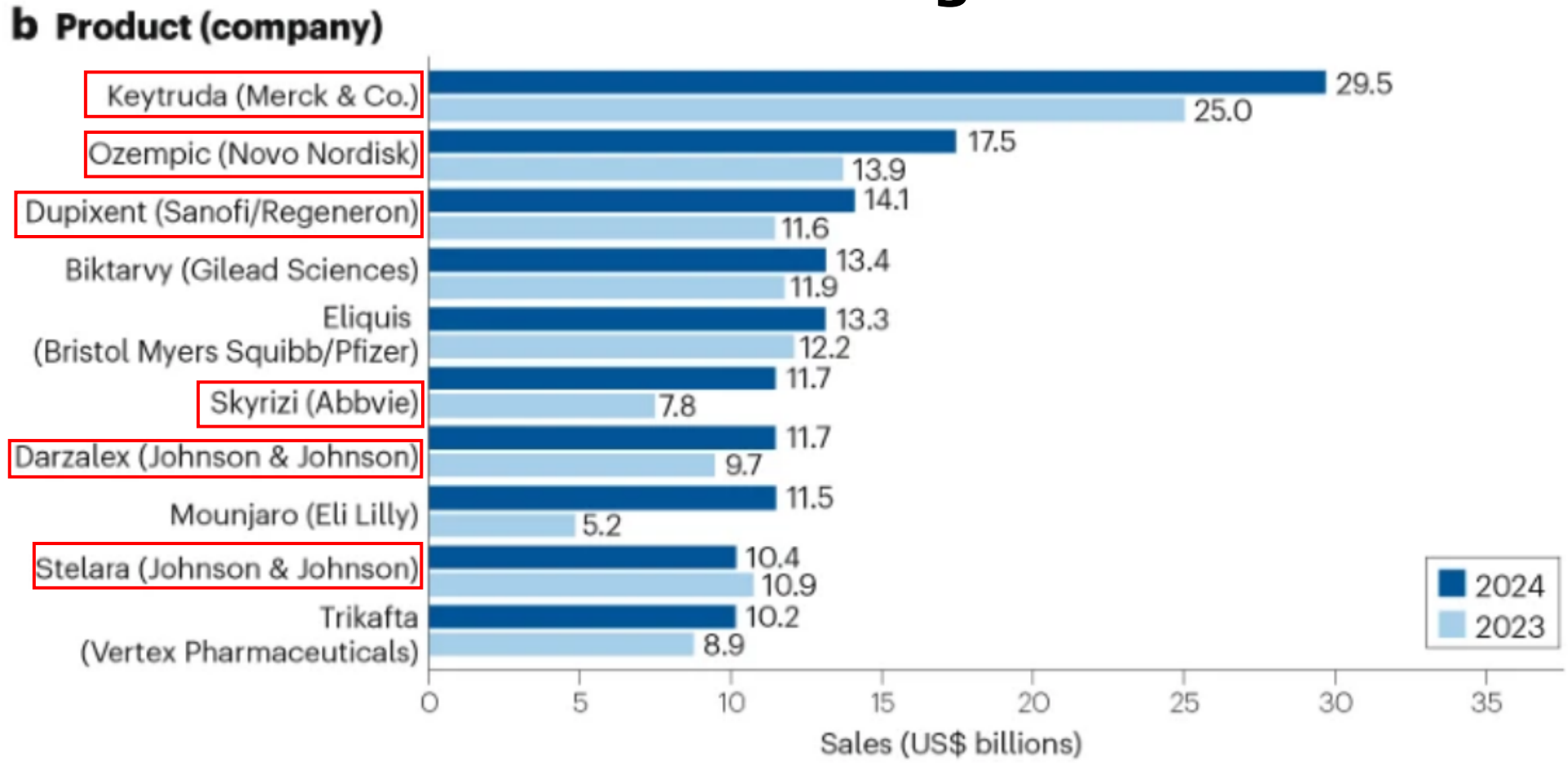


**Fig. 1** | Top companies and drugs by sales in 2024. **a**, Top ten companies by sales of prescription drugs. **b**, Top ten drugs by sales globally. Source: Evaluate Pharma.

doi: https://doi.org/10.1038/d41573-025-00049-3
https://www.nature.com/articles/d41573-025-00049-3



