BIOSIMILARS – SIMILAR BUT NOT THE SAME

Dr. Mark MacMillan, MD, FRCPC

Gastroenterology and Hepatology
Medical Director of Endoscopy
Assistant Clinical Professor Dalhousie University/Memorial University
Dr. Everett Chalmers Regional Hospital

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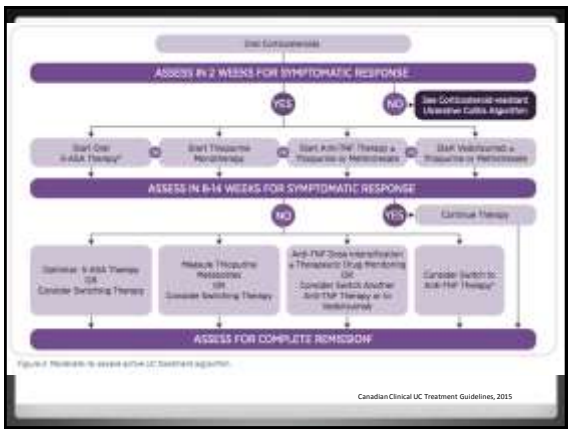
- Speakers fees/Advisory Boards
  - AbbVie, Janssen, Takeda, Pendopharm, AstraZeneca, Actavis/Allergan
- Research Support
  - Robarts, AbbVie

The IBD treatment landscape



Canadian Clinical UC Treatment Guidelines, 2015

Anti-Tumor Necrosis Factors

- Infliximab
  - Remicade
- Adalimumab
  - Humira
- Golimumab
  - Simponi

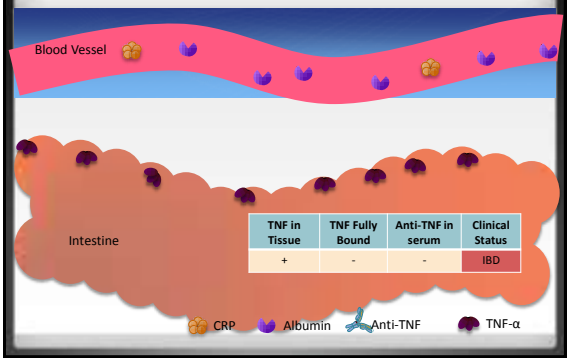
Alpha 4, Beta 7 integrin inhibitor

- Vedolizumab
  - Entyvio
  - humanized monoclonal antibody that inhibits adhesion and migration of leukocytes into the gastrointestinal tract by preventing the alpha4beta7 integrin subunit from binding to mucosal addressin cell adhesion molecule-1 (MAdCAM-1).

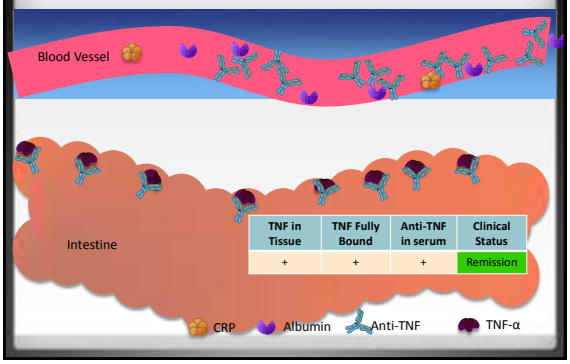
- Over the past several years, Subsequent Entry Biologics (SEBs) or biosimilars have been developed and are in the market place
- These drugs are available in Canada and are in the market place
- What does this mean for your patients?
- Who decides what drug your patients receive?

How do anti-TNFs work in the body?

