
Biologics: Practical Considerations for Plan Sponsors

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Objectives

1. Inflammatory bowel disease

One of many diseases that requires biologics to treat

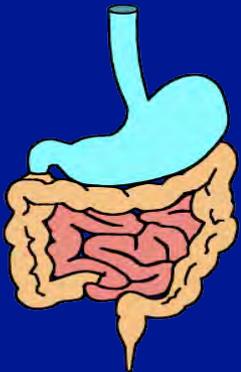
2. What is a biologic?

3. Impact of biologic on real life patients

Inflammatory Bowel Disease

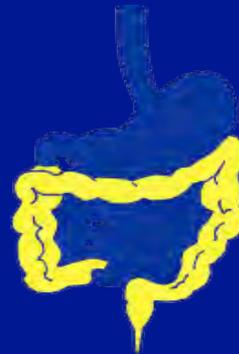
Crohn's disease:

An IBD that may affect any part of the GI tract. The inflammation penetrates the lining of the GI tract and often causes ulcers to form



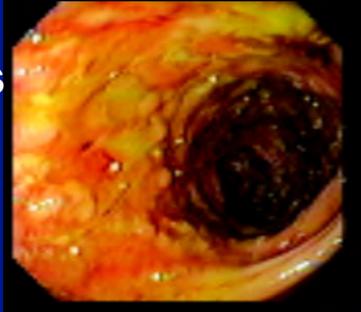
Ulcerative colitis:

An IBD exclusively located at the large intestine **always affecting the rectum and some or all the colon in continuity**. UC never affects the small intestine nor the anus



Inflammation and TNF Implications in Chronic Disease

Crohn's disease
Ulcerative colitis



Rheumatoid Arthritis



Ankylosing Spondylitis



Psoriasis

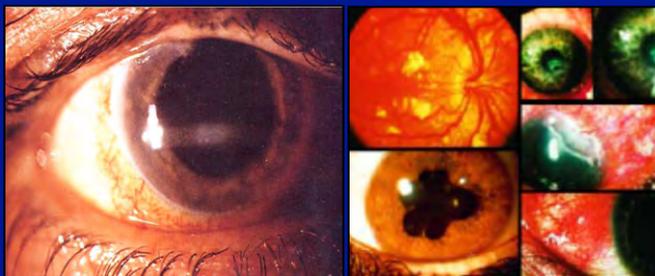


TNF α

Psoriatic Arthritis



Uveitis



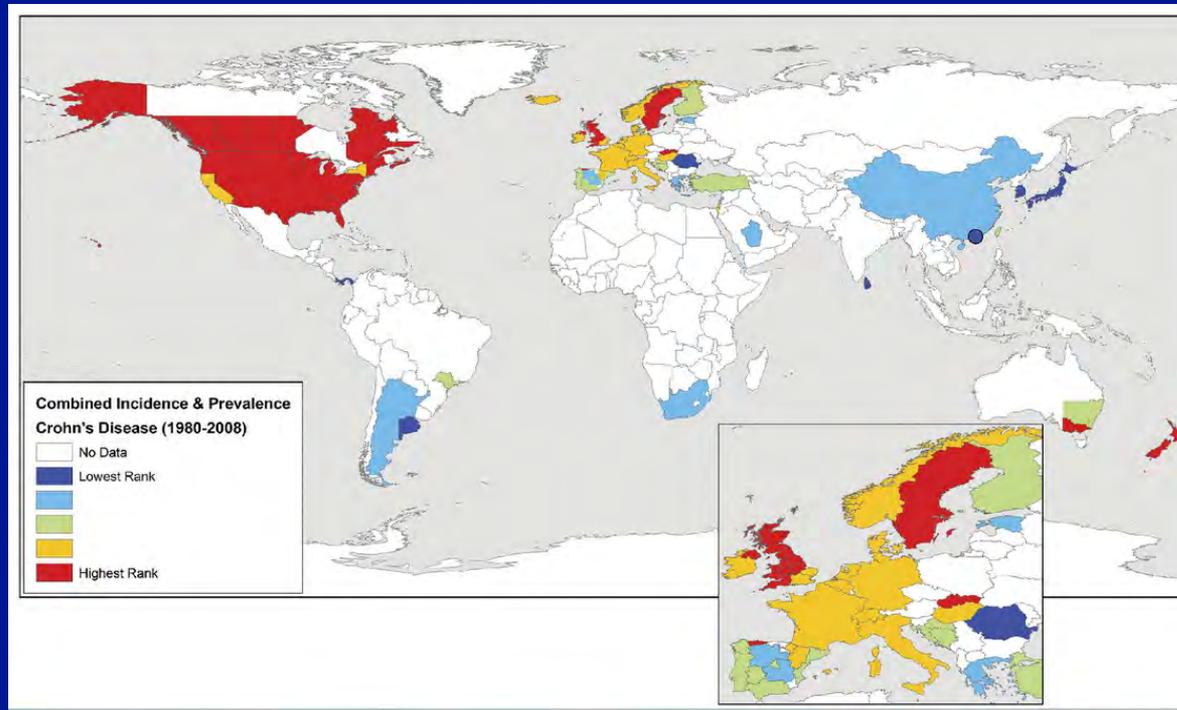
Why do we care?

