

# The Growing Impact of Biotechnology in Patient Care

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GIPC, Toronto ON  
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# BIOTECCanada

- BIOTECCanada is the national industry association dedicated to the sustainable commercial development of biotechnology in Canada.
- Non-profit organization supported by the developers of innovative biotechnology in health, agriculture and industrial sectors.



# Objectives

- Introduction to Biologic therapies and their value to health care
- The Value of Current and Future Advancement in Biologic Therapies
- The Role of Subsequent-Entry Biologics



# Introduction to Biologics



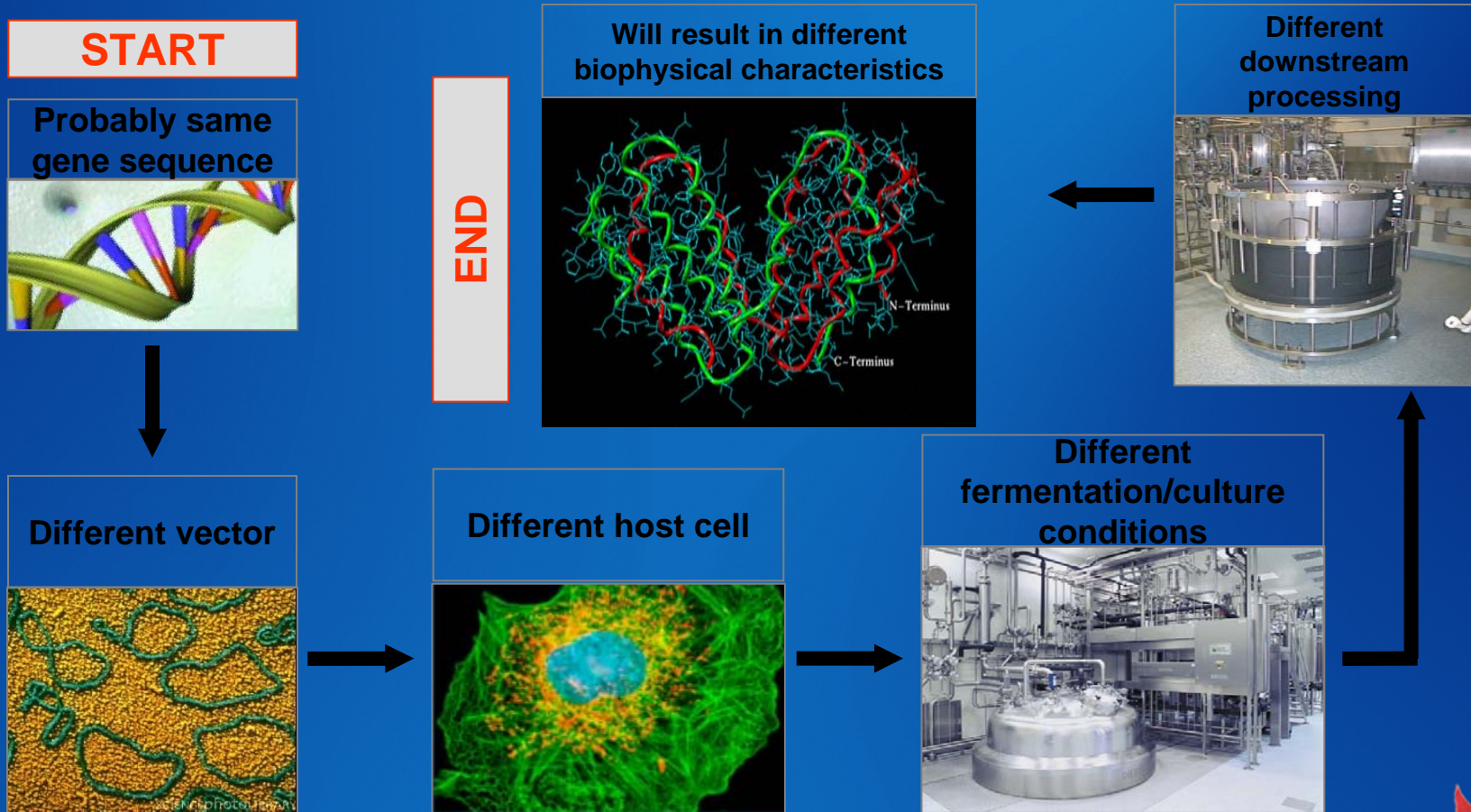
# Biologic Basics

- Proteins, hormones, antibodies, cell therapies, blood products, vaccines, etc.
- Produced in living cells – *E. coli*, CHO, yeast, etc.
- Large molecules commonly injected into the body
- Primary, secondary and tertiary structural characteristics
- Slight changes in structure can affect efficacy and safety



# Manufacture is a Complex Process

Different manufacturers will have different processes ...