Active IBD – No anti-TNF



Treatment with anti-TNF - Remission



Lets review what has happened to this point

- *Biosimilars* in the European Union, *follow-on protein product* in the United States and *subsequent entry biologics (SEBs)* in Canada
- SEBs are not generic biologics[1,2,3]
- SEBs are made using a different host cell line and a different manufacturing process[1,2,3]
- SEBs manufactured by different manufacturers are not identical to the innovative [1,2,3] product or reference biologic drug (RBD) nor to each other[3]
- SEB development fundamentally differs from manufacturing changes for innovator products and this is recognized in regulatory guidance by EMA[4] and FDA[5]

1. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp&mid=WC0b01ac058002958c
2.US FDA. Guidance for industry. Scientific considerations in demonstrating biosimilarity to a reference product. Draft Guidance. Feb 2012
3.http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf
4.Guidance for Industry Scientific Considerations in Demonstrating Biosimilarity to a Reference Product
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.
5. Guideline on Similar Biological Medicinal Products Containing Biotechnology-derived Proteins as Active Substance: Quality Issues EMA/CHMP/BWP/49348/2005

Health Canada Statements on Subsequent-Entry Biologics (SEB)

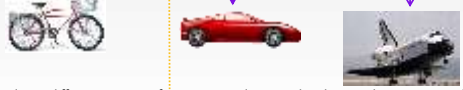
- SEBs are regulated as "New Drugs" by comparing to a reference product previously authorized and marketed in Canada with a reduced non-clinical and clinical package.
- The basis for accepting a reduced non-clinical and clinical data package for an SEB hinges on demonstrated similarity between the SEB and the suitable Reference Biologic Drug (RBD)
- **SEBs are not generics** (because biologics are more complex, SEB manufacturers cannot guarantee that their version is exactly identical to the original innovator's version). **Authorization of an SEB is not a declaration of pharmaceutical or therapeutic equivalence to the RBD**
- Once a Notice of Compliance (NOC) is issued, the SEB is a new biologic drug and regulated accordingly. However, an SEB cannot be used as a RBD for another SEB submission

Presentation by Dr. Agnes Klein to the Canadian DIA Meeting in Ottawa October 29, 2014

Are they the same or not???

Biologics Are Far More Complex Than Conventional Medicines

Conventional ("small-molecule") Medicine	Biologics	
Aspirin	Human Growth Hormone	Monoclonal Antibody
180 Daltons and Zero Amino Acids	22,125 Daltons and 191 Amino Acids *Non-Glycosylated* Protein	148,000 Daltons and 1,330 Amino Acids



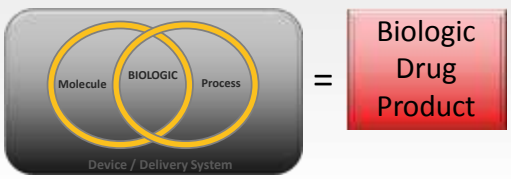
- Biologics differ in size, manufacturing complexity, and in the way they interact with cells and other proteins in the body
- Different systems of approval are necessary for small molecule generics and subsequent entry biologics

Graphic molecular structure of adalimumab available at http://www.healio.com/orthopedics/arthritis/news/online/%7b7bfa55f8-ff9a-4d03-bbe7-049421dbbdf9%7d/two-drugs-combined-better-for-ra-than-methotrexate-alone

What is a Biologic Drug Product?

Biologic = protein ***molecule*** + its specific manufacturing ***process***

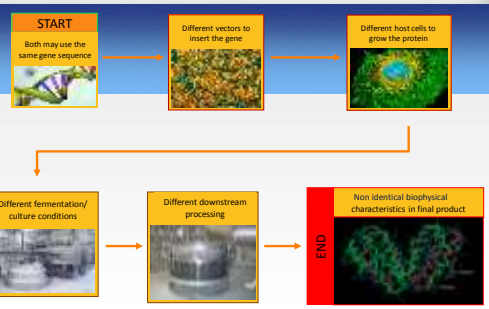
Biologic drug ***product*** = the biologic + the formulation + the delivery device



Each process, molecule, and device = unique biologic product

http://www.bio.org/articles/how-do-drugs-and-biologics-differ. Accessed November 19, 2013.