- Children - as young as infants
- Peak age of onset is 15-30 years old
 - Affects males and females equally
 - Affects people in their “prime” working age
- Risk of long term disability is high
 - Low quality of life
 - Hospitalizations
 - Surgeries
 - Co-existing depression



Inflammatory Bowel Disease: Prevalence in Canada

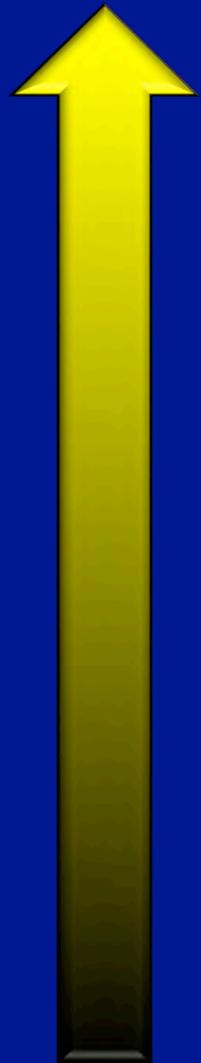
- Canada has a high prevalence and incidence
 - 195,000 Canadians live with IBD (0.6% of pop)¹
 - 110,000 with CD and 85,000 with UC
 - Approx. 13,500 new cases diagnosed each year¹



