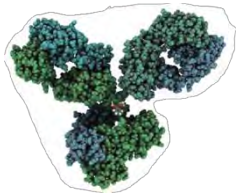
You Say Tomato, I Say Tomatomab, Let's Call the Whole Thing off



Biosimilars in Practice

MEDS Conference - January 29th, 2019

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UNIVERSITY OF MANITOBA

MEMORIAL UNIVERSITY
School of Pharmacy

Faculty/Presenter Disclosure

- Relationships with commercial interests:
  - No Conflicts to Declare

Objectives

- Recognize the difference between biosimilar and generics and the implications on drug choice for patients and prescribers
- Evaluate the clinician’s role in interpreting health policy related to biosimilar alternatives.

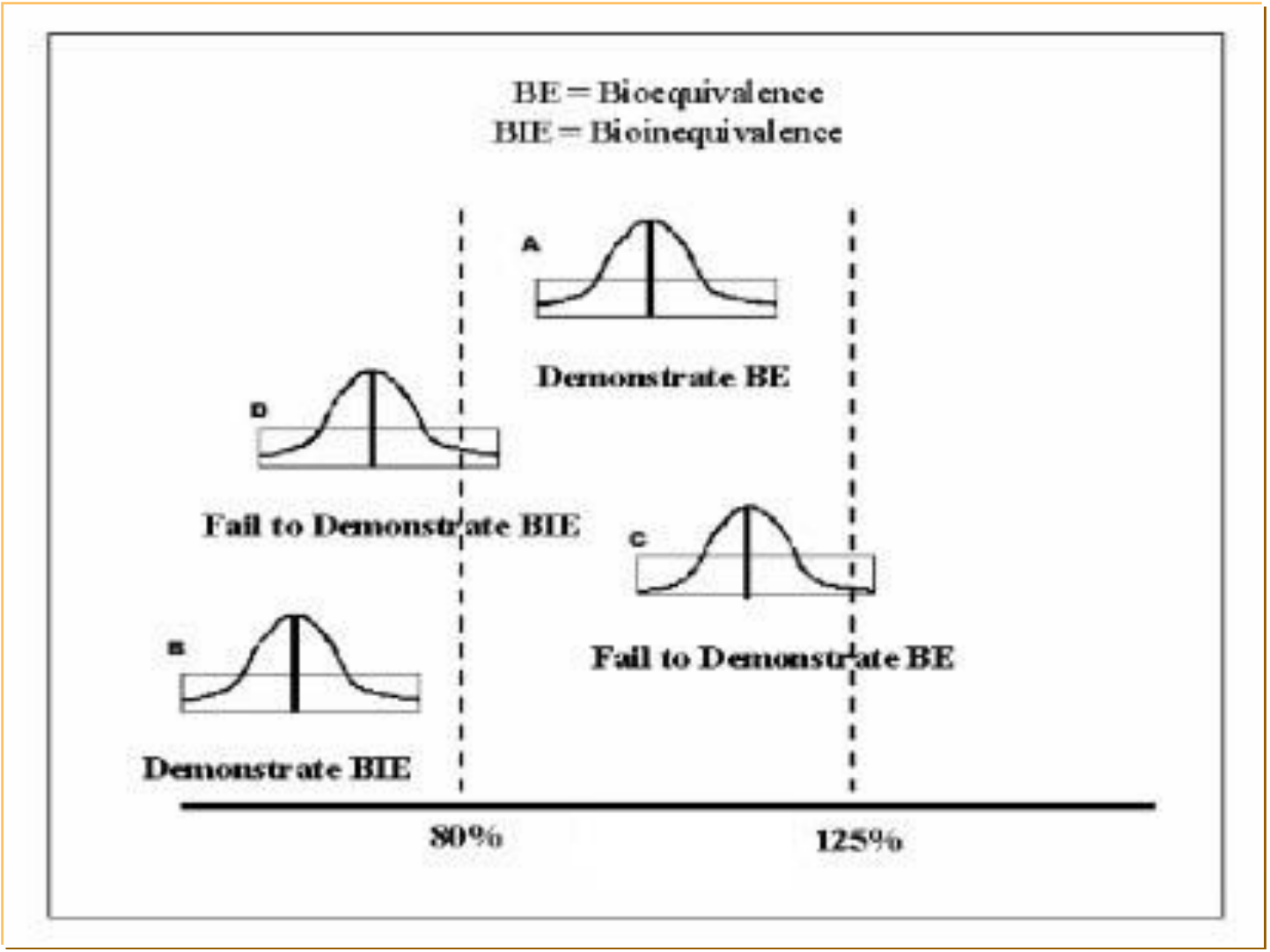
Generically Equivalent

- Pharmaceutically equivalent
- Therapeutically equivalent
- The *same* drug with the *same* effect, but the product is from a different manufacturer
- Excipients may differ

Bioequivalence

Bioequivalence is based on a comparison of ratios where the ratios of generic to brand name for each pharmacokinetic variable does not differ by more than 8:10 or the range for the confidence interval is defined as a lower limit of 80% and an upper limit of 125%. There is a common misperception that the variance maybe up to 45%. This is not true. Health Canada bioequivalence standards do say that the area under the curve(AUC) must be within 80% to 125% of the brand name based on a 90% confidence interval. A confidence interval is a range of measurements within which we can be confident that the true result lies. So for the entire confidence interval to fall within the 80% to 125% range, the variance has to be much less. The true variance is generally less than 5%