Two Different Processes Create Two Non-Identical Biologic Products



Biologics are Highly Sensitive to Process Changes:
Case studies of production process events with significant clinical impact

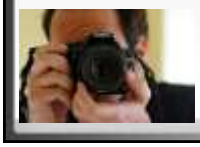
Product	Event	Impact
Myozyme/Lumizyme[1] (glucosidase alpha)	• 160 to 2,000 liter scale produced glycosylation differences	• New clinical trial • New biologics license application (stand-alone)
Eprex® (epoetin alpha)[2-4]	• Replaced HSA with sorbitol-80 stabilizer using un-coated stoppers in PFS	• 112 post-marketing case reports of neutralizing antibodies and PRCA • Withdrawn marketing authorization of new product
Binocrit® (HX575) (biosimilar epoetin alpha)[5]	• Undetected tungsten residue contamination from pin used to manufacture syringe	• Denaturation and Aggregation of epoetin alpha • Neutralizing anti-epo antibodies leading to two PRCA cases • Clinical trial discontinued
Omnitrope® (somatropin, rHGh)[6]	• Added new manufacturing facility • Spectrometric and physico-chemical data did not reveal significant differences • Registration trials: Unexpected immunogenicity from host cell protein	• Up to 60% of study subjects developed anti-GH antibodies from new mfg site's product • No influence on growth rate detected • Sponsor decided not to commercialize product from additional manufacturing facility
Raptiva (efalizumab)[7]	Change in production facility during phase III	• PK variations discovered during Ph III • FDA mandated new phase III trials to evaluate safety and efficacy • FDA approval delayed by 2 years

1. Mack. Nature Biotechnology 2008; 26, 592. 2. Kuhlmann M. et al. British Journal of Diabetes & Vascular Disease 2010;10: 90-97.
3. Boven K. et al. Kidney International 2005;67:2346-2353. 4. Bennett C. et al. N Engl J Med. 2004;351(14):1403-8. 5. Seidl A. et al. PharmRes 2012;29(6):1454–1467. Pure Red Cell Aplasia (PRCA)
6. EMEA 2006 Omnitrope EPAR: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000607/WC500069832.pdf
7. Strober B, et al. J Am Acad Dermatol 2012;66:317-22.)

Manufacturing Change vs. Biosimilar Development

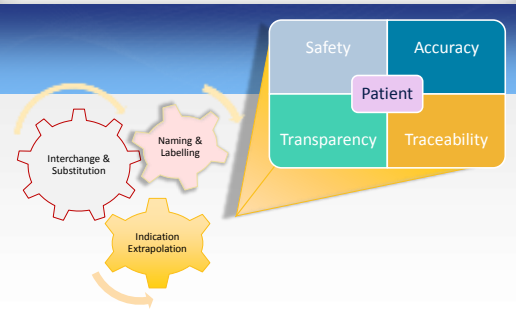
Manufacturing Change of Innovator Biologics
Optimizing an approved process for a product that has previously undergone significant R&D and a full pre-clinical and clinical regulatory approval process

Each governed by different regulatory requirements

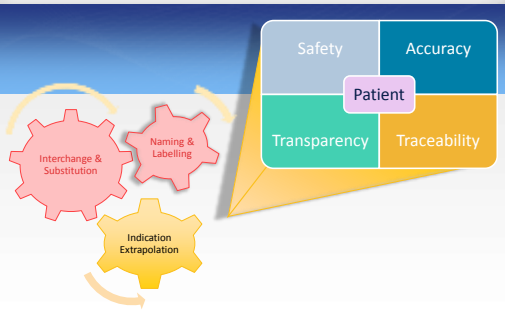


Biosimilar Development
Reverse engineering or recreating a version of the innovator's product starting from published information and the product on the market

Gearing Up a Patient-Centric System for All Biotherapeutics



Indication Extrapolation

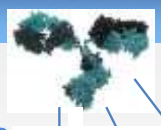


Indication Extrapolation

Reference product has been approved for Indications A, B, C and D

Approval in Indication **A**

2



1 Comparative CMC/quality, safety and efficacy studies of a subsequent entry biologic in a single disease or specific patient population (Indication **A**)

3 Extrapolation to other diseases or patient populations?


Indication **B**


Indication **C**


Indication **D**

Adapted from: 1.FDA Draft Guidance – Scientific Considerations in Demonstrating Biosimilarity to a Reference Protein Product (Feb 2012) – US Guidance 2. EMA: CHMP Guideline On Similar Biological Medicinal Products Containing Biotechnology-derived Proteins As Active Substance: Non-Clinical And Clinical Issues (20 February 2006) 3. WHO Guidance on Similar Biotherapeutic Product http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_JUNE06_2010.pdf 4.EMA