1. Molodecky et al. *Gastroenterology* 2012;142:46 –54

2. Lichtenstein and Rutgeerts. *Inflamm Bowel Dis* 2010;16:338-46

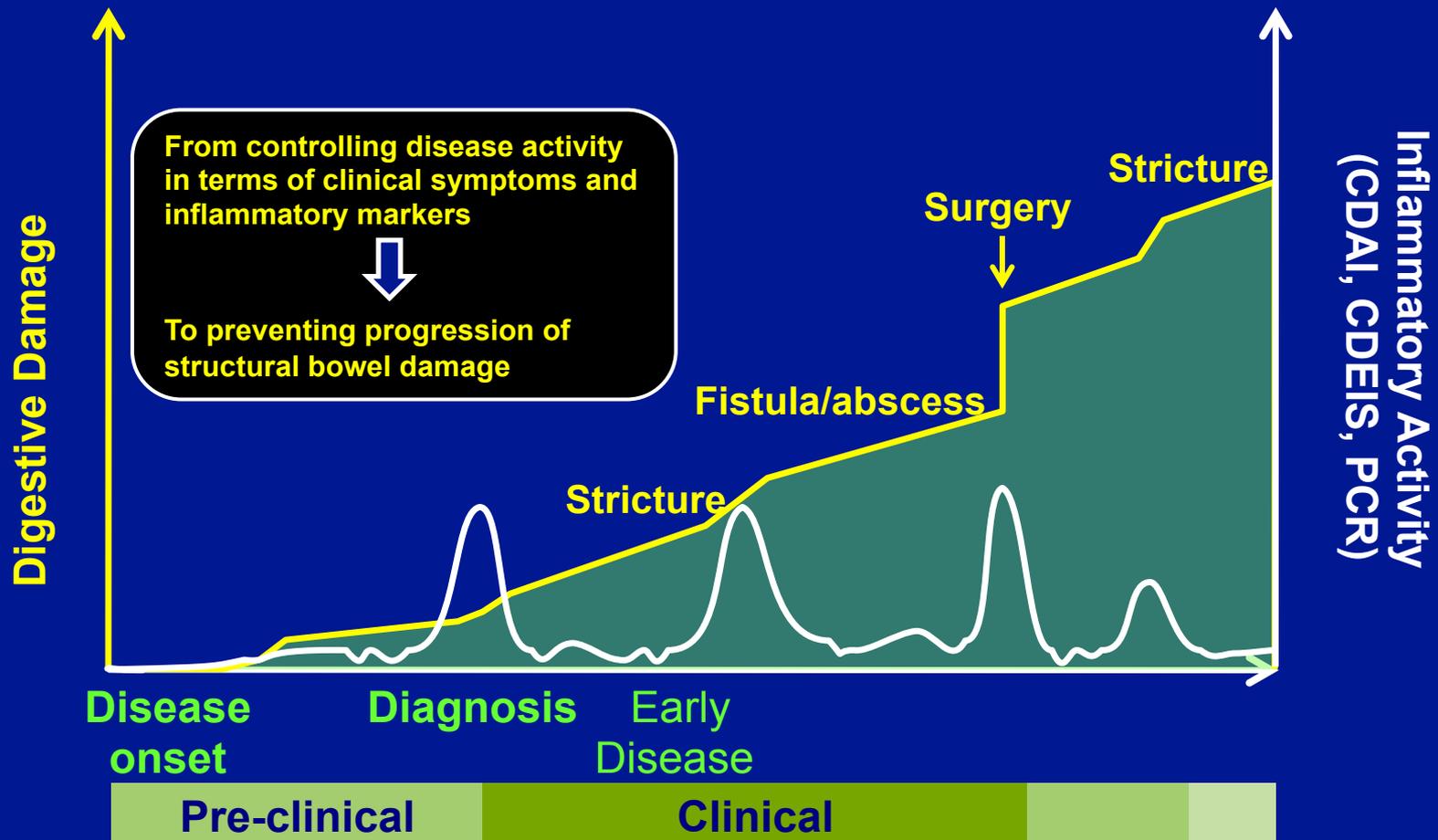
Today's Therapeutic Goals in IBD: Moving Beyond Symptomatic Remission



- **Altering the natural history of disease**
- **Endoscopic remission**
 - Complete mucosal healing
 - Reduction of inflammation
- **Quality of life**
 - Avoid complications: hospitalization/surgery
 - Other QoL issues: Employment/Schooling
- **Symptomatic remission**
 - Induce rapid response
 - Maintain steroid-free remission

