

## FAQs About Biosimilars

A number of biosimilar biologic drugs (“biosimilars”) are available in Canada, and the list is growing. Biosimilars are expensive. However, biosimilars are less costly than their reference biologic drug (up to 50% less), so many payers will prefer them.<sup>1,2</sup> More and more biosimilars are being covered by provincial and territorial programs, and some (e.g., British Columbia) are transitioning to coverage of only biosimilars for some drugs. The chart below addresses questions likely to arise in practice about biosimilars, including their approval process and interchangeability.

Clinical Question	Pertinent Information
<b>What is a biosimilar?</b>	<ul style="list-style-type: none"> <li>• <b>Biologic drugs</b> are large, complex molecules derived from living material (human, animal, or microorganism) or their cells.<sup>3,4</sup></li> <li>• Examples of biologics include insulin, monoclonal antibodies (e.g., adalimumab), interferons and other cytokines (e.g., interferon alfa), growth factors (e.g., filgrastim), and thrombolytics and other enzymes (e.g., streptokinase).</li> <li>• An approved <b>biosimilar</b> is a biologic drug that has been shown to be highly similar to an existing Health Canada-approved biologic drug, known as the <b>reference biologic drug</b>. In Canada, biosimilars were previously referred to as subsequent entry biologics (SEBs). Biosimilars may also be referred to as <b>original, originator, innovator, or follow-on biologics</b>.<sup>5</sup></li> </ul>
<b>How do biosimilars compare to the reference biologic drug in regard to efficacy and safety?</b>	<ul style="list-style-type: none"> <li>• Patients and prescribers can expect <b>no clinically meaningful difference in safety and effectiveness</b> between a biosimilar and its reference biologic drug when used as intended.<sup>4</sup></li> <li>• A review of 90 studies (n = 14,225) in which patients were switched to biosimilars from a reference biologic drug showed no clinical differences in safety or efficacy.<sup>6</sup></li> </ul>
<b>How do biosimilars receive Health Canada approval?</b>	<ul style="list-style-type: none"> <li>• Biosimilars are regulated as new drugs under the Food and Drugs Act and the Food and Drug Regulations.<sup>5</sup> They are listed in Schedule D of the Food and Drugs Act.<sup>4</sup></li> <li>• Manufacturers must follow strict guidance on the development of biosimilars, found in Health Canada’s Guidance Document: Information and Submission Requirements for Biosimilar Biologic Drugs.<sup>7</sup></li> <li>• Manufacturers must provide data which establishes that the biosimilar and reference biologic drug are similar with no clinically meaningful differences in safety and efficacy. <ul style="list-style-type: none"> <li>• Manufacturers are not required to independently establish safety and effectiveness of the proposed biosimilar drug.<sup>5</sup></li> <li>• New efficacy studies are not generally required for the biosimilar; however, scientific justification must be submitted to support extrapolation of efficacy data from the reference biologic drug to support efficacy of the biosimilar.<sup>4</sup></li> </ul> </li> </ul>
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Clinical Question	Pertinent Information
<b>Health Canada approval process for biosimilars, continued</b>	<ul style="list-style-type: none"><li>• Biosimilars cannot enter the market until the reference biologic drug patents and data protections have expired.<sup>4</sup></li><li>• Health Canada requires studies which show that there are no clinically meaningful differences in <b>immunogenicity</b> between a biosimilar and its reference biologic drug.<sup>4</sup><ul style="list-style-type: none"><li>• As foreign proteins, biologic drugs can cause immune system reactions. These reactions have the potential to affect the safety and efficacy of biologics.<sup>4</sup></li><li>• Manufacturers are also required to have a risk management plan for all biologic drugs which lays out an immunogenicity monitoring plan that can be put in place after a biosimilar is authorized.<sup>4</sup></li></ul></li><li>• Health Canada-approval of biosimilars is based on a risk benefit assessment of the provided data and on a comparison to the reference biologic drug.<sup>4,5</sup></li><li>• Once authorized by Health Canada, biosimilars are given a Notice of Compliance (NOC) and a Drug Identification Number (DIN). All biosimilars have a product monograph that details its indications and information for its safe and effective use.<sup>4</sup></li><li>• Complete information on the authorization of a particular biosimilar can be found in its Health Canada Summary Basis of Decision document.<sup>8</sup></li><li>• The majority of the product labelling for the biosimilar (dosing, administration, and warnings) will be the same as the reference biologic drug. However, the biosimilar may be approved for fewer indications than the reference biologic drug and labelling will reflect this difference.<sup>4</sup></li><li>• The biosimilar’s initial product monograph <b>safety information</b> is based on its reference biologic drug’s product monograph. However, once the biosimilar is authorized, any new safety issues with either the biosimilar or the reference biologic drug are assessed independently and may or may not affect both products’ labelling.<sup>4</sup><ul style="list-style-type: none"><li>• Biosimilar manufacturers must monitor the post-marketing safety information for both their own product and the reference biologic drug.<sup>4</sup></li><li>• If the product monograph safety information of a biologic drug is updated, Health Canada notifies the manufacturer(s) of any related biologic drugs (i.e., biosimilars, reference biologic drug) who must then assess the need to update their product monograph.<sup>4</sup></li></ul></li></ul>
<b>How does a biosimilar differ from a generic?</b>	<ul style="list-style-type: none"><li>• A biosimilar is <b>not considered a generic drug</b>, which is approved through a different pathway.<sup>4</sup></li><li>• Generic drugs are <b>identical</b> to the brand name drug. It is <b>not possible</b> to make an identical copy of a biologic because biologics are made from living cells.<sup>4</sup></li></ul>