Bioequivalence

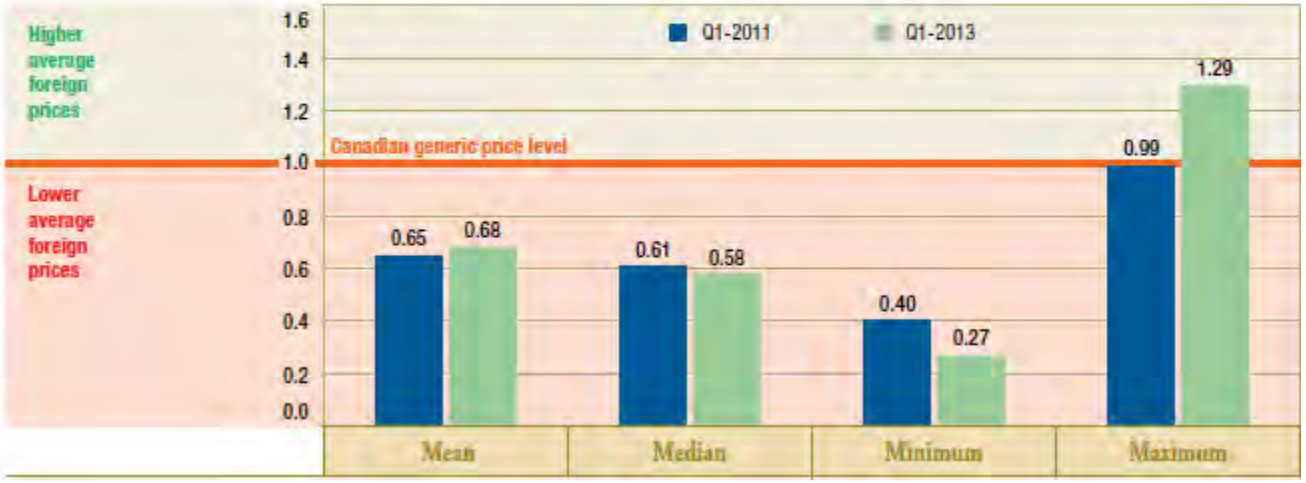


The Medical Post

- "Dr. [redacted], a medical director at the Toronto Dermatology Centre, finds that "pharmacists seem fairly respectful of (the no substitutions request)." One drug he routinely asks not to be replaced for a generic is Accutane (isotretinoin). Generic versions of the drug are approved with anywhere from 80% to 125% of the active ingredient, and he doesn't want a patient getting an 80% generic one day and then be switched to a 125% generic the next. "It's a very serious drug," he explained."

Generic Pricing

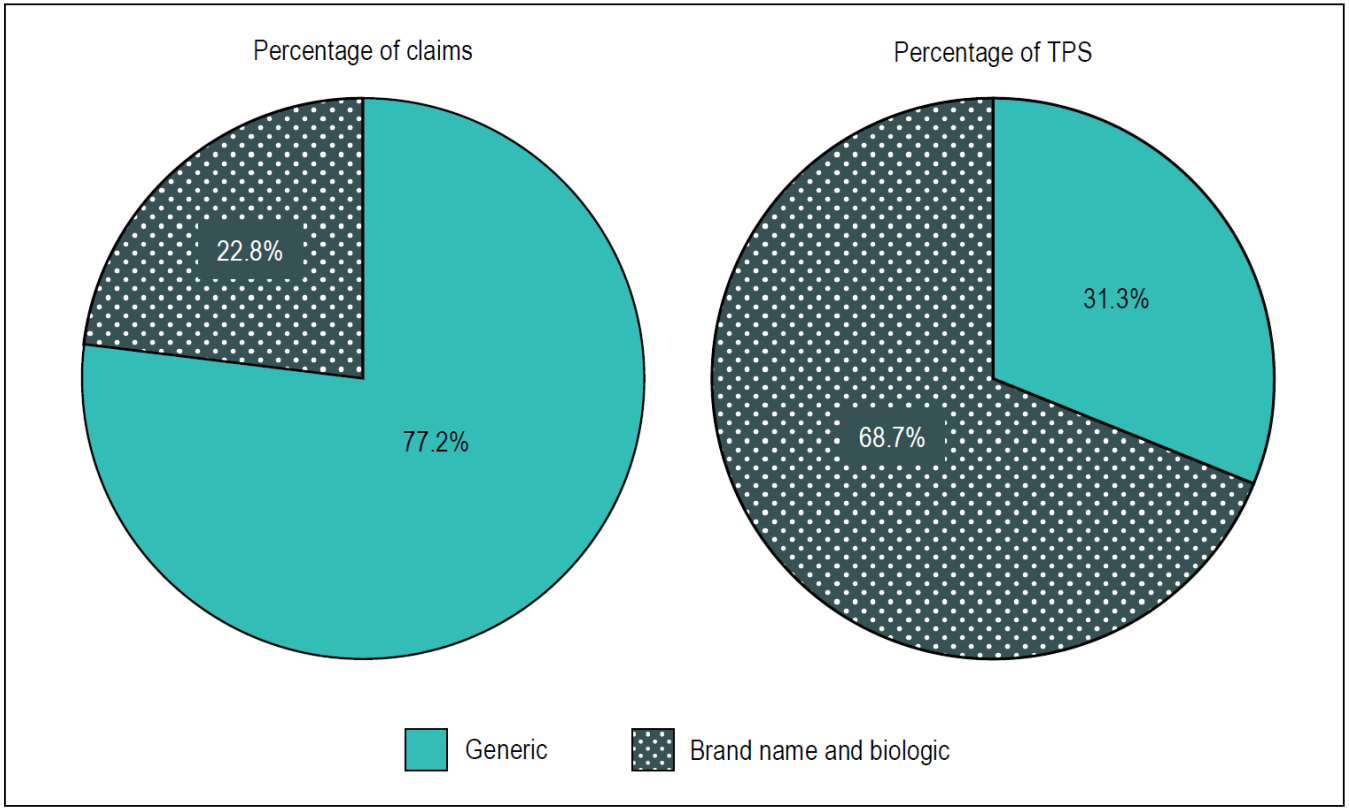
Figure 3.1 **Average multilateral foreign-to-Canadian generic price ratios**
Generic drugs, PMPRB-7*, Q1-2011 and Q1-2013



Published by the Patented Medicine Prices Review Board
Generic Drugs in Canada, 2013 is available in electronic format at www.pmprb-cepmb.gc.ca

Generic Cost

Figure 1 Percentage share of public drug program spending and of accepted claims, by type of drug,* 2017



Canadian Institute for Health Information. *Prescribed Drug Spending in Canada, 2018: A Focus on Public Drug Programs*. Ottawa, ON: CIHI; 2018.