CT-P13 Infliximab Indications by Type of Approval

Indication	S. Korea 2012	EU 2013	Canada 2014
Rheumatoid Arthritis (RA)	CT*	CT*	CT*
Ankylosing Spondylitis (AS)	CT**	CT**	CT**
Psoriatic Arthritis	E	E	E
Psoriasis	E	E	E
Crohn's Disease (CD)	E	E	-
Pediatric CD	-	E	-
Ulcerative Colitis (UC)	E	E	-
Pediatric UC	-	E	-

CT- Approved with a complete data package including a single phase III* or Phase I** clinical trial.
E- Extrapolated indication without a phase I or III clinical trial. Dash (-): Not approved
These examples are not meant to provide a complete overview of all indication extrapolation decisions for CT-P13. Other juridictions have provided marketing authorization to CT-P13

REMSIMA™ / INFLECTRA™ product information accessed February 24, 2014:

1. S. Korea : http://www.celltrion.com/en/BIO/bio01.asp?menu_num=1
2. EMA: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/002576/WC500150822.pdf
3. Canadian Product Monograph; Inflectra www.hc-sc.gc.ca

Extrapolation: Health Canada Summary Basis of Decision

- Extrapolation from RA and AS to adult and pediatric IBD cannot be recommended due to the absence of clinical studies in IBD
  - Observed differences in the level of afucosylation, FcγRIIIa receptor binding, and some in vitro Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC) assays
  - Differences in ability of ADCC induction could not be ruled out and ADCC cannot be ruled out as a mechanism of action in IBD
  - Position supported by observation that certolizumab pegol, an anti-TNF that lacks the ability to induce ADCC, displays only marginal efficacy in Crohn's patients compared to other anti-TNFs
- Pathophysiological differences between the rheumatic diseases and the IBDs making a direct extrapolation between the two groups challenging without clinical or PK/PD bridging data
- The safety profile of infliximab is also different between the rheumatic and inflammatory bowel diseases

From ECCO 2015: Biosimilar but not the same

Objectives
To compare surgery, readmission rates and other parameters of consecutive Remicade and Inflectra anti-TNF-naïve IBD patients in a hospital in Ireland.

Methods
- Review of 36 consecutive IBD patients was completed.
- 14 Inflectra patients from January-July 2014.
- 22 Remicade patients from Dec 2011 to 2013.
- No differentiation between ulcerative colitis (UC), crohns and indeterminate colitis (IC).
- Direct comparison of overall demographics, surgery rates, readmission rates, use of steroids, disease activity and CRP trends.

Murphy et al, ECCO 2015, P505

From ECCO 2015: Biosimilar but not the same

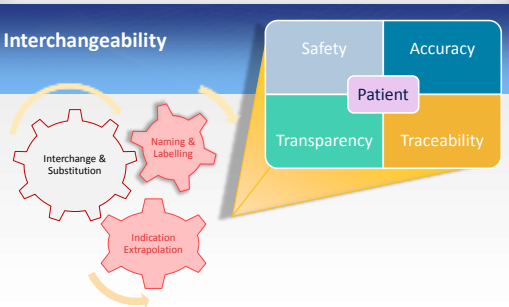
Results
Significant differences in the following parameters:
- Surgery
- Hospital readmission
- Median time to readmission (12 days Inflectra; 49 days Remicade/1 patient)
- Steroid augmentation (60% Inflectra vs. 8% Remicade)
- CRP over 8 weeks: 93% of Inflectra patients ***increase*** of CRP vs. 100% of Remicade ***de***crease of CRP
- Decrease in disease activity score in 57% of Inflectra pts vs. 95% of Remicade pts

Conclusions
- Study suggests biosimilars may be less efficacious as reference medicine.
- Highlights the need for large, prospective, RCTs of biosimilar IFX in IBD.
- Results reflect ECCO statement position about extrapolation and testing of biosimilars in IBD.

