



Global Insight Article

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Health Canada Advances Biosimilars
Approval Legislation

Canada: Health Canada Advances Biosimilars Approval Legislation

Canada is making steady progress towards creating an abbreviated approval mechanism for biosimilars or Subsequent Entry Biologics (SEBs), according to Health Canada representative Mary Alice Hefford, speaking at IBC's Fifth Annual Global Follow-on Biologics Conference.

| Global Insight Perspective | |
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| Significance | Unhindered by the legislative obstacles faced by the U.S. FDA, Health Canada can put forward abbreviated approval guidelines for Subsequent Entry Biologics (SEBs), or copies of biotech drugs. |
| Implications | The agency has made so much progress in clarifying the guidelines and its position that there are currently only two outstanding issues to be resolved before publication of the final guidelines. |
| Outlook | Health Canada is on track to become the second drug regulator after the European Medicines Agency (EMA) to introduce abbreviated approval guidelines for copies of biotech drugs. Global Insight expects the first guidelines to be finalised in Canada before the end of 2008. |

IBC Conference Presentation Clarifies Health Canada's Position

Mary Alice Hefford, research scientist at Health Canada's Centre for Biologics Research, discussed the agency's current thinking on SEBs approval at the IBC Fifth Annual Global Follow-on Biologics Conference which took place on 10-11 December in Reston, Virginia, U.S. Her presentation has provided much needed clarification on Health Canada's position and current progress with approval guidelines.

Canada currently has separate clearly differentiated pathways for biologics approval and for the approval of small-molecule (i.e., chemical) innovative drugs. Virtually all biologics, with the exception of some small synthetic peptides, are approved under the biologics pathway. Generics (traditionally copies of small-molecule drugs) are approved under a separate abbreviated pathway, and typically no clinical trials are required after a demonstration of "identity". Although it is clear that "identity" cannot be demonstrated between a complex biologic and SEBs using it as a reference product, Health Canada has been told by the health minister to use the existing legal framework for approval of SEBs, according to Dr Hefford. The expectation is that such an approach would create a level playing field for innovator biologics and SEBs.

Health Canada has been doing SEBs research for the past five years and has in fact already issued an analysis report that has been accepted by the health minister, according to the presentation. The agency is now writing guidance documents for drug application sponsors and expects to start consultations with the provinces on SEBs approval in early 2008.

Canada's Unique Challenges

Compared to its larger southern neighbour Canada appears to be making faster progress with biosimilars approval. Part of the reason for this is that Health Canada already has the legal authority to approve SEBs, while the U.S. FDA would require an Act of Congress to gain this authority. Health Canada, however, faces a set of other problems which could impede SEBs approval. The main problem appears to be the selection of a reference product by SEBs developers. Given the small size of its domestic market, Canada does not have each (or even most of) the available brands of innovator biologics on the market. If a company develops a SEB using as reference a product that has never been approved in Canada, it is unclear what it would mean for regulators. If they approve the SEB, would they also be giving indirect marketing approval to the innovator reference biologic? Should Canada limit its SEB guidelines to state that only biologics marketed in Canada could be used as a reference product? And if it did this would it close its market to all SEBs using another biologic as a reference product? It remains to be seen how serious these concerns are, but Dr Hefford's presentation indicates that for Health Canada this is the number one concern. It is so serious in fact that the agency is now seeking a legal opinion, which is expected sometime in early 2008.

The other key concern that Dr Hefford identified is so-called "indication creep". If a SEB is approved for the early indications of the reference innovator biologic and that biologic is later approved for additional indications, should the SEB also gain automatic approval for these? The jury is apparently still out on this issue, but Dr Hefford said that current Health Canada thinking is to grant approval to the SEB for the same indication as the reference product (and not the indications for the whole class of products to which the reference biologic belongs). This second issue is particularly pivotal for Health Canada because it has implications for the interchangeability between the reference biologic and its subsequent biosimilar copies. Notably, decisions on interchangeability or substitutability fall within the authority of provincial governments and not under Health Canada.

Outlook and Implications

Where does this leave Canada's SEBs approval process? It is apparently at a much more advanced stage than the corresponding process in the United States. In Canada, the drug regulator's authority is clear, the draft principles and

guidelines have been drawn up and the two outstanding issues could be resolved in the next few months. The first issue—allowing drug sponsors to use a biologic not marketed in Canada as a reference product—has practical implications as well as legal ones. The decision is currently in the hands of lawyers but Health Canada will have the final say. It will base its final decision on practical matters as well—namely ensuring that it does not unnecessarily exclude cheaper SEBs from entering the Canadian market.

The second question of interchangeability is expected to remain a thorny one for quite some time. Health Canada clearly does not wish to relinquish the opportunity to judge whether SEBs should be interchangeable with the originator product. On the one hand, the agency is better equipped from a scientific perspective to make the right call in comparison to the provinces, which will be approaching substitutability from a pricing and reimbursement perspective. On the other hand, the risk of immunogenic reactions with SEBs is high and could become higher as a result of substitution of one biologic or SEB with another in a patient's treatment regimen. Global Insight expects Health Canada's thinking on this second issue to evolve over time as post-marketing data is accumulated—hence, drastic changes in SEBs labelling on interchangeability are likely.

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