A Comparison

Small Molecule	Biologic
Produced by chemical synthesis	Produced by living cells (animal, bacteria, yeast)
Predictable and consistent manufacturing means you can precisely define the final molecule	Manufacturing change can impact final product • Living systems are intrinsically complex and are sensitive to very minor changes • Process/manufacturing differences could alter the biologic in terms safety and/or efficacy
Low molecular weight	Large molecular weight
Mostly well defined physicochemical properties	Complex physicochemical properties (tertiary structure, modifications). Intrinsically variable. Glycosolation
Generally stable	Sensitive to heat, pH, shear, etc.
Single entity, essentially pure	Heterogeneous mix (including process-related impurities)
Simple assay to characterize	Multiple complex assays needed to completely characterize

Biologics

- Account for 21.6% of drug expenditure in Canada in 2017
- 3 of top 10 drug classes by cost are biologics
- Approximately 30% of new drugs are biologics
- Subsequent Entry Biologics or Biosimilars have begun to entry the Canadian market

SEBs Are Not Generics

Generics	SEBs
Small molecule drug	Large complex molecule
Chemically synthesized	Manufactured in living system
Fully characterized molecule	Challenging to fully characterize
Mechanism of action well understood	May not be well understood
Can be duplicated exactly	Impossible to duplicate exactly
Active ingredient is chemically identical to reference product	Active ingredient is highly similar to reference product
Approved on the basis of analytical similarity and bioequivalence	Approved on the basis of extensive in vitro comparability testing and reduced clinical comparability testing (pharmacokinetics, safety, and efficacy)

Biosimilars in Canada

Drug / Médicament (trade name / nom commercial)
Epoetin alfa / Époétine alfa (Eprex)
Filgrastim / Filgrastim (Neupogen)
Infliximab / Infliximab (Remicade)
Follitropin alfa / Follitropine alfa (Gonal-f)
Insulin glargine / Insuline glargine (Lantus)
Etanercept / Étanercept (Enbrel)
Adalimumab / Adalimumab (Humira)
Bevacizumab / Bévacizumab (Avastin)
Natalizumab / Natalizumab (Tysabri)
Omalizumab / Omalizumab (Xolair)
Ranibizumab / Ranibizumab (Lucentis)
Rituximab / Rituximab (Rituxan)
Trastuzumab / Trastuzumab (Herceptin)

NPDUIS National Prescription Drug Utilization Information System
"Supporting health care decision making in Canada"