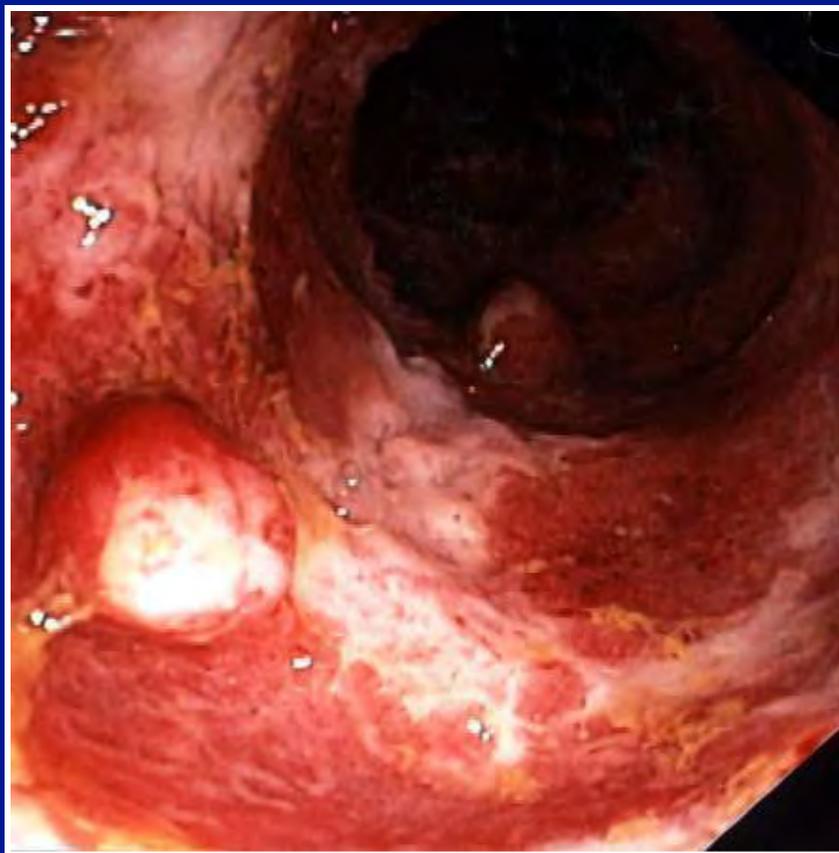
The Window of Opportunity in IBD

Progression of digestive damage and inflammatory activity in a theoretical CD patient



Endoscopic Evidence of Mucosal Healing in UC Following Infliximab

Baseline (Week 0)



After infliximab (Week 30)



What is a biologic?



Biologics

- **Monoclonal antibodies**
 - **Infliximab**
 - **Adalimumab**
 - **Golimumab**
 - **Vedolizumab**
- **Vaccines**
- **Hormones**
- **Blood factors**

Biologics versus Non biologic drugs

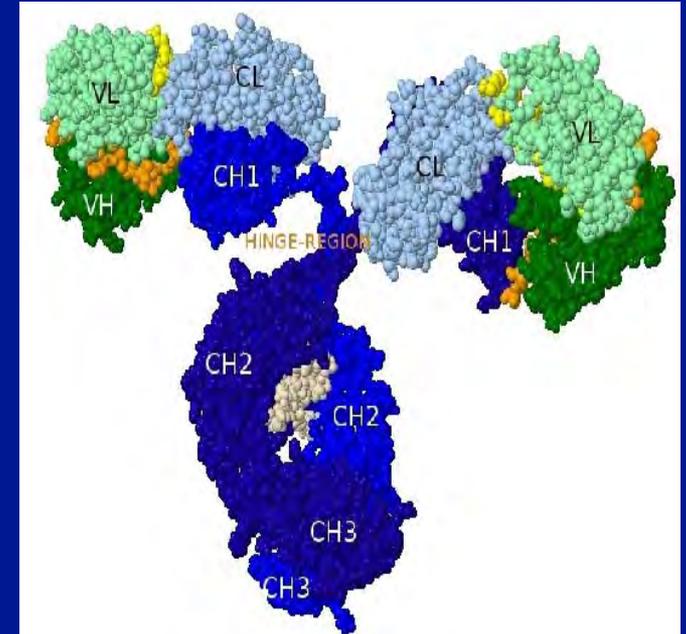
- Genetically engineered proteins
 - The process is what “guarantees” the product
- Made in a living organism
 - Highly sensitive to minor changes
 - Tight control of the starting materials
- Process is unique
 - Cannot have the same “biologic” between manufacturers
 - Minor changes can change not only the biologic structure but how it affects the body
- Chemical synthesis
 - Specific chemical structure
 - Analyze a finished product to ensure it is the same as another product “made differently”

