Frequently Asked Questions (FAQs):

Regulatory requirements for biosimilar product registration

1. **For the comparability studies, does the selected reference product have to be from a single source (as per the approved manufacturing site in Malaysia) even if the same reference product is manufactured at multiple manufacturing sites as approved in other reference countries?**

   In an ideal scenario, it is advisable to have a reference product from a single source to be used throughout the comparability studies.

   However, for a biosimilar product, the practice may not always be feasible. NPRA allows for the use of a non-local reference product (manufactured at different sites other than the Malaysian-approved site) as a comparator to enable faster development of and access to biologic therapies. Hence, a non-locally registered reference product of the same brand and approved in the reference countries (Australia, Canada, the EU (via procedure), the United Kingdom, France, Japan, Sweden, Switzerland, and the USA) can be considered a reference product.

2. **Can an applicant submit a registration application for a biosimilar product if its innovator has never been registered in Malaysia?**

   A biosimilar is defined as a biologic product that is shown to be highly similar in terms of its quality, safety, and efficacy to an already registered reference product in Malaysia. Meanwhile, a reference product, also known as an innovator is a biological product that has been registered in Malaysia based on the full evaluation of the dossier and marketed for a suitable period of time demonstrating proven quality, safety and efficacy.

   Generally, registering a biosimilar when the innovator has never been registered in Malaysia is not allowed.

   However, submission of a biosimilar when the innovator has never been registered in Malaysia but has been approved in any reference country can be considered on a case-to-case basis, depending on the country's needs. A discussion with NPRA is warranted prior to the application of dossier submission.

3. **Should the content of the package insert (PI) of the biosimilar product be the same/identical with the reference product's approved PI in Malaysia (word-by-word), or a content with similar meaning be acceptable? Should the reference product's study-specific data and results be included in the biosimilar package insert, or should it be replaced with the biosimilar's own clinical data?**

   The content of a biosimilar's package insert should align word-by-word for the indication and posology parts only. However, the other sections in the PI should be as similar as possible to that of the reference product except for product-specific aspects such as the use of different excipient(s) and/or presentations. For a biosimilar, its own clinical data should be incorporated, while reference product's specific data can be included for clinical studies in patients not covered in the biosimilar studies.

   This requirement is applicable for all biosimilar products submitted under various pathways including Facilitated Review Pathway (FRP).

4. **The current Malaysian biosimilar guidance document states that "it is at the discretion of NPRA to waive or not to waive a requirement for additional nonclinical in vivo animal studies, taking into account the totality of quality and nonclinical in vitro data." In what circumstances can in vivo animal studies be waived?**

   Generally, in vivo animal studies will not be required if the quality comparability exercise and the nonclinical in vitro studies have shown similarity and the level of residual uncertainty is considered acceptable.

5. **Is there any flexibility where a comparative clinical efficacy trial can be waived?**

   The need for a comparative clinical efficacy and safety trial for the proposed biosimilar will be influenced by seven factors, including how well the biosimilar can be characterized and the existence of a relevant pharmacodynamics (PD) parameter. Current examples of biologics that can be comprehensively characterized and have a well-established mechanism of action include (but are not limited to) teriparatide, insulin, G-CSF, and somatropin, in which clinical efficacy trials can be waived.

   However, if there is any uncertainty, applicants are encouraged to seek technical advice from the NPRA and to discuss the need to conduct this study as soon as they have sufficient comparative analytical and functional data. However, the final registration approval is based on the overall scientific assessment of the dossier.