Key Takeaway: This results in the context of others presented at ECCO suggest more robust clinical studies might be necessary to clarify the use of infliximab Biosimilar in IBD. The two "cohorts" of patients compared match in all the relevant data collected (exp. Disease severity, time from diagnose, CRP) according to the authors. A publication is planned with all the data. Still need to consider the limitations of the sample size, design and the fact it is not a non-randomized trial.

Murphy et al, ECCO 2015, P505

Interchangeability

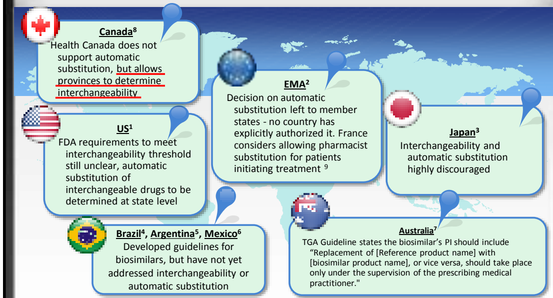


Interchangeability, Substitution and Switching

- **Interchangeability – Health or Regulatory Authority Designation**
  - Primarily a US standard :FDA can designate a subsequent entry biologic as interchangeable if [1]
    - It is expected to produce the same clinical result as the reference product in any given patient;
    - Repeated switching between subsequent entry biologic and reference product presents no greater safety or efficacy risk than continued use of the reference product
- **Substitution – Pharmacist Action**
  - When a pharmacist substitutes a certain prescribed product by another equivalent product
  - If without the prescribing physician's involvement, it is considered "automatic" or "involuntary" substitution

1. BPCI Act. Biologics Price Competition and Innovation Act of 2009. Federal Register 2010; H.R. 3590-686-702;. 2.European Commission: What you need to know about biosimilar medicinal products . Consensus Information Paper 2013.

Interchangeability and Substitution



1: FDA Biosimilar Guidance Webinar, February 15, 2012; 2: EMA, Questions and Answers on biosimilar medicines; European Biopharmaceutical Enterprises (EBE) Survey on Biosimilars, May 2011; 3: MHLW Guideline for Ensuring Quality, Safety and Efficacy of Biosimilar Products, March 2009 ; 4: FDLI Update, July 2012; 5: ANMAT, Disposición N° 7729/2011 (publicado el 21 de Noviembre de 2011); 6: Proyecto de PROY-NOM-257-SSA1-2013; 7: TGA Biosimilar Guidance; 30 July 2013; 8:; Health Canada Interchangeability and Substitutability of Subsequent Entry Biologics, July 2010 http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/guides/seb-pbu/01-2010-seb-pbu-qa-qr-eng.php#q15 9: GaBiOnline.net France to allow biosimilars substitution Accessed 2/24/2014 http://www.gabionline.net/Policies-Legislation/France-to-allow-biosimilars-substitution

Health Canada: Interchangeability and Substitution for Biosimilars[1]

- Biosimilars are not generic biologics
- Authorization of a biosimilar is not a declaration of pharmaceutical or therapeutic equivalence to the RP*
- Health Canada :
  - Does not support automatic substitution of a biosimilar and its RP*
  - **Recommends that physicians be involved in interchange of biosimilars and RP***

Scientifically based

1. **Pharmaceutics:** drug substances of the biosimilar and RP* are not identical
2. **PK/PD:** biosimilar is not bioequivalent to the reference drug
3. **Safety:** as a consequence of their complexity and impurity profiles, automatic interchangeability of biologics or biosimilars could give rise to different clinical consequences
4. **Immunogenicity:** repeated switches between biosimilar and RP* may increase immunogenicity with potential negative effects
5. **Clinical use:** a biosimilar may not receive authorization for all indications or uses
6. **Post-market:** data used in the demonstration of "similarity" are only valid at the time of market authorization due to possible significant port-market changes and "manufacturing drift"

*RP= Reference Product

1. Bradley J Scott, PhD; Agnes Klein, MD,PhD; Jian Wang,MD,PhD: Journal of Clinical Pharmacology June 2014; DOI 10.1002

Interchangeability and Substitution

Summary

- Given the limitations of post authorization data, it is currently impossible to conclude an absence of a risk of switching biologics.[1]
- According to the FDA, approval of biosimilarity alone is insufficient to establish interchangeability or substitutability with the reference product[2]
- Some physicians have therefore expressed that interchangeability of mAbs should be evaluated on an individual basis by the treating specialist and should not be routinely recommended[3]

1.Ebbers H ,et al.Expert Opin. Biol. Ther. (2012) 12(11). 2.Biologics Price Competition and Innovation Act of 2009 . 3. B Gecse Gut, published on line March 16, 2013 as 10.1136/gutjnl-2012-303824.

