Biosimilars and Exclusivity

The 2010 Patient Protection and Affordable Care Act ("PPACA") includes a subtitle called the Biologics Price Competition and Innovation Act of 2009 ("BPCIA"), which created an abbreviated approval pathway for biological products that are biosimilar to or interchangeable with an FDA-licensed reference biological product.

Under the BPCIA, the approval of a biosimilar product may not be made effective by the FDA until 12 years from the date on which the reference product was first licensed. During this 12-year period of exclusivity, another company may still market a competing version of the reference product if the FDA approves a full BLA for the competing product containing the sponsor's own preclinical data and data from adequate and well-controlled clinical trials to demonstrate the safety, purity and potency of their product. The BPCIA also created certain exclusivity periods for biosimilars approved as the first interchangeable for biologic products.

Canadian Review and Approval Process

In Canada, our biologic product candidates and our research and development activities are primarily regulated by the *Food and Drugs Act* and the rules and regulations thereunder, which are enforced by Health Canada. Health Canada regulates, among other things, the research, development, testing, manufacture, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, post-approval monitoring, marketing and import and export of pharmaceutical products. Drug approval laws require licensing of manufacturing facilities, carefully controlled research and testing of products, and government review and approval of experimental results prior to giving approval to sell drug products, including biologic drug products. Regulators also typically require that rigorous and specific standards such as cGMP, GLP and cGCP are followed in the manufacture, testing and clinical development, respectively, of any drug product. The processes for obtaining regulatory approvals in Canada, along with subsequent compliance with applicable statutes and regulations, require the expenditure of substantial time and financial resources.

The principal steps required for drug approval in Canada are as follows:

Preclinical Toxicology Studies and Clinical Trials

Non-clinical studies are conducted *in vitro* and in animals to evaluate pharmacokinetics, metabolism and possible toxic effects to provide evidence of the safety of the drug candidate prior to its administration to humans in clinical studies and throughout development. Such studies are conducted in accordance with applicable laws and GLP.

In Canada, the process of conducting clinical trials with a new drug cannot begin until a Clinical Trial Application ("CTA") is submitted and the required number of days has lapsed without objection from Health Canada. Biological drugs carry additional risks, as compared to traditional small-molecule drugs, associated with complexity and variability in manufacturing that can contribute to increased lot-to-lot variation of the final product, and with the potential for adventitious agents. Therefore, the content requirements for the quality information for biological drugs to be used in clinical trials are different from those for standard small-molecule pharmaceutical drugs (for example, the inclusion of information on manufacturing facilities is required for biological drugs). In addition, it is necessary to have more stringent controls on the release of biologic drug lots used in authorized clinical trials.

Similar regulations apply in Canada regarding clinical trials as in the United States. In Canada, Research Ethics Boards ("REBs"), instead of IRBs, are used to review and approve clinical trial plans. Human clinical trials are typically conducted in three sequential phases, as discussed above in the context of government regulation in the United States.

The manufacture of investigational drugs for the conduct of human clinical trials is subject to cGMP requirements. Investigational drugs and active pharmaceutical ingredients imported into Canada are also subject to regulation by Health Canada relating to their labeling and distribution. Progress reports detailing the results of the clinical trials must generally be submitted at least annually to Health Canada and/or the applicable REBs, and more frequently if serious adverse events occur.

New Drug Submission

Upon successful completion of Phase 3 clinical trials, the company sponsoring a new drug then assembles all the preclinical and clinical data and other testing relating to the product's pharmacology, chemistry, manufacture, and controls, and submits it to Health Canada as part of a New Drug Submission ("NDS"). The NDS is then reviewed by Health Canada for approval to market the drug.