# Examples of Biologics

- abatacept (Orencia) – rheumatoid arthritis
- alefacept (Amevive) – chronic plaque psoriasis
- etanercept (Enbrel) – rheumatoid arthritis, AS, PsA
- infliximab (Remicade) - rheumatoid arthritis, AS, PsA, psoriasis, Crohn's disease
- trastuzumab (Herceptin) – breast cancer
- ustekinumab (Stelara) – chronic plaque psoriasis
- filgrastim (Neupogen) – neutropenia
- interferon alfa-2a (Roferon) – hepatitis C
- Interferon beta-1a (Rebif) – multiple sclerosis
- erythropoietin alfa (Eprex) – anemia
- insulins (Humulin, Novolin, Lantus, Levemir) – diabetes



# New HC Biologics 2009-2010 (so far)

(Register of Innovative Drugs March 15, 2010)

## Therapeutic Agents

- canakinumab (Ilaris) - cryopyrin-associated periodic syndrome
- certolizumab pegol (Cimzia) – rheumatoid arthritis
- ecolizumab (Soliris) - paroxysmal nocturnal haemoglobinuria
- golimumab (Simponi) – rheumatoid arthritis, (PRA, AS)
- romiplostim (Nplate) –immune thrombocytopenic purpura

## Vaccines

- Prevnar -13 – pneumococcal vaccine



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## Biologics will dominate in 2014

June 18, 2009 — 7:52am ET | By Maureen Martino

According to forecasting firm EvaluatePharma, six of the top ten drugs in 2014 will be biologics. Analysts predict that Roche's cancer antibody Avastin will lead the pack at \$9.2 billion in annual sales, with Abbott and Eisai's Humira a close second at \$9.1 billion in sales. Rituxan (Roche), Enbrel (Wyeth, Amgen and Takeda) Lantus (Sanofi), Herceptin (Roche) and Remicade (J&J and Schering Plough) make up the other biologics that will dominate the market in 2010. Of these seven, only three--Rituxan, Remicade and Avastin--were top 10 drugs in 2008. And not only will biotech drugs make up the majority of the bestsellers, Evaluate predicts that half of the top 100 drugs in 2014 will be biologics.

Noticeably absent from this list are current bestsellers Lipitor, Plavix, Advair, Diovan and Nexium, which will all see sales drop due to generic competition.

"Anti-cancer antibodies appear set to easily become the most valuable therapeutic class of drug, justifying a large proportion of Roche's recent move to acquire Genentech outright." It also validates the trend of Big Pharma players acquiring small and mid-sized biotech now, while valuations are down.

The report underscores how important it is for Big Pharma to invest in biotechnology. While companies like Roche may be sitting pretty, big-name companies like Pfizer and GlaxoSmithKline are missing from the top 10 list in 2014. The "...weight of evidence for a shift to biotech products as the industry's growth driver is overwhelming, making the recent moves by Big pharma to access biotech platforms, not only for generating innovative medicines but also to launch bio-similar products, all the more compelling," observed the firm in its report.

- here's 2008's sales and 2014's projections
- see the report
- read the Reuters' write-up

