# WHAT DO I NEED TO KNOW ABOUT BIOSIMILARS?

## INDICATION EXTRAPOLATION

### BIOLOGIC AND BIOSIMILAR MEDICINES

Biologic medicines are large, complex molecules that are made in living cells, grown in a laboratory. Some examples include vaccines and therapeutic proteins that help your body to fight illnesses such as cancer and arthritis.

Biosimilars are attempts to copy biologic medicines. However, exact copies of biologic medicines are not possible. Biologics are made in living cells, and because of this, there will always be small differences between a biosimilar and the biologic medicine it is based on. The extreme complexity and large molecular size of biologic medicines mean that even minor differences between two similar biologics can cause unexpected reactions in patients, including unwanted immune reactions. Evaluating biosimilars in patients as part of a clinical trial is very important in evaluating whether these small differences have any effect on the way the medicine works in the body.

### HOW ARE BIOLOGIC AND BIOSIMILAR MEDICINES TESTED IN CLINICAL TRIALS?

For new biologic medicines, a company will conduct a clinical trial that looks at whether the medicine works and is safe for patients with a specific disease, for example, breast cancer. Regulatory authorities will review the data and approve the drug for use in that specific disease only. To demonstrate to regulatory authorities that the medicine works and is safe in other patients, for example, those with colorectal cancer, a clinical trial enrolling patients with colorectal cancer is required. Each specific disease that the medicine is used for is termed an INDICATION, and a drug may have many indications on its label. For example, it may have an indication for both breast cancer and colorectal cancer.

For biosimilars, a company will conduct a clinical trial that looks at whether the biosimilar medicine works as well as and is as safe as the original medicine. This trial is often conducted in a single specific disease, for example breast cancer. Then, as long as there is robust scientific and clinical reasoning, the biosimilar can be used in all the diseases that the original biologic is used for. No clinical testing is required. This is known as INDICATION EXTRAPOLATION.

### WHY SHOULD I CARE ABOUT INDICATION EXTRAPOLATION?

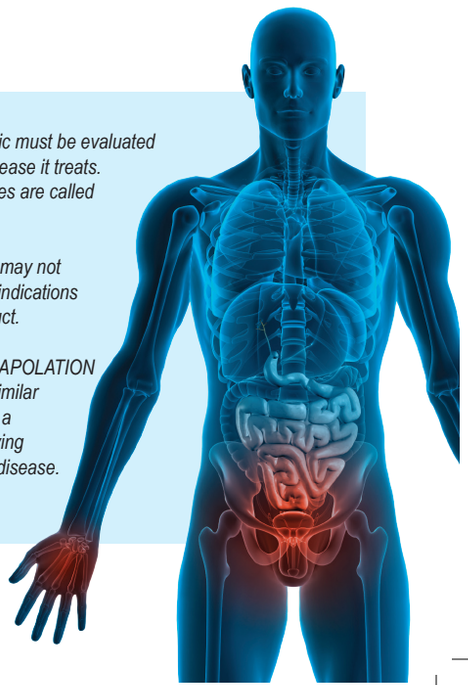
In some instances, there is strong scientific rationale to support the use of biosimilars in diseases in which they have not been clinically tested. However, in some instances, there is disagreement among members of the medical community and global regulatory authorities as to whether clinical testing is a critical part of evaluating safety and efficacy.

One example is the use of **infliximab,** a very large, very complex biologic used to treat a number of diseases affecting the skin and joints: rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis; and some diseases affecting the bowels: Crohn's Disease, and Ulcerative Colitis.

*An originator biologic must be evaluated in each different disease it treats. These approved uses are called INDICATIONS.*

*A biosimilar may or may not be approved for all indications of the original product.*

*INDICATION EXTRAPOLATION occurs when a biosimilar is approved to treat a disease without having been tested in that disease.*



## CLINICAL DATA REQUIREMENTS FOR INFLIXIMAB BIOSIMILAR APPROVAL

For approval in all these uses, the original biologic sponsor conducted clinical testing in each indication. However, the two infliximab biosimilar sponsors have proven biosimilarity, safety, and efficacy in one or two patient populations: those with rheumatoid arthritis and those with ankylosing spondylitis. Regulators around the world disagreed on whether the infliximab biosimilars could be used in all of diseases (or indications) in which the original biologic is used.

| ARE CLINICAL DATA REQUIRED TO SHOW SAFETY AND EFFICACY PRIOR TO APPROVAL? | | EMA | | Health Canada | | FDA | |
|---|---|---|---|---|---|---|---|
| | | Original Biologic | Biosimilar | Original Biologic | Biosimilar | Original Biologic | Biosimilar |
| SKIN/JOINT INFLAMMATION DISEASES | Rheumatoid Arthritis | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ |
| | Ankylosing Spondylitis | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ |
| | Psoriatic Arthritis | ✔ | ✖ | ✔ | ✖ | ✔ | ✖ |
| | Plaque Psoriasis | ✖ | ✖ | ✖ | ✖ | ✖ | ✖ |
| BOWEL INFLAMMATION DISEASES | Crohn's Disease | ✔ | ✖ | ✔ | ✔ | ✔ | ✖ |
| | Ulcerative Colitis | ✔ | ✖ | ✔ | ✔ | ✔ | ✖ |

- Both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved an infliximab biosimilar for all indications for which the original biologic is approved without additional clinical testing in those diseases; many physicians and patient groups around the world disagreed.

- Health Canada, however, initially approved an infliximab biosimilar only for the diseases affecting the skin and joints. It required additional clinical data before approving for bowel diseases two years later, due to concerns that differences between the original biologic and the biosimilar that may have affected clinical safety and efficacy.

ASBM believes that each biosimilar should be evaluated on a case-by-case basis. Patient safety should be the primary consideration, and if there are any gaps in the clinical or scientific rationale used to support indication extrapolation, clinical testing should be performed.

## HOW DOES INDICATION EXTRAPOLATION AFFECT INTERCHANGEABLE BIOSIMILARS?

Interchangeable biosimilars have met a higher regulatory standard in that it has been shown they can be safely switched back and forth with the originator product, without any additional risk to the patient. ASBM, and many others in the clinical community believe that to gain approval as an interchangeable biosimilar, there should be strong scientific and clinical rationale to use the interchangeable biosimilar in all the diseases for which the original biologic is approved.

## HOW SHOULD BIOSIMILAR LABELING REFLECT INDICATION EXTRAPOLATION?

In a 2015 survey of more than 800 U.S. healthcare providers conducted by ASBM, 80% of physicians, and 76% of pharmacists agreed or strongly agreed that the information in a biosimilar product label should specifically state for which indications approval was based on study in that disease, vs. approval granted based on extrapolation from studies in other diseases.

For patients to enjoy the benefits of biosimilars, providers need to have confidence in them. ASBM supports informative, transparent labeling that will build that confidence.

*The Alliance for Safe Biologic Medicines is a diverse group of stakeholders including physicians, pharmacists, patients, researchers, and manufacturers of both biologics and biosimilars. ASBM is an organization focused on promoting the use of biologic medicines, while ensuring their safety and efficacy.*

*Learn more at **www.safebiologics.org**.*

SafeBiologics
ALLIANCE *for* SAFE BIOLOGIC MEDICINES