Patented Medicine Prices Review Board

Conseil d'examen du prix des médicaments brevetés

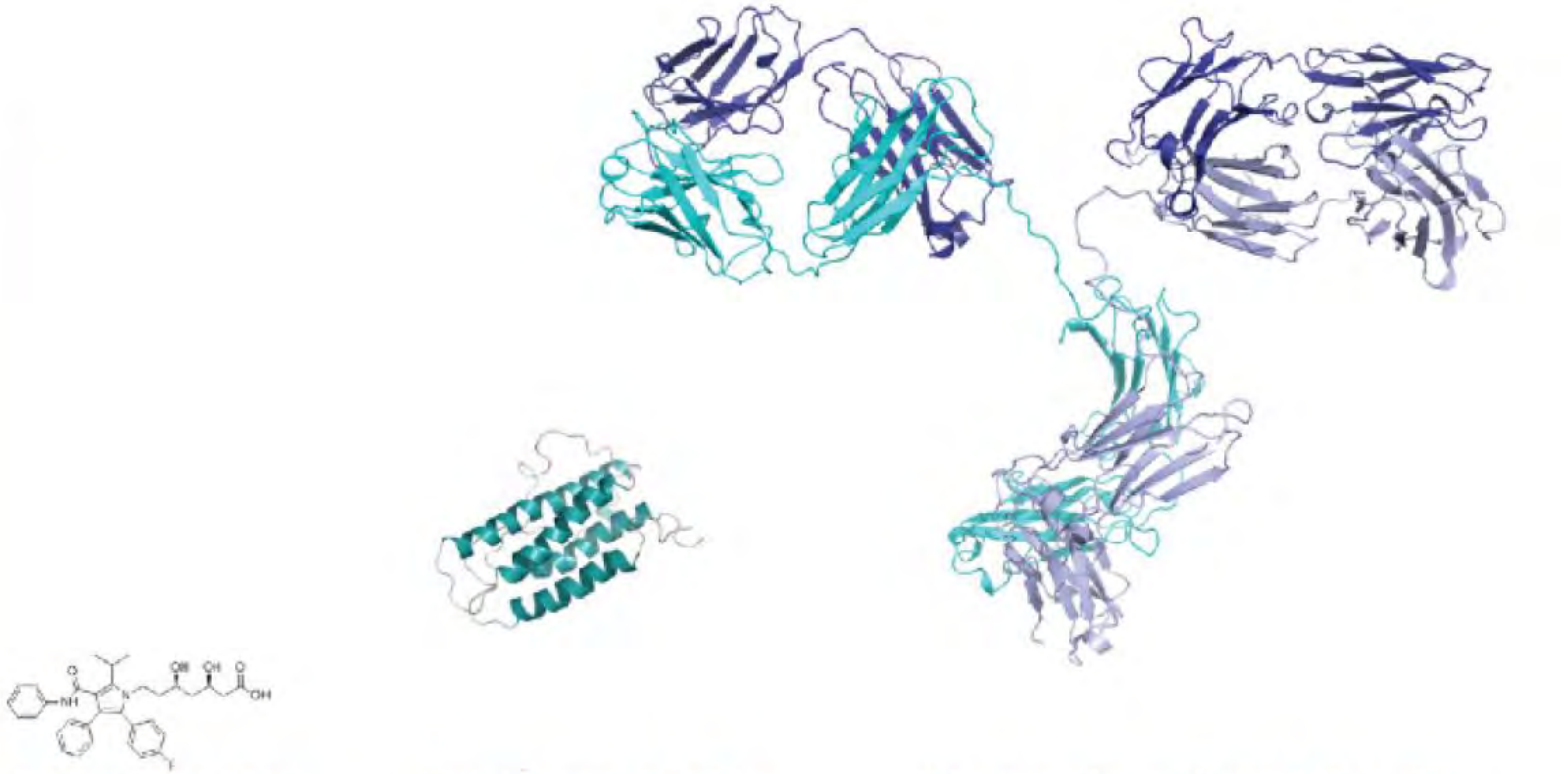
Biosimilars in Canada

ESTIMATED POTENTIAL SAVINGS IN THE THIRD YEAR FOLLOWING BIOSIMILAR ENTRY, CANADA

ÉCONOMIES POTENTIELLES ESTIMÉES LA TROISIÈME ANNÉE SUIVANT L'ARRIVÉE DES PRODUITS BIOSIMILAIRES, CANADA

	Drug / Médicament	2016 Sales* / Ventes* en 2016	Forecast / Prévision		Low estimate / Estimation basse (13% savings / Économies de 13 %)	High estimate / Estimation élevée (43% savings / Économies de 43 %)
			Year 3 / Année 3	Sales† / Ventes†		
Acute / Aigu	Filgrastim / Filgrastim	$126M	2019	$145M	$18M	$62M
	Epoetin alfa / Époétine alfa	$99M	2021	$75M	$10M	$32M
	Follitropin alfa / Follitropine alfa	$14M	2022	$20M	$3M	$8M
					(8% savings / Économies de 8 %)	(43% savings / Économies de 43 %)
Chronic / Chronique	Infliximab / Infliximab	$1004M	2018	$1,210M	$91M	$514M
	Adalimumab / Adalimumab	$649M	2021	$974M	$73M	$414M
	Etanercept / Étanercept	$337M	2020	$347M	$26M	$147M
	Ranibizumab / Ranibizumab	$337M	2021	$337M	$25M	$143M
	Insulin glargine / Insuline glargine	$241M	2019	$306M	$23M	$130M
	Rituximab / Rituximab	$241M	2021	$286M	$21M	$122M
	Trastuzumab / Trastuzumab	$180M	2021	$202M	$15M	$86M
	Bevacizumab / Bévacizumab	$104M	2022	$110M	$8M	$47M
	Omalizumab / Omalizumab	$106M	2021	$184M	$14M	$78M
	Natalizumab / Natalizumab	$50M	2022	$62M	$5M	$27M

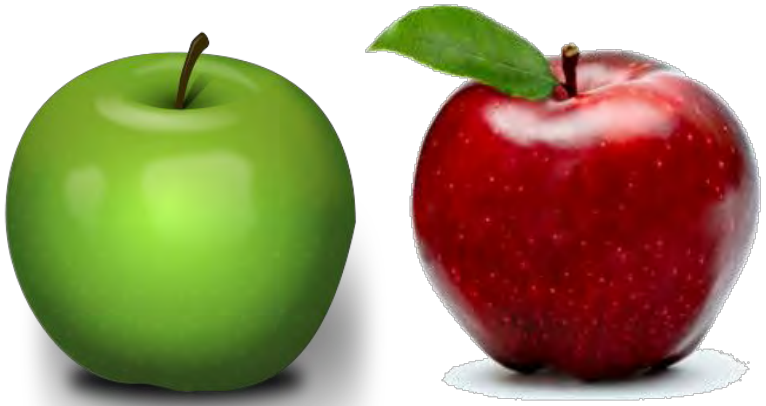
Complexity


Atorvastatin
~0.5 kDa
Erythropoietin
30 kDa
Monoclonal Antibody
150 kDa

Subsequent Entry Biologics

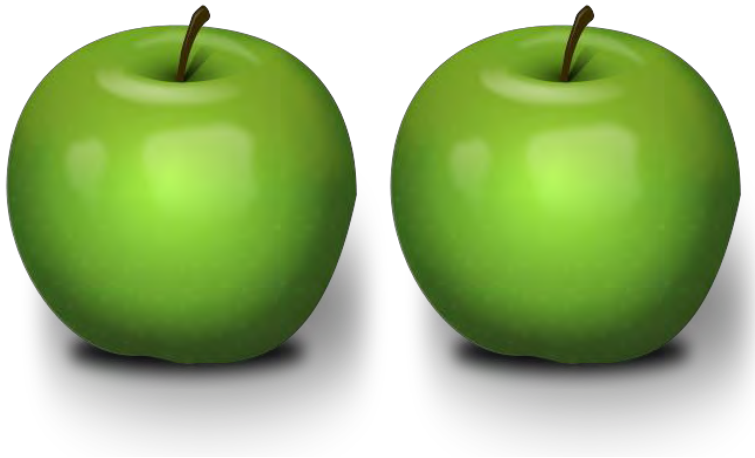
Health Canada definition: An SEB is biologic drug that enters the market *subsequent to a version previously authorized* in Canada, and with *demonstrated similarity* to a reference biologic drug.[1]

SEBs are similar...