High Complexity of Monoclonal Antibodies



Aspirin

**Molecular weight
= 80 daltons
0 amino acids**

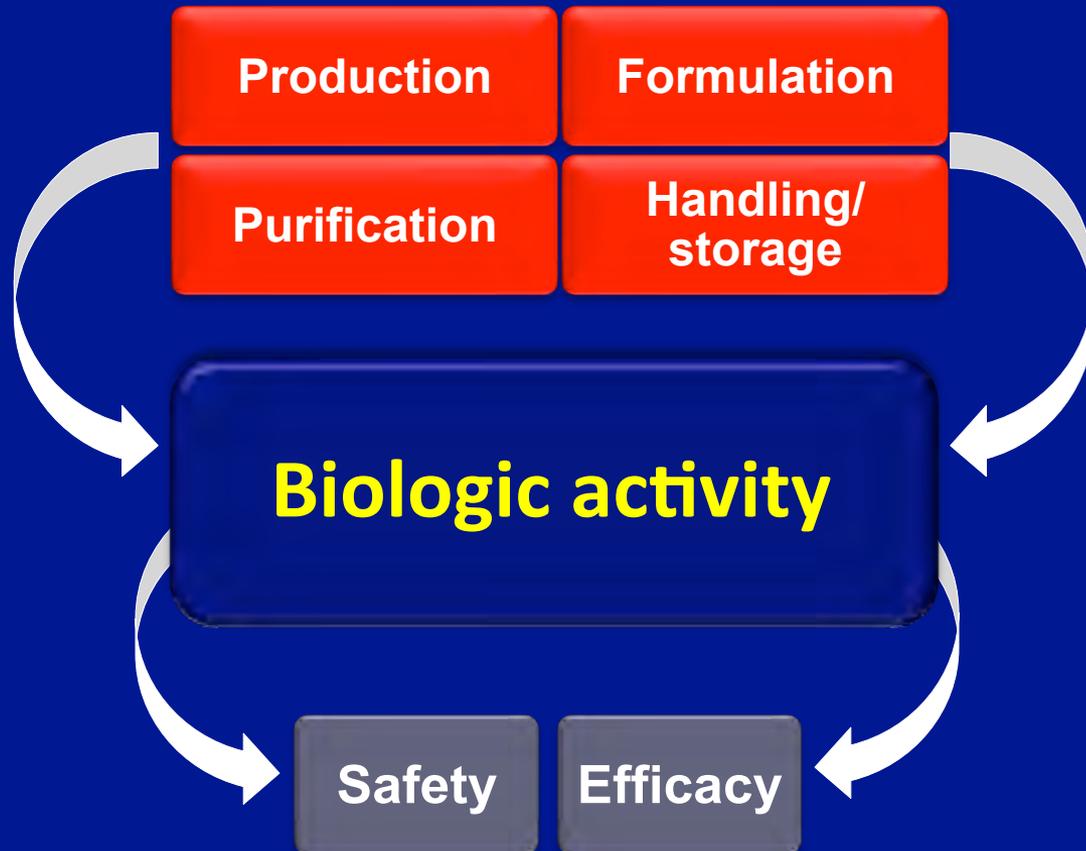


Antibody (IgG)

**Molecular weight
= 150,000 daltons
~1,300 amino acids**

The Process is The Product

Manufacturing details are proprietary



Production cell lines:

- Variations in media design (nutrients/metabolites)
- Variations in post-translational modifications

Manufacturing process is sensitive to:

- Slight changes in buffer, pH, temperature, pressure
- Design of bioreactor
- Change of production site

Variations of the active pharmaceutical ingredient can affect downstream safety and efficacy

REMICADE® and REMSIMA/ INFLECTRA Indications

INDICATION	REMICADE® (infliximab) 	REMSIMA (infliximab) 	REMSIMA/INFLECTRA (infliximab) 	REMSIMA/INFLECTRA (infliximab) 
Rheumatoid Arthritis	✓	✓	✓	✓
Ankylosing Spondylitis	✓	✓	✓	✓
Psoriatic Arthritis	✓	✓	✓	✓
Crohn's disease	✓	✓	✓	✓
Pediatric Crohn's disease	✓	✓	✓	✓
Ulcerative Colitis	✓	✓	✓	✓
Pediatric Ulcerative Colitis	✓	✓	✓	✓
Psoriasis	✓	✓	✓	✓

Health Canada Position 2014: Interchangeability

SEBs are not “generic” biologics, and authorization of an SEB is not declaration of pharmaceutical or therapeutic equivalence to the reference biologic drug.” Furthermore, Health Canada “... does not support automatic substitution of an SEB for its reference drug ...”^{1,2}