Summary: What Is Known/Agreed Today About Biosimilars

- Biosimilars are not generic copies of their reference product (RP)[1,2,3]
- Can be developed through abbreviated clinical development pathway [1,2,3]
- Indication extrapolation is possible with adequate justification[1,2,3]
- Biosimilarity status does not imply interchangeability[4,5]
- Immunogenicity profile may differ from RP, and may only show when used in a larger, real life patient population[6,7]
- Biologics are not biosimilars of themselves after a manufacturing change fulfilling ICHQ5E specifications[8]

*MA= Marketing Authorization

1.http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp&mid=WC0b01ac058002958c 2.US FDA. Guidance for industry. Scientific considerations in demonstrating biosimilarity to a reference product. Draft Guidance. Feb 2012 .http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf 4.FDA Biosimilar Guidance Webinar, February 15, 2012; 5: EMA, Questions and Answers on biosimilar medicines; European Biopharmaceutical Enterprises (EBE) Survey on Biosimilars, May 2011;6.Edwin Choy & Jacobs IA Seminar in oncology, Vol.41, Nº S1, Feb 2014, S3-S14.; 7.Mould DR and Greens B- Concepts and Lessons for drug development Biodrugs 2010; 24(1): 23-39. 8.ICH Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process.

Summary cont…

- SEBs are not generics, as the manufacturing process is the product
- SEBs may be less expensive than brand name biologics, but present uncertainty with respect to safety, efficacy, and extrapolation to other indications
- SEBs should have unique names and should not be interchangeable or substitutable
- Patient support programs are an important aspect of patient care and management with biologic drugs
- There is a need for pharmacovigilance with SEBs, and registry programs are recommended to monitor for long-term safety and efficacy outcomes

CAG position statement regarding SEBs for IBD

1. SEBs represent a potentially effective and cost saving option for the management of IBD that may serve to enhance access to biologic therapy.
2. SEBs should be regarded as stand-alone products, and should be supported by well-designed nonclinical and clinical studies in a population relevant to Canadian patients.
3. SEBs cannot be regarded as interchangeable with the reference biologic drug (RBD).
4. Prescriptions for RBDs should not be automatically substituted for less expensive SEBs by dispensing pharmacies.
5. SEBs should be supported by long-term pharmacovigilance data in a fashion similar to RBDs.
6. Companies bringing SEBs to the Canadian market should be committed to improving patient care by acquiring new scientific data beyond that which is required as a minimum to satisfy regulatory authorities and their commercial imperatives.

CAG: Key questions moving forward

- The impact of immunogenicity on an SEB?
  - No guarantee that our understanding of the impact of immunogenicity to infliximab and adalimumab will easily be extrapolated to an SEB that may be subtly different in molecular structure
- How will clinical trials involving patients with IBD proceed and how will they be designed?
  - What will be the requirement with respect to the design of the clinical trial performed (superiority, noninferiority, etc).
  - Will regulatory agencies require both induction and maintenance data or only induction data?
  - Where will these clinical trials be conducted?

But why should we care…???