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<b>Are biosimilars interchangeable with the reference biologic drug?</b>	<ul style="list-style-type: none"><li>• Biosimilars are <b>not</b> automatically considered interchangeable with their reference biologic drug.<sup>4</sup></li><li>• Each province and territory in Canada determine the interchangeability of drugs.<sup>4</sup></li><li>• Biosimilars do not fall under the same rules for generic substitution and interchangeability as traditional drugs.<sup>13</sup></li><li>• Biosimilars are in a class of their own. They are not considered brand-name drugs or generic drugs.<sup>13</sup></li></ul>
<b>How are biosimilars named?</b>	<ul style="list-style-type: none"><li>• Per Health Canada, biologic drugs should be identified by both their brand name and their non-proprietary or common name (e.g., “filgrastim [<i>Grastofil</i>]”). Each biologic drug has its own Drug Identification Number (DIN).<sup>9</sup></li><li>• Note that in the U.S., the naming convention for all biosimilar drugs is a “core name” followed by an FDA-designated suffix composed of four lowercase letters attached to the core name with a hyphen.<sup>10</sup> For example, filgrastim biosimilars are named filgrastim-sndz (<i>Zarxio</i> from Sandoz) and filgrastim-aafi (<i>Nivestym</i> from Pfizer).</li></ul>
<b>How are biosimilars handled at the provincial/territorial level?</b>	<ul style="list-style-type: none"><li>• Health Canada approves biologic drugs for use, and then the interchangeability and coverage of specific biologics is determined by the provincial and territorial programs.</li><li>• Previously, once Health Canada approved a biosimilar, the Canadian Agency for Drugs and Technologies in Health (CADTH) evaluated and then made recommendations to the Pan-Canadian Pharmaceutical Alliance (pCPA) and provincial/territorial governments regarding formulary listings and reimbursement. However, beginning June 1, 2019; CADTH will (in most cases) no longer review biosimilar drug submissions.<sup>11</sup><ul style="list-style-type: none"><li>• Manufacturers will work directly with pCPA and provincial/territorial governments to determine their formulary listings and the funding terms of biosimilars.<sup>11</sup></li></ul></li><li>• By November 25, 2019, British Columbia plans to transition to payment for biosimilars rather than reference biologic drugs for the treatment of several conditions (ankylosing spondylitis, diabetes, plaque psoriasis, psoriatic arthritis, and rheumatoid arthritis).<sup>2</sup><ul style="list-style-type: none"><li>• This change is expected to affect over 20,000 patients.<sup>2</sup></li><li>• There are plans to expand to biosimilars for Crohn’s disease and ulcerative colitis.<sup>2</sup></li><li>• Exceptions may be possible and will be assessed on a case-by-case basis.<sup>2</sup></li><li>• For example, patients on the below biologic therapies will be transitioned from the listed reference biologic drug to the listed biosimilar(s):<sup>2</sup><ul style="list-style-type: none"><li>• etanercept: from <i>Enbrel</i> to <i>Brenzys</i> or <i>Erelzi</i></li><li>• infliximab: from <i>Remicade</i> to <i>Inflextra</i> or <i>Renflexis</i></li><li>• insulin glargine: from <i>Lantus</i> to <i>Basaglar</i></li></ul></li></ul></li><li>• Another example is the filgrastim biosimilar, <i>Grastofil</i>, which is the preferred biologic drug in some provinces (e.g., Ontario, British Columbia). In Ontario, patients on the reference biologic drug, <i>Neupogen</i>, are not switched to <i>Grastofil</i>; however, new starts for filgrastim are encouraged to consider <i>Grastofil</i>.<sup>12</sup></li></ul>