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# Number of Approved Biosimilars



| | Number | Refer from |
|---|---|---|
| FDA | 67 | https://www.fda.gov/drugs/biosimilars/biosimilar-product-information<br>Searched at March 7th. |
| EMA | 101 | https://www.ema.europa.eu/en/search?f%5B0%5D=ema_med_status%3A100108&f%5B1%5D=ema_med_status%3Aauthorised&f%5B2%5D=ema_medicine_bundle%3Aema_medicine&f%5B3%5D=ema_medicine_type_fields%3Afield_ema_biosimilar&f%5B4%5D=ema_search_categories%3A83&f%5B5%5D=ema_search_first_published%3A%28min%3A%2Cmax%3A%29&landing_from=73303<br>Searched at March 7th. |

There could be several reasons why the number of approved biosimilars in Japan is fewer than in US and EU.

- ✓ Market Size
- ✓ Patents
- ✓ Regulation
- ✓ ・・・



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# Guideline and QA on Biosimilar



- Marketing Approval Application for Biosimilars
  (*PFSB Notification 0304004 / March 4, 2009*)

- Nonproprietary Name and Drug Name of Biosimilars
  (*PFSB/ELD Notification No. 0214-1, Administrative Notice / February 14, 2013*)

- Guideline for Ensuring Quality, Safety, and Efficacy of Biosimilars
  (*PSEHD/PED Notification No. 0204-1 / February 4, 2020*)

- Questions & Answers on Guideline
  (*PSB/PED Administrative Notice / January 25, 2024*)

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



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# Revision of QA on Guideline



Question & Answer on Guideline (before the revision)

Q. If you have a basic idea about the acquisition of clinical data on Japanese, please indicate it.

A. At least either the clinical trial to verify PK equivalence with original biopharmaceuticals or the clinical trial to verify efficacy (including PD) equivalence with the original biopharmaceuticals must be realized with the clinical trial with Japanese subjects. …

| | |
|---|---|
| PK study | Non-Japanese subject |
| Efficacy study | |

⇩

Not acceptable

| | |
|---|---|
| PK study | Japanese subject |
| Efficacy study | Non-Japanese subject |

⇩

Acceptable

| | |
|---|---|
| PK study | Non-Japanese subject |
| Efficacy study | Non-Japanese and Japanese subject |

⇩

Acceptable



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# Revision of QA on Guideline



Question & Answer on Guideline (after the revision)

Q. 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?

A. … 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. …

| | |
|---|---|
| PK study | Non-Japanese subject |
| Efficacy study | |

⇩

Acceptable

| | |
|---|---|
| PK study | Japanese subject |
| Efficacy study | Non-Japanese subject |

⇩

Acceptable

| | |
|---|---|
| PK study | Non-Japanese subject |
| Efficacy study | Non-Japanese and Japanese subject |

⇩

Acceptable



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# Revision of QA on Guideline



Question & Answer on Guideline (after the revision)

Q. 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?

A. 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.

In a clinical consultation, we can discuss about a clinical data package without Japanese subject.

We have received 8 consultations about a clinical data package without Japanese subject.



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# Brief Summary



- PMDA have revised the guideline and QA on biosimilars to encourage biosimilar development in Japan.
- In the recent revision, we changed the way of thinking about Japanese subject enrollment.
- We recommend sponsors to apply a consultation to discuss about a clinical data package without Japanese subject.



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# Differences between Generic drugs and Biosimilars



| | Generic Drugs | Biosimilars |
|---|---|---|
| Quality | Dissolution studies | Comparability assessment |
| Clinical | PK BE studies | PK studies<br>Efficacy studies |

Because of efficacy studies, biosimilars development takes much more cost and time than generic drugs development.



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# Reevaluating the need of comparative efficacy study



BioDrugs
https://doi.org/10.1007/s40259-023-00631-4

ORIGINAL RESEARCH ARTICLE

## Do the Outcomes of Clinical Efficacy Trials Matter in Regulatory Decision-Making for Biosimilars?

Nadine Kirsch-Stefan[1] · Elena Guillen[2] · Niklas Ekman[3,7,8] · Sean Barry[4,8] · Verena Knippel[1] · Sheila Killalea[4,9] · Martina Weise[5,7,10] · Elena Wolff-Holz[6]

Accepted: 27 September 2023
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BioDrugs. 2023; 37(6): 855-871.