Different cell lines
Different manufacturing processes

....but not identical

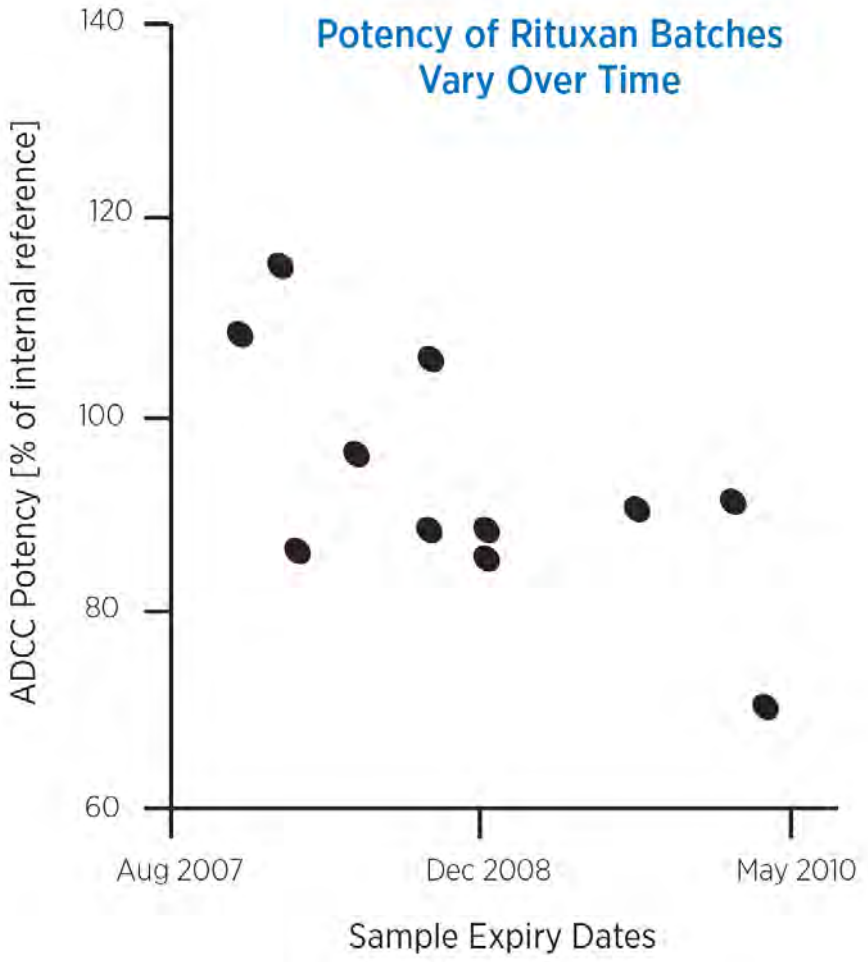


Impact of small differences in either biological or manufacturing process could lead to different clinical efficacy and safety for patients[2,3]

[1]Health Canada Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs), 2010/03/05

Roger SD. *Nephrology.* 2006;11:341-346;Power DA, et al. *J Pharm Pract Res.* 2008;38:137-139.

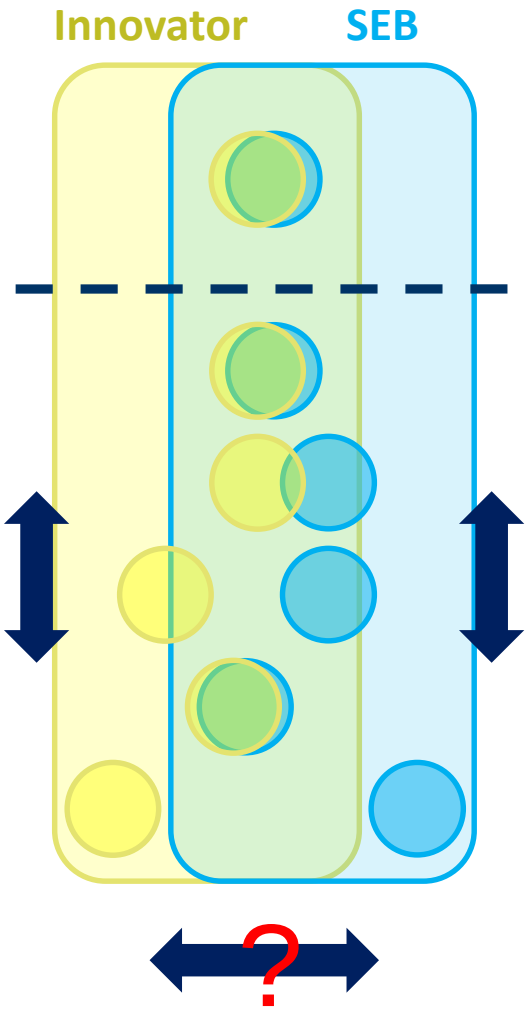
Complex for Everyone



Evolution Over Time

At Approval by Health Canada:
SEB must demonstrate similarity to innovator biologic

After Health Canada Approval:
SEB stand-alone product, therefore **regular assessments of similarity between SEB and innovator biologic drug not performed**



