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WHAT IS INDICATION EXTRAPOLATION AND SHOULD IT BE ALLOWED WITH BIOLOGICAL MEDICATIONS?

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If a prescription medication is approved for the treatment of a specific disease or condition, do you assume that it has undergone full testing for that condition? This assumption is usually valid: New medications approved in the United States must undergo extensive testing for the conditions they are approved to treat, which then, if approved by the FDA, become known as *indications* for that drug. However, shortcuts do exist for generic drugs—conventional medications with exactly the same chemical composition as the original innovator drug. Because drugs such as generic aspirin and ibuprofen are chemically identical to the innovator brand drugs, it is assumed that they will act the same way as the brand drugs in all diseases and conditions. Consequently, generic drugs require only basic testing in healthy volunteers before being approved by the FDA for all indications of the original brand drug.

But this logical assumption doesn't apply to biological medications—those made by living organisms or cells. Unlike generic drugs, biological medications or biologics cannot be exact copies of one another. As a result, follow-on biologics designed to be similar to already-approved innovator medications are known as *biosimilars*—not generics. Policymakers are currently considering to what extent biosimilars should be tested in patients with different diseases or whether they should be automatically approved for all of the innovator biologics' indications, an alternative process known as *indication extrapolation*.

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Given that biosimilars cannot be exact copies of the original innovator biological medications, they may not act the same way in every disease state, possibly triggering unforeseen adverse effects. For this reason, indication extrapolation should not be automatic for biosimilars. Instead, each biosimilar should be considered on a case by case basis to determine the extent of evidence required for patients with different diseases.

Indication extrapolation:
(noun)

1. the approval of a biosimilar for diseases or conditions for which it has not been studied based on its similarity to an approved, innovator biological medication.[1]

REASONS THAT INDICATION EXTRAPOLATION SHOULD NOT BE ROUTINE FOR BIOSIMILAR MEDICATIONS

Biological Medications Are Typically Complex Proteins That Are Difficult to Duplicate

Biological medications are typically large proteins whose complex chemical structures consist of numerous twists and turns that are essential to their biological activity. This

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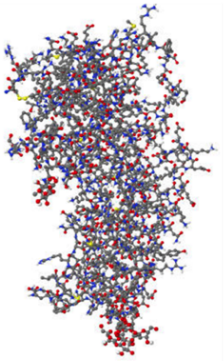
complexity makes it difficult to determine their exact chemical structures [2] and, consequently, whether they are the same as those of other biological medications.

Other key features make biologics unique and distinguish them from conventional drugs, as shown in the following table. For instance, biologics can be 100 to 1,000 times larger than conventional drugs and are highly sensitive to their manufacturing processes.[2] Small differences or changes in the manufacturing process can affect how biologics act in the body, in some cases leading to unexpected adverse events.[2]

SOME DIFFERENCES BETWEEN BIOLOGICAL MEDICATIONS AND CONVENTIONAL DRUGS[3]

Characteristic	Biological Medication	Conventional Drug
Source	Made by living cells or organisms	Made in a laboratory using chemical reactions
Size	Large	Small
Structure	Complex	Simple
Example of structure	 Protein structure from RCSB Protein Data Bank, Identifier #1AU1	
Generics possible?	No	Yes

Effects of Biological Medications on the Immune System

One of the ways that the underlying chemical differences in biosimilars may cause different effects in patients is via their impact on the immune system. Even minor differences in biological medications can affect the immune response in ways that may not always be predictable.[4] In some cases, this may lead to unforeseen adverse events that could compromise patient safety, as happened with a biologic known as epoetin used for the treatment of chronic kidney disease. In this case, a small change to the biologic's manufacturing process led to an increase in the development of antibodies, which caused severe anemia in some patients.[2]

Route of Administration and Dose

Another important situation in which differences between biosimilars and innovator biologics may be apparent is when they are administered at different doses and/or via different routes (e.g., intravenous, intramuscular, or subcutaneous). Given the different composition of body tissues, it cannot be automatically assumed that a biological product will act the same way when administered via different routes and at different doses. For example, a medication may be more rapidly distributed or eliminated from the body following intravenous administration than intramuscular administration. Additionally, when administered subcutaneously, a biological medication is generally more likely to stimulate the immune system than when administered intravenously.[5,6] For these reasons, it cannot be assumed that the immune profile of a complex biosimilar will be the same as that of the innovator biologic when administered via different routes and at different doses.