Patient Support Programs- what our patients want

- Treatment initiation
  - Manage reimbursement issues
  - Cost barriers
  - Scheduling/administration of drug
- Ongoing treatment
  - Update medical orders
  - Monitor adverse events
  - Track contraindications
- Communication
  - Provide consistent point of contact
  - Post treatment reports
- Disease support
  - Living with chronic disease
  - Manage comorbidities
  - Exercise programs, diet, nutrition
  - Patient association partnerships

Dr. Edmond –Jean Bernard, NICE Summit 2015

Adalimumab biosimilar		Etanercept biosimilar		Infliximab biosimilar	
Phase III • Amgen [primary endpoint completed] • Sandoz • Samsung Bioepis/Merck/ Biogen • Boehringer Ingelheim [recruiting] • Zydus Cadila [completed] • Reliance Life Sciences **Phase I** • LG Life Sciences • Coherus [completed] • Pfizer • Kyowa Hakko Kirin [Phase I restarted after protocol redesigning] • Oncobiologics and partners [InVentiv/Liomont/ Ipca/Huahai] [Phase I protocol approval]	**Preclinical** • Celltrion • Baxter/Momenta • Mabion • Teva • Merck Serono • Mylan/Biocon • Dr. Reddy's Laboratory • Alteogen • IVB/PharmaPraxis • BahiaFarma/Libbs/ mAbxience/Fosun • Bio-Manguinhos/ Orygen • Epirus • Qilu Pharma • Fosun • Lupin • Cipla • Genor Pharma/ BIOCND • Innovent Biologics **Early development** • BioXpress/AET • Meridian • Intas • Dong-A	**Marketed** • Cipla/BioMab • Shanghai Celgen Bio • Shanghai CPGJ /LatAm partners **Pre-registration** • Hanwha • Hisun • Landsteiner **Phase III** • Samsung Bioepis/Merck/ Biogen[completed recruitment] • Sandoz [completed recruitment] • Coherus/Baxter/ Daiichi Sankyo • Intas [dossier preparation] • TTY Biopharm/ Mycenax **Phase I** • LG Life Sciences [Phase III ready] • Daewoong [Phase I on hold] • Avesthagen	**Preclinical** • Celltrion/Hospira • Dong-A/Meiji • Zenotech [suspended] • Teva • Biocon/Mylan • BioXpress/AET • Harvest Moon • Sanofi • Kyowa Hakko Kirin • Zydus Cadila **Early development** • PharmaPraxis • Bionovis • Orygen • Lupin/Yoshindo	**Marketed** • Celltrion/Hospira/ Egis **Approved** • Nippon Kayaku [approved in Japan] • Sun Pharma/Epirus [India] **Phase III** • Samsung Bioepis/Merck/ Biogen • Nichi-iko/Aprogen/ Sanofi • Shanghai CPGJ /LatAm partners **Phase I** • Pfizer [completed Phase I, Phase III preparations ongoing]	**Preclinical** • Amgen • LG Life Sciences • Hanwha • Dr. Reddy's Laboratory • Intas • Sandoz • Teva • Cipla/BioMab • BioXpress • PharmaPraxis • Harvest Moon **Early development** • mAbxience/Libbs • Bionovis • Orygen

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Quebec Listing For Inflectra/Remicade under "Prix le Plus Bas"

INFLIXIMAB

Pd, Perf, I.V.			100 mg	
02244515	Remicade	Janss. Inc	1	940.00

INFLIXIMAB-POLYARTHRITE RHUMATOÏDE SPONDYLITE ANKYLOSANTE, ARTHRITE PSORIASIQUE ET PSORIASIS EN PLAQUES

Pd, Perf, I.V.			100 mg PPB	
02419475	Inflectra	Hospira	1	650.00
99101167	Remicade	Janss. Inc	1	940.00

- INESSS states products are not interchangeable but listing as PPB allows pharmacists to dispense SEB without physician consent
- RAMQ suggests physicians use "Do Not Substitute" due to limits on infusion capacity and physician concerns about switching.
- Quebec announces restrictions on "Do Not Substitute" effective April 24.

Discussion

- Should therapeutic substitution be allowed with Biologic products?
- Define any risk (to patient and prescriber) associated with therapeutic substitution policy?
  - What are the risks to the patients and the prescriber associated with cost containment policy?
- How do we ensure therapeutic substitution is not being driven by a new business model or cost containment? What criteria would you like to see in place to protect patient and your choice of therapy?
- How does therapeutic substitution and cost containment policies impact innovation and investment?
- What is the value of innovation, clinical trial research, and patient assistance programs ?
  - What role do these factors play in your message to the government?