Independent manufacturing change

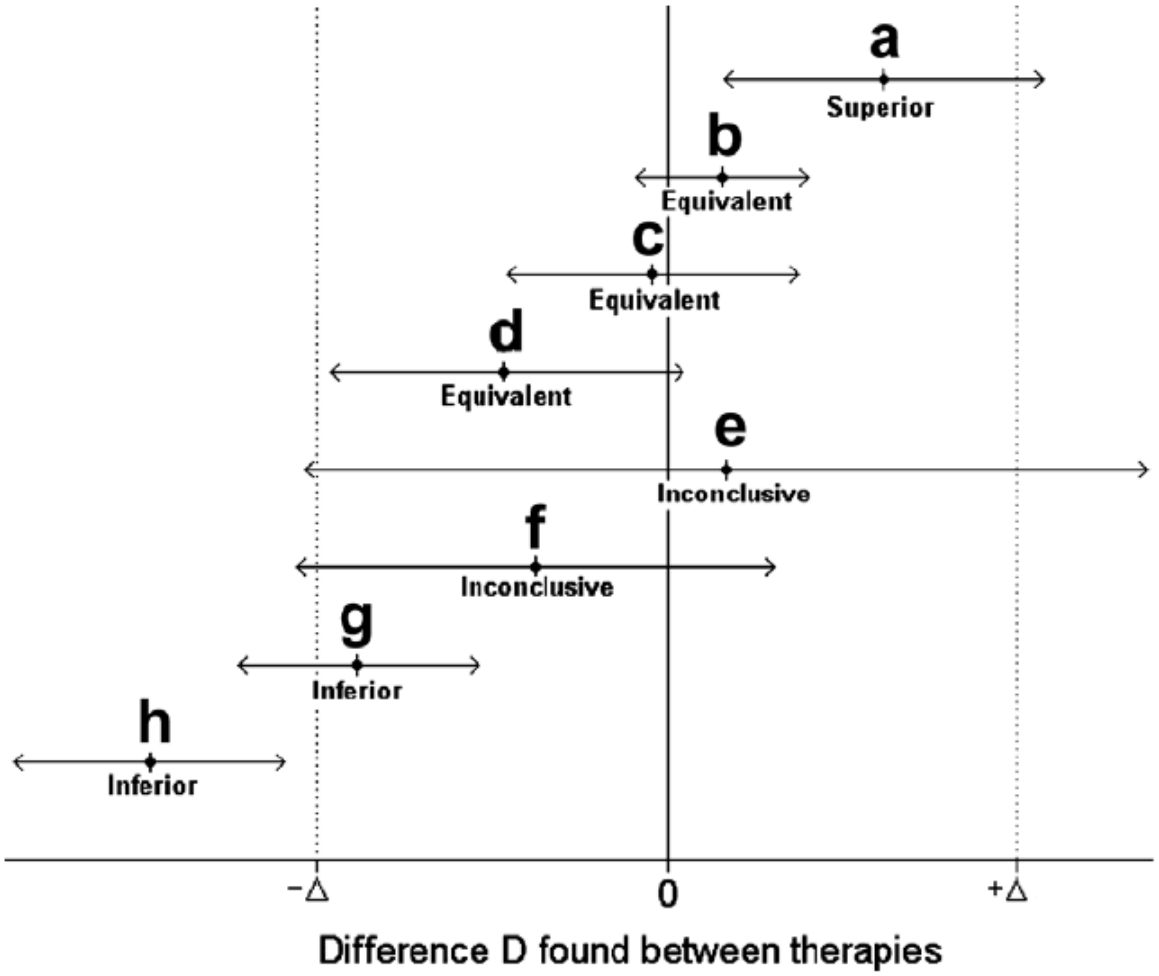
References in notes

Same Medication = Different Immunogenicity Rates by Indication

Infliximab Pivotal Clinical Trials per Indication	Anti-drug Antibody Incidence
Rheumatoid arthritis (ATTRACT)	8%–11%
Psoriatic arthritis (IMPACT 2)	16%
Ankylosing spondylitis (ASSERT)	6%
Crohn's disease (ACCENT 1)	7%–10%
Ulcerative colitis (ACT 1/2)	6%–11%
Psoriasis (EXPRESS)	27%

References in notes

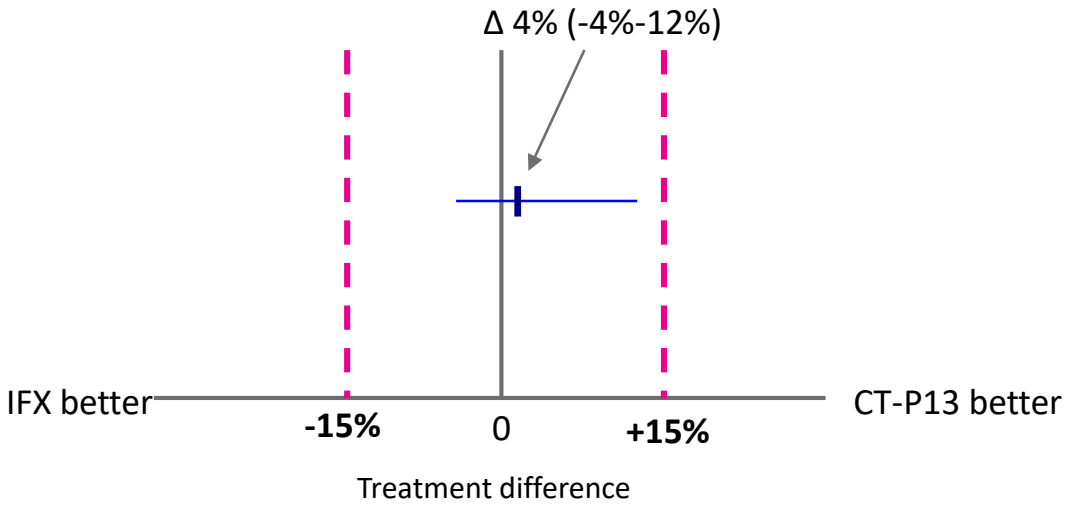
Equivalence



PLANETRA Results

ACR 20 at Week 30

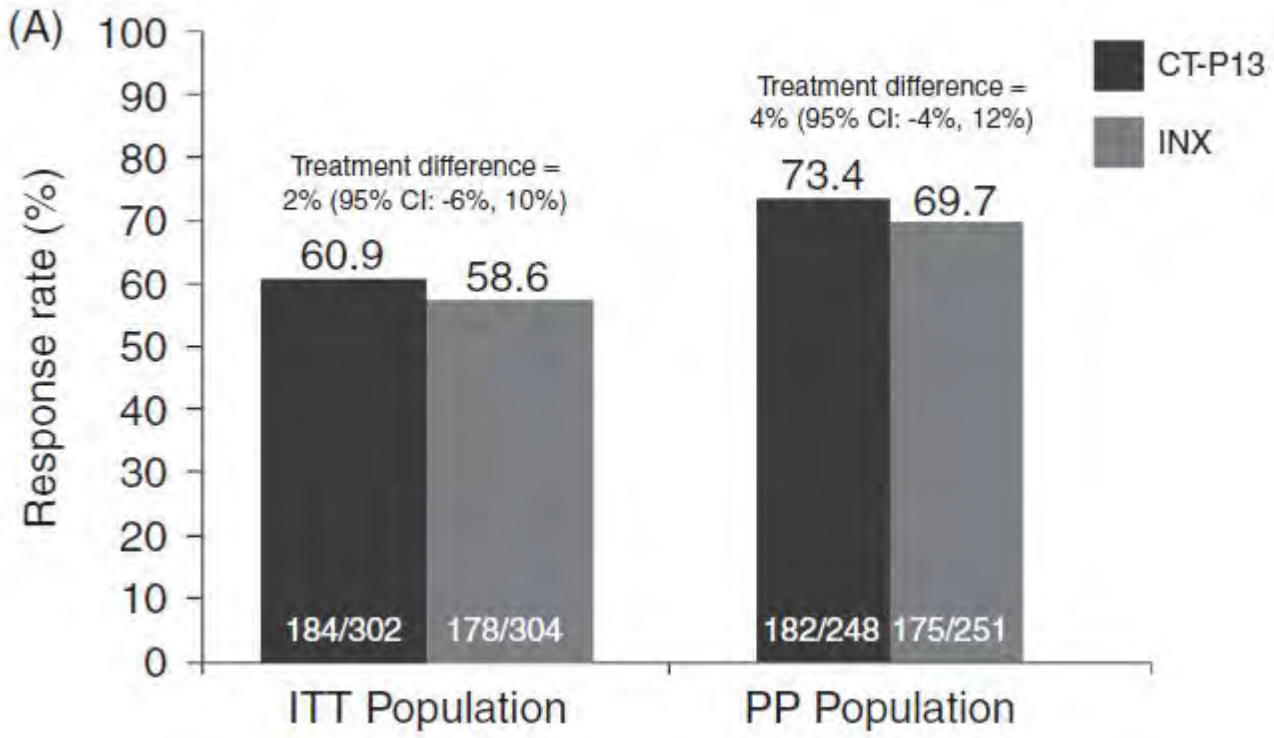
Result reported as treatment difference between CT-P13 and IFX (Δ) and 95% CI



Margin for equivalence in CT-P13 trials: Δ 30%

Yoo DH, et al. *Ann Rheum Dis* 2013;72:1613–20.