Mechanism of Action

As complex proteins, many biologics have more than one mechanism of action. For example, a group of medications known as monoclonal antibodies may act through multiple mechanisms. In one disease, the medication may act through only one of these mechanisms, whereas in another disease, all of the mechanisms may be important.[4] Even one single change in a chemical group can change the mechanism of action. Consequently, it cannot be assumed that a biosimilar has the same mechanism of action as an innovator biologic unless their structures are identical—a point that can be difficult or impossible to determine given the complexity of large proteins.

Differences In Disease States and Patient Characteristics

Finally, differences in disease states and patient characteristics present problems for indication extrapolation. In some diseases, the immune system may be more active than others, leading patients to respond differently to biosimilars. Patients with some diseases may be older, more prone to certain adverse effects of the medication, or taking other medications that could alter the effects of a biosimilar.

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COMPARISON OF TWO BIOLOGICAL MEDICATIONS: A SMALL PROTEIN AND A LARGE MONOCLONAL ANTIBODY PROTEIN

	HUMAN GROWTH HORMONE[7]	INFLIXIMAB[8,9]
PROTEIN SIZE	Relatively small	Large
MOLECULAR WEIGHT (kiloDaltons)	22	~144 to 149
NUMBER OF ATOMS	3,091	18,080
CHEMICAL FORMULA	$C_{990}H_{1532}N_{262}O_{300}S_{7}$	$C_{6428}H_{9912}N_{1694}O_{1987}S_{46}$

Particular caution may be warranted in attempting to extrapolate indications to diseases that are highly dissimilar. Some biological medications, such as the monoclonal antibodies, are indicated for very different diseases; for instance, rituximab is indicated for both rheumatoid arthritis and a type of cancer known as non-Hodgkin's lymphoma.[4] Not only are the disease mechanisms likely quite different in these two conditions, but the patient characteristics are also dissimilar. For instance, a large cancer burden in non-Hodgkin's lymphoma may lead to dramatically different drug distribution and elimination characteristics of the monoclonal antibody.[4] Thus, indication extrapolation is difficult to defend in conditions that are substantially different from one another.

CONCLUSIONS

Given the complex chemical nature of large biological medications, even minor differences between innovator biologics and biosimilars raise serious concerns for patient safety. Therefore, caution is warranted when attempting to extrapolate the indications from an innovator biologic that has undergone extensive clinical trials in actual patients to a biosimilar that has not. In order to err on the side of safety, the extent of evidence required for a biosimilar to be granted indication extrapolation should be considered carefully and on a case by case basis.

INDICATION EXTRAPOLATION IN CANADA AND THE EUROPEAN UNION

Canada and the European Union (EU) have had regulations in place for the approval of biosimilars longer than the United States and thus have more experience with biosimilar-related issues such as indication extrapolation. In both of these regions, the first biosimilar approved was human growth hormone, or somatropin, a small protein used to treat children and adults who do not make enough of the hormone naturally.

As proteins go, human growth hormone is extremely small, with a molecular weight of 22 kiloDaltons.[7] The monoclonal antibody infliximab weighs more than six times as much.[8,9] Due to its small size, human growth hormone is not a highly complex protein and thus it is easier to characterize and demonstrate similarity of structure. In both Canada and the EU, biosimilar human growth hormones have received full indication extrapolation based on the reference biological medication.

The most complex biosimilar medication to be approved in Canada and the EU is infliximab, a large monoclonal antibody. In the EU, biosimilars were granted indication extrapolation for the eight indications of the innovator biologic (Remicade®) based on clinical data for only two of these indications.[10,11] However, Health Canada has taken a more cautious route, granting approval for only a subset of indications.

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