ARTICLE

## A Data Driven Approach to Support Tailored Clinical Programs for Biosimilar Monoclonal Antibodies

Elena Guillen[1,2,*], Niklas Ekman[3], Sean Barry[4], Martina Weise[5] and Elena Wolff-Holz[6]

Clin Pharmacol Ther. 2023; 113(1): 108-123. https://doi.org/10.1002/cpt.2785



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# Reevaluating the need for comparative efficacy study



IPRP hosted a workshop, “Increasing the Efficiency of Biosimilar Development Programs — Reevaluating the Need for Comparative Clinical Efficacy Studies”, in September 2023.

IPRP (International Pharmaceutical Regulators Programme)
https://www.iprp.global/page/biosimilar-activities

Throughout this workshop, stakeholders identified opportunities to streamline the use of CESs for biosimilar development. Both regulators and industry experts recognized the limitations of these studies. They broadly agreed that CES are not sensitive enough to detect anything but very large analytical differences between proposed biosimilars and RPs, and a very large analytical difference would likely cause a proposed biosimilar to not be able to meet the “highly similar” standard based on analytics alone.

…

From the regulatory perspective, the stepwise approach calls for understanding what uncertainty needs to be resolved based on analytical differences, and it is difficult to make this assessment early in development, when there may only be small scale production lots of the proposed product available. As a result, regulators may not be comfortable providing definitive recommendations on whether a CES is needed or not because of the limited data available early in development.



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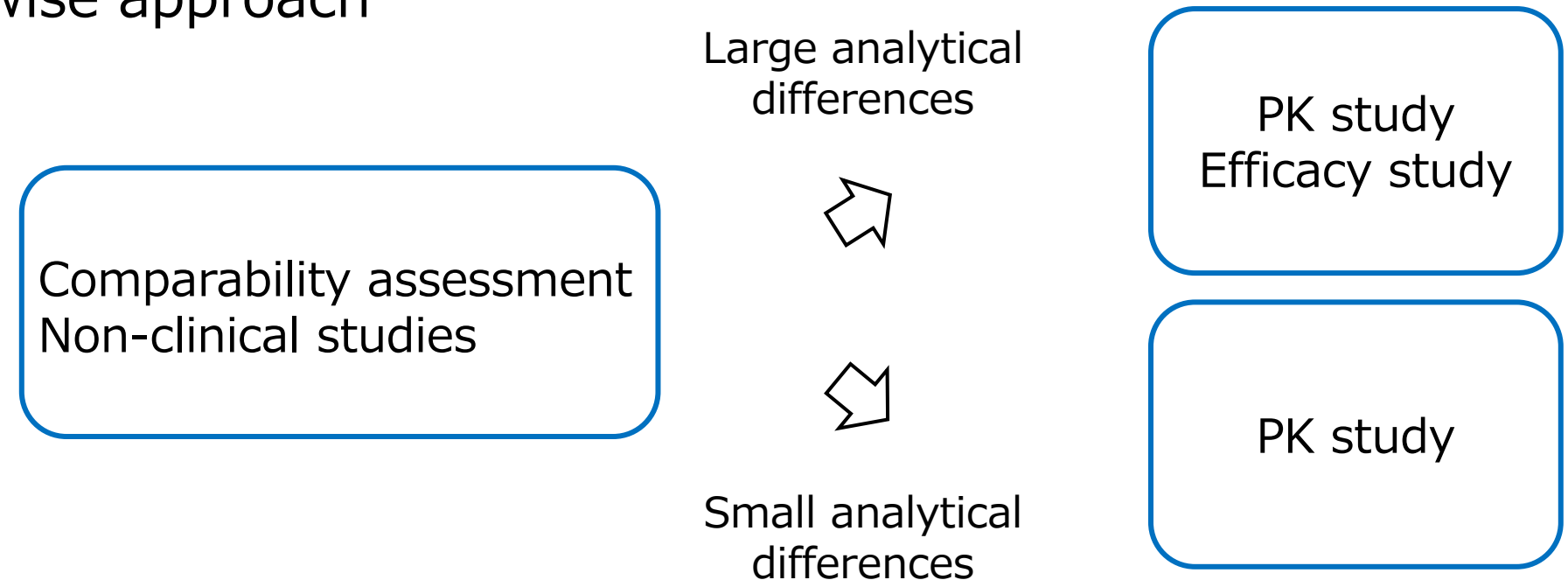
# Reevaluating the need for comparative efficacy study



Stepwise approach




The timing is a key challenge.
Basically, sponsors plan efficacy studies early in developments.



