

# Takeda's position on Biosimilar medicines

## Summary

Takeda believes that the safe and effective regulation of biosimilars must be centered on the following five core principles and five guiding points:

### Five core principles:

- Science-based data
- Regulatory transparency
- Educated patient choice
- Patient safety
- Informed healthcare provider

### Five guiding points:

- Indication extrapolation
- Brand name prescribing
- Pharmacy level substitution
- Labeling
- Interchangeability

## BACKGROUND

The term “biologics” refers to a broad range of biotherapeutic products that include monoclonal antibodies, recombinant proteins and cell therapies. In contrast to “small molecules,” which are comparatively simpler, biologics are highly complex molecules. Manufacturing processes are different for these two types of medical products. While small molecules are synthesized through chemical reactions, purified and analyzed in the lab, biologics require production in living cells (e.g., bacteria, yeast and mammalian cells) followed by more complicated purifications and characterization.

Biologics have transformed the field of medicine and most importantly the lives of many patients who continue to benefit from them. With fast-paced advances in science and biotechnology, many more opportunities lie ahead to discover and develop innovative biologics. At the same time, patent expiry of successful biologic products has drawn attention from various stakeholders to the development and marketing of biosimilars of the original biologic products; The word “biosimilar” was introduced to designate a biotherapeutic product that claims to be “similar” in its properties but “not identical” to an approved biologic.

Because of the substantial complexities highlighted above, generating biosimilars of an existing biologic is not possible without thorough and accurate knowledge of the underlying science, quality, safety and efficacy profile derived from robust clinical and non-clinical data.

## POSITION

Takeda's mission is to strive towards better health for people worldwide through leading innovation in medicine. We act on our mission by championing our corporate values, and prioritizing the following considerations in descending order of importance: Patients, Trust with Society, our Reputation, and our Business. Helping to save and improve the lives of patients globally and building trusting relationships with society drives our business.

This philosophy also impacts our views on biosimilars. Takeda is in favor of biosimilars after the end of patent period as a positive cycle of innovation while we believe the safe and effective regulation of biosimilars must be centered on the following five core principles and five guiding points:

### Five core principles:

- **Science-based data:** Evaluation of molecular properties, safety, quality and efficacy comparable to the existing reference biologic product should be driven by the availability and the rigorous interpretation of high-quality sets of non-clinical and clinical data.
- **Patient safety:** Risks to the patient should be minimized through a robust risk/benefit assessment that includes clinical evaluation of the risk of immunogenicity, post-approval pharmacovigilance and risk-management plans.
- **Regulatory transparency:** Regulators and policymakers should implement a predictable and transparent regulatory framework, covering development, approval and post-approval procedures, with clear guidelines and predictable and consistent processes in place.
- **Informed healthcare provider:** Prescribers should be kept fully informed about the biosimilar data and approval process in order to make recommendations that are in the best interest of the patient's health rather than being primarily driven by healthcare cost savings.
- **Educated patient choice:** Patients should be given opportunities to learn from their healthcare providers and understand the different therapeutic options available to them, especially differences in their risk/benefit profile, so that they are empowered to make fully informed decisions about their treatment choices.

### Five guiding points to support safe and effective development and regulation of Biosimilars:

- **Indication extrapolation:** The simple extrapolation of data from one disease state to another without direct evaluation may miss important differences in disease state and patient populations. Post-marketing surveillance, particularly in extrapolated indications, should be required for a period of time in order to determine whether the safety and efficacy profile of the biosimilar remains consistent. This is likely to be particularly relevant for chronic indications where evidence of long term safety and efficacy should be monitored to demonstrate biosimilarity in the long term.
- **Labeling:** Prescribers and patients should be able to easily understand what data were

generated with the biosimilar and what data were generated with the reference product. Clinical safety and efficacy data that supports the biosimilar's approval must be displayed on the label to provide clarity on what data were used to support the approval and extrapolation. This information should be included in the prescribing information for ease of reference by the patient and prescriber:

- Approved biosimilar indications and routes of administration must be stated
- The reference product must be identified on the label.
- The labeling for reference products may expand over time, and additional information may be accumulated with wider use for the biosimilar product as well as for reference products. Public health safety necessitates that sponsors of both reference products and biosimilars separately update their label with the requisite safety and efficacy data.
- **Brand name prescribing:** Brand name prescribing is important when prescribing biological medicines. INN(International Nonproprietary Name) prescribing may lead to unintended switching, and may also reduce the traceability of the biological medicine.
- **Interchangeability:** There is currently limited data and understanding whether switching or alternating multiple times between two products (i.e. reference and biosimilar) may lead to inferior clinical results or other risks to patient health. In view of this lack of scientific evidence and the possible risks to patients from inadvertent substitution, Takeda does not support interchangeability of biologics/biosimilars except when regulatory authorities have made a determination of interchangeability.
- **Pharmacy level substitution:** Given the complexity of developing and reproducing biosimilar medication, it's critical that the prescribing physician should be equipped with sufficient safety and efficacy data to ultimately decide which biological product should be dispensed to the patient. Therefore, Takeda believes that substitution should only be permitted when:
  - the prescribing physician designates in writing, or electronically that substitution is allowed;
  - the patient, or the patient's authorized representative, is notified of the substitution;
  - the prescribing physician is notified of the substitution, including the name and manufacturer of the interchangeable biosimilar dispensed; and,
  - the pharmacist keeps a written record of the substitution for a certain period of time.

## CONCLUSION

The field of biosimilars is still evolving. Patient safety needs and prescriber decision-making responsibilities warrant regulation based on the highest standards of scientific evidence. Takeda is prepared to offer its expertise to policymakers and regulators, as appropriate, in order to assist them in facilitating discussion on important and complex implementation issues.