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<b>What are some practical prescribing and dispensing implications for biosimilars?</b>	<ul style="list-style-type: none"><li>• The decision to switch from a reference biologic drug to a biosimilar should be made by the prescriber in consultation with the patient.<sup>4</sup><ul style="list-style-type: none"><li>• Clinical evidence and provincial/territorial policies may help guide the decision.<sup>4</sup></li><li>• Patients will need to go to their prescriber for a new prescription to switch to a biosimilar.</li></ul></li><li>• Patients who are enrolled in patient assistance programs for a reference biologic drug will need a new enrollment if they are switching to a biosimilar. For example, some infliximab infusion centres may be tied to a drug’s patient assistance program, so some patients may need to switch infusion centres.</li><li>• It is important to review the product monograph to determine the indications for which the biosimilar has been approved before prescribing or dispensing it.<ul style="list-style-type: none"><li>• A biosimilar can only be approved for those indications previously approved for the reference biologic drug, but a biosimilar can be approved for <b>fewer indications</b> than the reference biologic drug.<sup>4</sup> This could happen if the reference biologic drug has an unexpired patent(s) on an indication, the biosimilar manufacturer only applies for certain indications, or Health Canada does not allow the indication after reviewing the submitted data.<sup>4</sup></li></ul></li><li>• If a specific biologic brand is desired, prescribers should write for that particular brand (e.g., <i>Neupogen</i>) and specify “dispense as written” or “brand medically necessary.” However, reimbursement from provincial/territorial programs may not be available for all biologic brands and products.</li><li>• Prescribers should specify the biologic’s brand and common name to ensure the desired product is dispensed. Be aware that in the hospital setting, a formulary-directed substitution might be made.</li><li>• Pharmacists should be aware of provincial/territorial laws on dispensing biosimilars.</li><li>• Watch carefully for differences between biosimilars and biologic reference drugs in storage and expiration dates, syringe size and strength, etc. For example, for infliximab, <i>Remicade</i> can be kept at room temperature for up to six months, but <i>Inflectra</i> and <i>Renflexis</i> must always be stored in the refrigerator.<sup>16-18</sup> For etanercept, <i>Erelzi</i> comes as 25 mg and 50 mg prefilled syringes, while <i>Enbrel</i>’s prefilled syringe is only available as 50 mg.<sup>14,15</sup></li></ul>

Users of this resource are cautioned to use their own professional judgment and consult any other necessary or appropriate sources prior to making clinical judgments based on the content of this document. Our editors have researched the information with input from experts, government agencies, and national organizations. Information and internet links in this article were current as of the date of publication.

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