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# Summary



- PMDA have revised the guideline and QA on biosimilars to encourage biosimilar development in Japan.
- The need for clinical efficacy studies have been reevaluating .
- The reevaluating have to be done globally, and a framework for streamlining biosimilar development should be harmonized.
- MHLW has set a goal to promote biosimilars in Japan.
  Increase the rate of APIs, of which biosimilars market share exceeds 80%, to 60% by the end of 2029.

MHLW (Ministry of Health, Labour and Welfare)
https://www.mhlw.go.jp/content/12401000/001309914.pdf (In Japanese)



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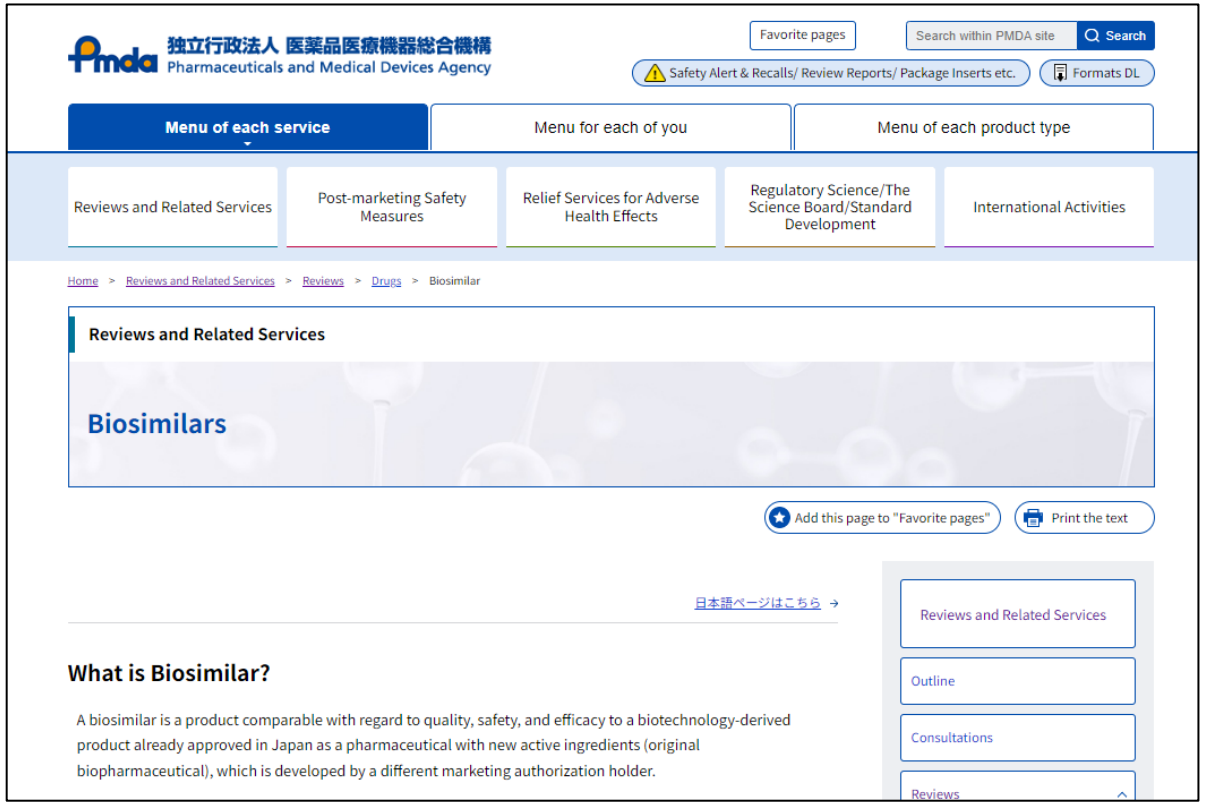
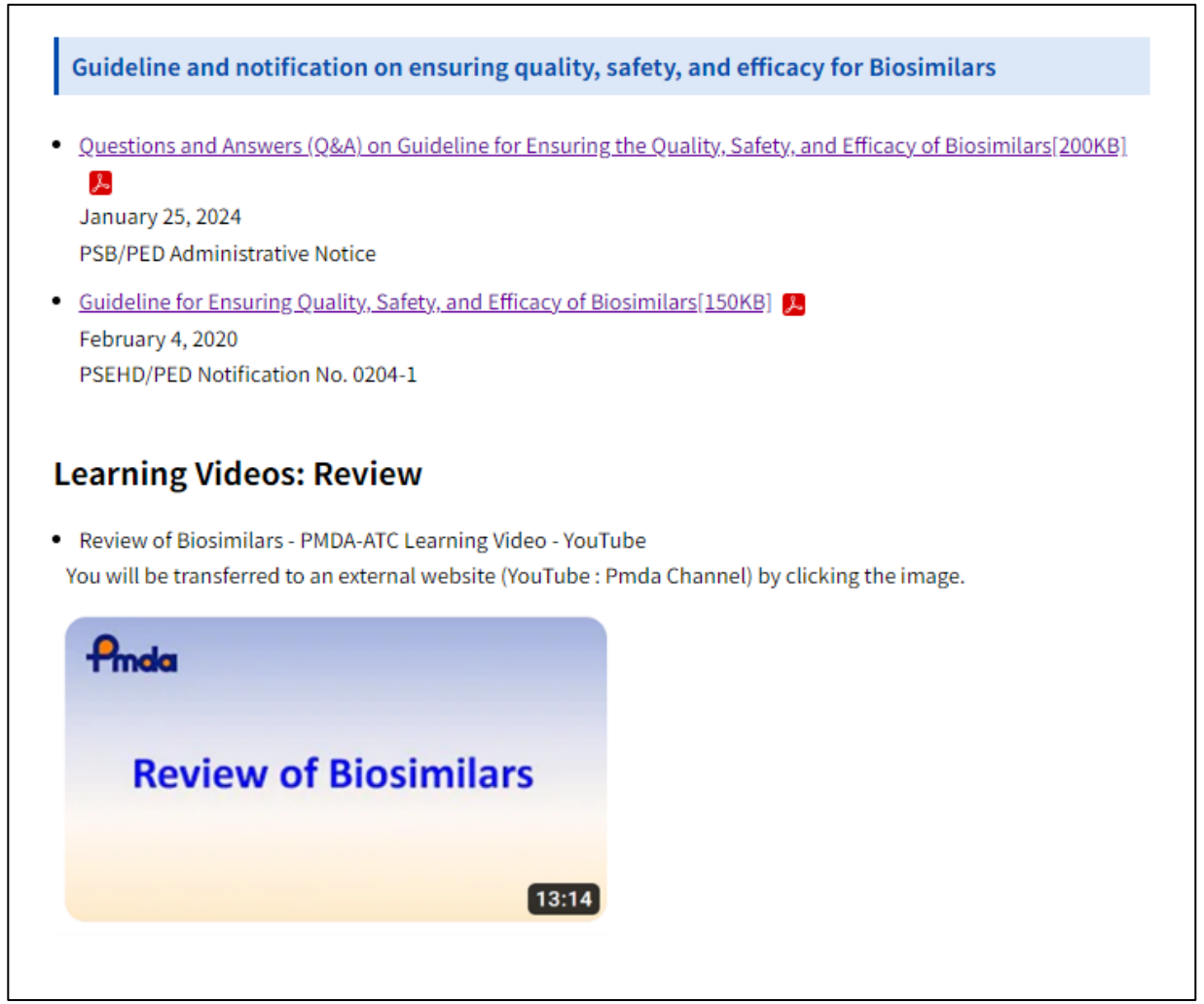
# Website






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

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# Recent publication from PMDA colleagues




- Kuribayashi R, Hariu A, Saino Y, Shinohara K. Efforts of P harmaceuticals and Medical Devices Agency of Japanese Regulatory Agency in Supporting Biosimilar Development and Disseminate Information. Naunyn-Schmiedeberg‘s Archives of Pharmacology. 2025 (in press). https://doi.org/ 10.1007/s00210-025-03874-w
- Kuribayashi R, Goto K, Ogawa T. Trend Analysis of Regulatory Approvals for Generics and Biosimilars in Japan: 15 Years History of PMDA During Fiscal Years 2009–2023. AAPS J. 2024; 26(6):113. https://doi.org/10.1208/s12248-024-00989-5
- 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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