Health Canada’s concerns are scientifically based on the following elements:²

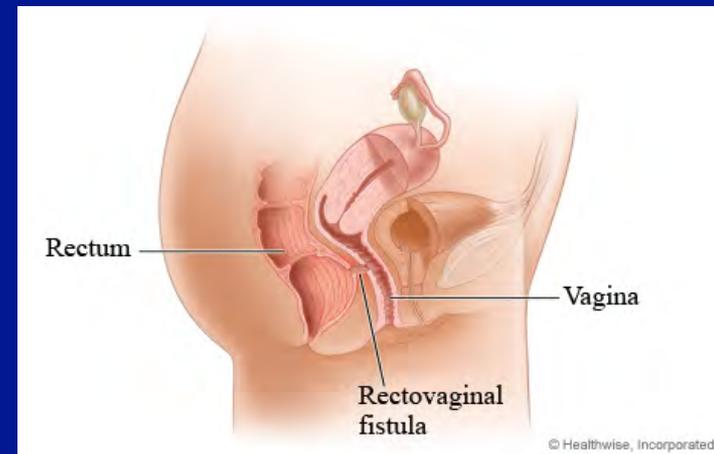
- 1) **Pharmaceuticals:** drug substances of the biosimilar and reference are not identical.
- 2) **PK/PD:** the biosimilar is not “bioequivalent” to the reference.
- 3) **Safety:** as a consequence of their complexity and impurity profiles, automatic interchangeability of biologics or biosimilars could give rise to different clinical consequences.
- 4) **Immunogenicity:** repeated switches between biosimilars and originator products may increase immunogenicity with potentially 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 postmarket changes and “manufacturing drift”.

1) Biologics and Genetic Therapies Directorate: Letter to Provincial/Territorial Drug Plan Directors. Re: Interchangeability/ Substitutability of SEBs July 29, 2010 10-116885-569 <http://www.safebiologics.org/pdf/Health-Canada-Letter.pdf>

2) Scott, BJ, Klein, AV, Wang, J. Biosimilar Monoclonal Antibodies: A Canadian Regulatory Perspective on the Assessment of

Case #1

- Samantha is a 35 year old who was diagnosed with Crohn's disease 5 years ago
- Diarrhea - more than 10 times a day
- Abdominal pain
- Leakage of bowel contents from her vagina
- No relationship. Lived in isolation



Case #1

- Was on pentasa, and then azathioprine
 - No data that these medications are beneficial in this form of Crohn's disease
- Was told that a “more expensive” medication (biologic) would require too much paperwork and she wasn't sick enough yet by previous physician
- Depressed
 - Went on disability
 - Lost her relationship
 - Fears of intimacy, assumption she could never have a child

Case #1

- Severe symptoms
- Poor quality of life
- Depression
- Unable to work
 - Longterm disability



Case #1

- Imaging and colonoscopy confirmed active disease
- Infliximab
- At month 3 visit
 - No diarrhea
 - No abdominal pain
 - No further drainage
 - Off antidepressants
- Last visit she had to rebook
 - Work reasons!



Case #2

- 55 year old male with ulcerative colitis
- Recent flare , was put on prednisone
- Continued to flare, no coverage for biologic
 - Research at that time already showed that infliximab would be helpful for his type of disease

Case #2

- **Admitted to hospital with a stroke**
- **His colitis was so severe that the neurologists did not want to treat his stroke**
- **Due to recent stroke surgeon did not want to operate on his colitis**
- **Chronic paraplegia, unable to see half of his visual field, long term disability**

Why surgery is not a cure for IBD

- For ulcerative colitis if you take out the whole colon some people consider that a “cure”
- Does a cure have
 - Risk of dying from the surgery
 - Risk of recurrent disease in the small bowel
 - Risk of decrease in ability to have children in the females
 - Risk of need chronic medications for recurrent disease in the small bowel

Why surgery is not a cure for IBD

- Surgery for Crohn's disease also not a cure
- Disease comes back
- Everytime you operate there's a risk of death and complications
- Poor nutrition, complications from tube feeding
- Ileostomy



Summary

- **Chronic immune mediated diseases**
 - Significant impact on individuals, families and society
 - Risk of disability is high
 - Affected individuals typically young and should be able to otherwise contribute to the work force

- **For the right person who requires biologics**
 - Can be life saving
 - Avoids surgery, poor quality of life and disability
 - No data that SEBs are as effective as or as safe