HKAPI responses to the draft Guidance Notes for Registration of Biosimilar Products

General Comments:

1. HKAPI members support the principle that biosimilar products should have been registered with at least one reference agency including the US Food and Drug Administration, European Medicines Agency, Japan Ministry of Health, Labour and Welfare, Australia Therapeutic Goods Administration and Health Canada.

   This requirement ensures that only good quality, efficacious and safe biosimilar products which have been evaluated and accepted for use by either one of these reputable health authorities can be introduced into Hong Kong for our patients.

2. HKAPI members also support the principle to make sure the reference product must have been registered in Hong Kong for over 8 years before an applicant can submit its biosimilar product to the Drug Office for registration approval.

   This is in line with the current registration requirement on generic chemical products.

Comments on Clinical Documents:

A number of member companies have expressed concerns on the requirement as stated in clause 24 and clause 26 of the draft guideline.

Clause 24 states:

In certain cases, comparative PK/PD studies may be sufficient, provided that the following conditions are met:

- *The PK and PD properties of the reference products are well characterized;*
- *At least one PD marker is accepted as a surrogate marker for efficacy;*
- *The relationship between dose/exposure relevant PD marker(s) and response/efficacy of the reference product is sufficiently characterized.*

It is, however, not clear if all the above **THREE conditions** have to be met in order to fulfill the requirement **OR** if only **ONE condition** would be sufficient to justify the application. Further clarification on the requirement is therefore required.

Clause 26 states:

In certain cases, it may be possible to extrapolate therapeutic similarity demonstrated in one indication to other indications of the reference product. Justification will depend on e.g. clinical experience, available literature data, whether or not the same mechanism of actions, or the same receptor(s) are involved in all the indications.

There are concerns to use extrapolation from one indication to other indications as this may compromise the potential risk of immunogenicity of different indications and as a result, compromising the safety of patients. Therefore, our member companies would like the Drug Office to consider following WHO's guidelines on "Extrapolation of efficacy and safety data to other clinical indications" and to state clearly the conditions under which data extrapolation will be considered.

Comments on Immunogenicity:

Clause 29 states:

If an applicant intends to extrapolate efficacy and safety data of one indication to other indications of the reference product, care should be taken to ensure that immunogenicity is investigated in the patient population with the highest risk of an immune response and immune-related adverse events.

Similar to the above comments on data extrapolation, it is recommended to follow the WHO's guidelines on "Extrapolation of efficacy and safety data to other clinical indications".

Comments on Pharmacovigilance:

It is not clear from the draft guidelines whether the applicant has to report <u>both local and overseas</u> adverse drug reactions (ADR) to the Drug Office.

Drug Office should consider modifying the reporting requirement and its existing ADR Report Form so that applicants understand they have to indicate <u>brand names, registration number and batch number on the form</u> to facilitate better

pharmacovigilance monitoring in the Hong Kong market.

Clause 30 (iii) states:

Providing information on the Risk Management Plan and/or Risk Evaluation and Mitigation Strategy for the biosimilar product as required by the reference agency(ies) if applicable, and any proposed local risk management plan activities and risk mitigation strategies.

It could be useful to elaborate on the points to be taken into consideration when preparing local risk management plan activities and risk mitigation strategies. Hence, we suggest to add the following sentence to clause 30 (iii):

Providing information on the Risk Management Plan and/or Risk Evaluation and Mitigation Strategy for the biosimilar product as required by the reference agency(ies) if applicable, and any proposed local risk management plan activities and risk mitigation strategies. <u>These activities and strategies should take into account identified and potential risks associated with the use of the reference product and, if applicable, additional potential risks identified during the development programme of the biosimilar and should detail how these issues will be addressed in post-marketing follow-up. Immunogenicity should specifically be addressed in this context.</u>

Comments on Labelling:

Please define and clarify the term “label“ on the guidance document. It is not clear whether “label” refers to the carton, label, package insert or all three components.

Clause 32 states:

The information on the label of a biosimilar product should include…….. (iv) A warning statement on the risks associated with the switching of products during treatment, and against product substitution.

HKAPI supports to include such important warning information on all biosimilar product labels (carton, label and package insert) as biosimilar product is similar but not identical to the reference product. In order to emphasize that these products are not interchangeable, the Drug Office shall recommend a standard warning statement in the guideline. This can ensure consistent wordings will be used to address this important risk.

Clause 33 states:

As biosimilar product is similar but not identical to the reference product, claims for any bioequivalence or clinical equivalence between the biosimilar and reference products will not be allowed.

Similar to our comments on clause 32, Drug Office may consider revising this clause by requesting each applicant to include a standard statement in the package (carton, label and package insert) to highlight that biosimilar product is not bioequivalence or clinically equivalence to the reference product, therefore product substitution is not recommended.

Other Comments:

1. Product patent

   Clause 2 states:

   The expiration of patents and/or data protection for the originator's biological products leads to the development of products that are designed to be "similar" to the original's products because of their differences in molecular structure and manufacturing process….

   There is no patent expiration information in the chemical drug registration guidelines. It is not clear to the industry why this information is being stated in the biosimilar guidance notes. Some members are interested to learn if the Drug Office starts to take patent expiry information into consideration during the product registration process.

2. Scope

   Clause 4 states: The scope of this document is confined to those biosimilar products containing well-characterized proteins derived through biotechnological methods, such as the use of recombinant DNA and/or cell culture, as the active substances.

   HKAPI would suggest the Drug Office to modify this paragraph for consistency with the scope of the WHO Guidelines on Similar Biotherapeutic Products as underlined below:

The scope of this document is confined to those biosimilar products containing well-established and well-characterized biological active substances such as recombinant DNA-derived therapeutic proteins.

3. Naming of biosimilar products

The industry recommends the Drug Office to include in the guideline guidance on the nomenclature of biosimilars. Biological Qualifier An INN Proposal by the WHO may serve as a reference. Please refer to the following link for details:

http://www.who.int/medicines/services/inn/bq_innproposal201407.pdf?ua=1

4. Approval of additional indication after product approval

This guideline does not include information to illustrate how an applicant can apply to add new indication(s) onto its packages insert once a biosimilar product is approved in HK. Can we assume any new indication must also be approved by one of the five mentioned reference health agencies before submission to the HK Drug Office?

5. Rearrangement of some clauses

According to clause 9 and clause 10, a product must be registered with at least one reference agency and its reference product must have been registered in Hong Kong for over 8 years in order to be “qualified“ as a biosimilar product. We would like to suggest moving clause 9 and 10 to follow clause 4 of the Purpose and Scope section so that applicants can quickly decide if their products fulfill the biosimilar registration criteria.

6. References

Many international guidelines include a reference section. Drug Office may consider to add a Reference Section and indicate all the references used in this guidance document.