Regulatory Approach for Subsequent Entry Biologics in Canada

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Outline

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- Scientific Basis
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Fundamental concepts and underlying principles

REGULATORY AUTHORITY

- *A New Drug Submission shall contain sufficient information to assess the safety and effectiveness of a new drug C.08.002 (2) Food and Drug Regulations*

- The information and submission requirements for authorization outlined in “Draft Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics”

Fundamental concepts and underlying principles

- Regulatory decision making regarding SEBs will be based on science and regulatory principles existing within the *Food and Drugs Act and Regulations*.

- The principles within the existing regulatory frameworks for biologic, pharmaceutical, and generic pharmaceutical drugs is the basis for the regulatory framework for SEBs.

Fundamental concepts and underlying principles

- The basis for a product being authorized as a SEB hinges on the ability to demonstrate similarity to a suitable reference biologic product.

- SEBs are not “generic biologics” and many characteristics associated with the authorization process and marketed use for generic pharmaceutical drugs do not apply.

Fundamental concepts and underlying principles

- Authorization of an SEB is not a declaration of pharmaceutical and/or therapeutic equivalence to the reference biologic product.

- Once a Notice of Compliance (NOC) is granted the SEB is a new biologic product and regulated like any other new biologic product.

Fundamental concepts and underlying principles

- *All the laws, patent and intellectual property principles outlined within the Patent Act, Food and Drug Regulations (Data Protection), and Patented Medicines Notice of Compliance Regulations are applicable to SEBs*
  - Subsequent manufacturer approval on the basis of direct or indirect comparison with the 'innovator drug' is prohibited until 8 years after the approval of the innovative drug
  - 6 year 'no-filing period' during which SEB sponsors are prohibited from filing a submission that compares directly or indirectly with the innovative drug
  - 6 month paediatric extension is applicable

Fundamental concepts and underlying principles

- The onus is on the sponsor to provide the necessary evidence which may include data and/or scientific rationale that will be satisfactory to Health Canada to support all aspects of the application including choice of reference product and indications sought.

- Authorization of an SEB is not an indication that the product may be automatically substituted with its reference biologic product.

Scientific Basis - Quality Requirements

- Full Chemistry and Manufacturing data plus
  - Comparability between SEB and Reference Product
  - Extensive side by side characterization of SEB and Reference Product
- Comparability Exercise
  - To ascertain if the SEB and the chosen reference biologic product are comparable in terms of quality, safety, and efficacy.
  - Comprehensive quality studies evaluating both the drug product and drug substance

Scientific Basis – Quality Considerations

- Criteria in the conduct of the comparability exercise:
  - *Physicochemical Properties, Biological Activity, Immunochemical Properties , Purity, Impurities, and Contaminants , Specifications, Stability*
- Battery of tests for CE should be carefully selected and optimized to detect differences in the quality attributes of the SEB and the reference product
- Quality attributes for batch release should be validated in accordance with ICH guidelines (Q2A, Q2B, Q5C, Q6B).

Scientific Basis – Demonstration of Similarity

- The demonstration of comparability does not necessarily mean that the quality attributes of the two products being compared are identical, but that they are highly similar with two consequences
  - that the existing knowledge of both products is sufficient to predict that any differences in quality attributes should have no adverse impact upon safety or efficacy of the SEB; and
  - that non-clinical and clinical data previously generated with the reference biologic product is relevant to the SEB.

Scientific Basis – Demonstration of Similarity

- A final determination of similarity can be based on a combination of analytical testing, biological assays, and non-clinical and clinical data.

Non-clinical and Clinical Requirements

- Results from the Comparability Exercises determine the extent of non-clinical and clinical data requirements
- Comparative non-clinical studies designed to detect differences between the SEB and the reference biologic product should be conducted prior to clinical studies.
- Clinical studies should be provided for each indication being sought. In some cases, comparative PK/PD data to bridge two or more indications may be sufficient.

Non-clinical and Clinical Requirements

- Comparative clinical trials are required to demonstrate the similarity in efficacy and safety profiles between the SEB and the reference biologic product.
- Comparative clinical studies must have the statistical power to detect major safety changes.
- Safety data from sufficient number of patients and sufficient study duration should be provided to compare the nature, severity, and frequency of adverse reactions between the SEB and the reference biologic product.

Non clinical and clinical requirements

- The immunogenicity of the SEB shall be tested using state of art methods from both efficacy and safety perspectives.

- Full and complete non-clinical and clinical data required when similarity cannot be established.

Post Market Requirements

- A Risk Management Plan required prior to issuance of authorization.
  - The RMP should be designed to monitor and detect both known inherent safety concerns and potentially unknown safety signals that may result from the impurity profile and other characteristics of the SEB.
  - The RMP should be maintained and implemented throughout the life-cycle of the product.
- Adverse Drug Reporting as per *Food and Drug Regulations*
- Periodic Safety Update Reporting as per ICH E2E

Approach to use of Reference product

- The onus is on the sponsor to demonstrate that the chosen reference product is suitable to support the submission
- The chosen reference biologic product shall be used throughout the studies supporting the safety, quality, and efficacy of the product.
- The dosage form, strength, route of administration of the SEB shall be the same as that of the reference biologic product.

Approach to use of Reference product

- The active substance of the reference biologic product and the SEB must be shown to be similar.
- A SEB shall not be used as a reference biologic product.
- The use of a reference biologic product that is not approved in Canada may be considered on request to the Minister.
- Reference biologic products from jurisdictions that have an established relationship with HPFB have a better chance of being approved.

Approach to use of Reference product

- A reference product that is widely marketed in a jurisdiction which has regulatory standards and principles for evaluation of medicines, approach to comparability with Canada is preferable.
- The use of a non-Canadian reference product in clinical studies in Canada will require complete chemistry and manufacturing information as per C.05.005 of the *Food and Drug Regulations.*
- In instances where a non-Canadian reference product is used, the sponsor is encouraged to contact Health Canada earlier in the drug development process.

Approach to Indications & Substitutability

- The indications granted to a SEB shall be based on data provided by the sponsor.
  - As such if the SEB sponsor does not provide data to support all the indications of the reference product, the SEB shall not automatically be granted all the indications of the reference biologic product.
- Indications not held by the reference biologic product will require supportive clinical trial data.
- SEBs should be eligible to apply for indication(s) within those granted to the reference biologic product.
- Interchangeability remains a provincial decision.

Conclusions

- Canada is a regulated marketplace, but unlike USA & Europe, it is smaller in market size and unlikely to be primary target for SEB development and submissions.
  - Flexibility in choice of reference product
- Use of existing new drug submission pathway for new biologic drugs.
- A framework that is suitable to meet the needs of Canadians, flexible to enable the Regulator and sponsors, and adaptable for changing legislative environment.

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