PLANETRA Results



Yoo DH, et al. *Ann Rheum Dis* 2013;72:1613–20.

Clinical Data Evidence: Remicade vs. CT-P13

Company Sponsored Clinical Trials	REMICADE* (infliximab)			CT-P13 (SEB to infliximab)		
	Patients Exposed to Drug	Number of Studies [1-34]		Patients Exposed to Drug	Number of Studies [35,36]	
		Phase I/II	Phase III/IV		Phase I	Phase III
Rheumatoid Arthritis [1-11, 35]	3,293	5	6	302[35]		1
Ankylosing Spondylitis [12, 13, 36]	385	1	1	125[36]	1	
Psoriatic Arthritis [14-16]	311		3			
Crohn's Disease (Adult) [17-23]	1393	4	3			
Crohn's Disease (Pediatric) [24, 25]	133	1	1			
Ulcerative Colitis [26-28]	647	1	3			
Ulcerative Colitis (Pediatric)[29]	60		1			
Psoriasis [30-34]	2,496	1	4			
Total	**8,718**	**35**		**427**	**2**	

Extrapolation in Korea/EU; Canada (PsA/PSO)

***Over 19 years of clinical trial experience with over 1.8 million patients treated across all indications (cumulative exposure since approval)[37]**

References in notes.

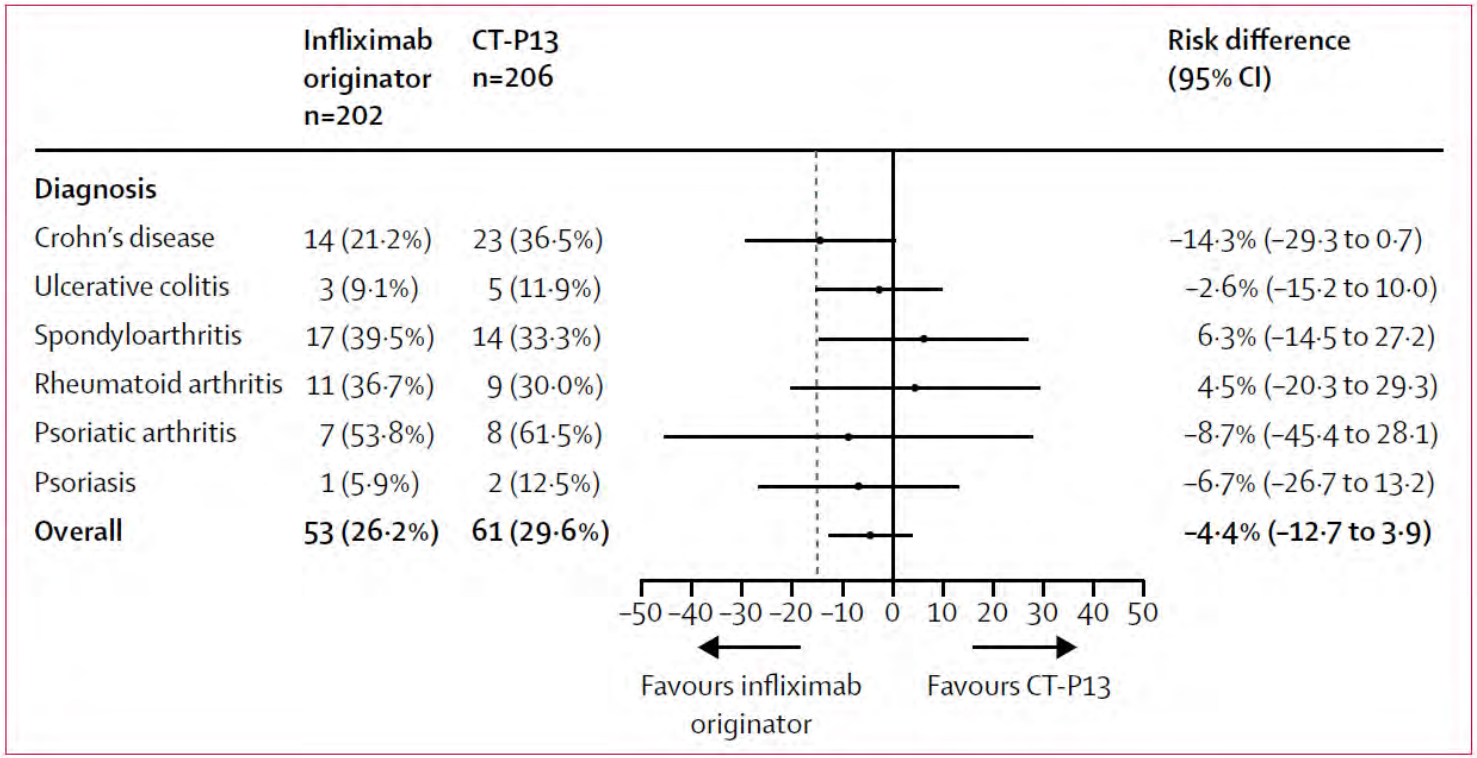
Health Canada Guidance on SEBs Extrapolation of Indications

- *"It may also be possible to extrapolate clinical data to other indications where rationales are sufficiently persuasive."*
- Extrapolation may be justified based on:
  - Mechanism of action
  - Pathophysiological mechanism(s) of the disease(s) or conditions involved
  - Safety profile in the respective conditions and/or populations
  - Clinical experience with the reference biologic

Health Products and Food Branch, Health Canada. 2010. Guidance for sponsors: Information and submission requirements for subsequent entry biologics

Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial

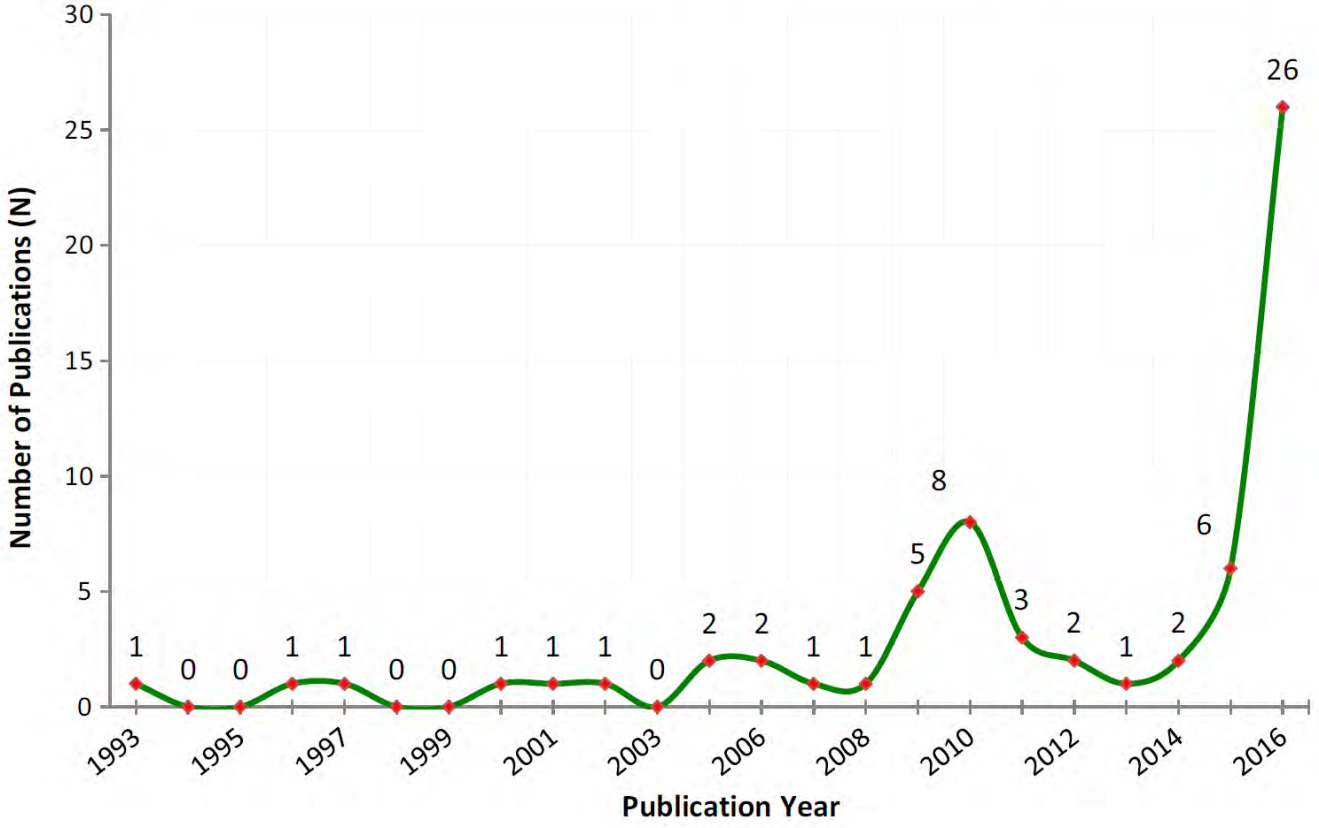
Kristin K Jørgensen, Inge C Olsen*, Guro L Goll*, Merete Lorentzen*, Nils Bolstad, Espen A Haavardsholm, Knut E A Lundin, Cato Mørk†, Jørgen Jahnsen†, Tore K Kvien†, on behalf of the NOR-SWITCH study group*



Lancet 2017; 389: 2304–16

Switching Reference Medicines to Biosimilars: A Systematic Literature Review of Clinical Outcomes

Hillel P. Cohen[1] · Andrew Blauvelt[2] · Robert M. Rifkin[3] · Silvio Danese[4] · Sameer B. Gokhale[5] · Gillian Woollett[6]



Drugs (2018) 78:463–478

Switching Reference Medicines to Biosimilars: A Systematic Literature Review of Clinical Outcomes

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Keypoints

Scientific literature (1993 up to 30 June 2017) was reviewed to identify publications that contained primary data on single or multiple switching from reference biological medicines to biosimilars.

A total of 90 studies were identified involving seven molecular entities that treated 14 disease indications, and enrolled a total of 14,225 individuals.

The great majority of studies did not report differences in safety, efficacy, or immunogenicity after a single switch event compared to patients that were not switched. Only a small number (three) of multiple switch studies have been published to date, but likewise no differences were detected.

Overall, the results suggest a low risk of either a safety concern or a loss of efficacy after switching to a biosimilar.

Drugs (2018) 78:463–478

Biosimilars in Canada

> HEALTH CANADA RECOMMENDS THAT A DECISION TO SWITCH A PATIENT BEING TREATED WITH A REFERENCE BIOLOGIC DRUG TO A BIOSIMILAR SHOULD BE MADE BY THE TREATING PHYSICIAN IN CONSULTATION WITH THE PATIENT AND TAKING INTO ACCOUNT AVAILABLE CLINICAL EVIDENCE AND ANY POLICIES OF THE RELEVANT JURISDICTION.[6]

https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/pdf/brgtherap/applic-demande/guides/biosimilars-biosimilaires-qa-qr-eng.pdf

Key learning from Scotland

NHS SCOTLAND

- Opportunity is broader than biosimilar switch –improvement in biological medicine use
- Specialty specific approach necessary-oncology new challenges
- Mix of interventions– targets, peer pressure, infrastructure changes, improvement & shared learning approaches
- Clinical engagement and leadership critical to success
- Strategic ownership (helped reduce barriers)
- Complex cross-health system collaboration necessary
- Multidisciplinary team- pharmacists and nurses within clinics
- **Minimal clinical or patient concern**
- **No safety or loss of response (IBD audit ongoing)**

IHE INSTITUTE OF HEALTH ECONOMICS ALBERTA CANADA

Glargine Insulin

If all the Glargine insulin prescriptions in Manitoba were filled with Basaglar® instead of Lantus® – the province would save.

a) About $50
b) About $500
c) About $5000
d) About $50,000
e) About $500,0000

Questions


Lois Lois Lois Lois Lois Lois mom mom mom mommy mommy
momma momma momma ma ma ma ma mom mom mom mom
mommy momma momma
Hi
WHAT!!??