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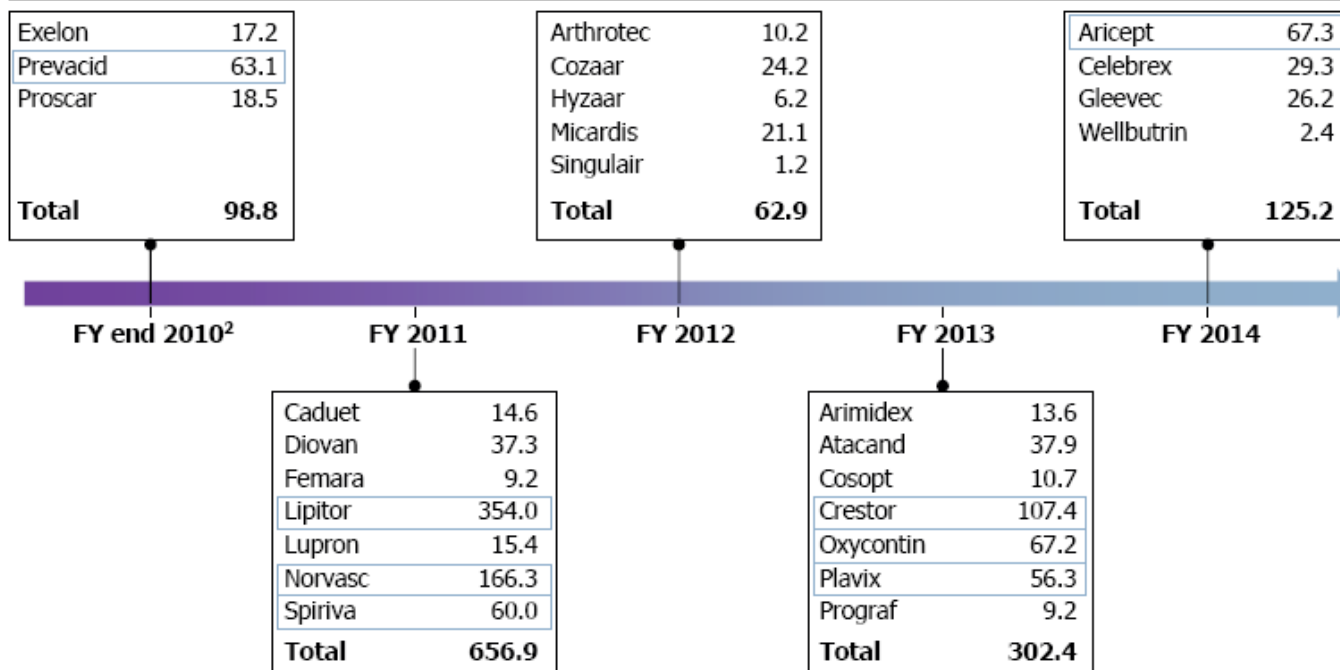
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FEATURED JOBS

# Patent Cliff Explains Some of the Shift

## Drugs coming off patent (with FY 2008/09 ODB spend)<sup>1</sup>

Canadian \$ in millions



<sup>1</sup>Includes government and recipient pay portions

<sup>2</sup>Fiscal Year is defined as April to March, e.g., FY end 2010 is 4/09 – 3/10

Source: ODB Database; Mylan; Brogan; team interviews



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# Biologics Growing But Still Minority

Analysis of Sales by Technology			
Sales by Tech (\$bln)	2000	2008	2014
Biotechnology	28	108	169
Conventional	222	408	406
Other Unclassified Sales	60	127	163
Total Rx & OTC Sales	310	643	738
<b>% of total Rx &amp; OTC sales</b>			
Biotechnology	9%	17%	23%
Conventional/Unclassified	91%	83%	77%

Source: EP Vantage 2009



# Value of Biologics Now and Into the Future



# Value of Biologic Therapies

- Reduced productivity losses in Rheumatoid Arthritis patients
  - Advantages with earlier start with biologic (Rheum 2009: 48:1283)
  - Patients remain productive and
- Control of complications from diabetes
  - 33% of cost of diabetes is from treating the complications.
  - Studies show that earlier insulin intervention reduces the incidence of complications (Diabet Med 2006;23(7):736-42)
- Treatment with Rituxan cuts deaths in non-Hodgkin's Lymphoma in half
- Treatment for previously untreatable, rare diseases
  - Enzyme replacement therapies allow patients to lead normal lives, reduce burden on care-givers
- Patient Training and Support Programs



# Vaccines are Effective Biologics

- Today, more than 25 infectious diseases are vaccine-preventable.
- Vaccines are inexpensive compared to the long-term care required for disease treatment (polio, hepatitis A&B) but Canadian spending on vaccines accounts for less than 0.17% of the annual healthcare budget (PHAC, 2007 & CIHI, 2006).
- In Canada, the introduction of childhood vaccines has decreased infection rates and saved lives.
  - By 2005, immunization with the pneumococcal meningitis vaccine had decreased rates of infection in infants aged 0–23 months by 84% in Vancouver, BC (Bjornson et al., 2007).
- The benefits of immunization often extend from the individual to the overall population.
  - Vaccination for infants against invasive pneumococcal infection have helped decrease the incidence in adults 65 years or older by 75.1% (Kellner et al., 2006).
- New vaccines approved for both infant and adult populations can reduce burden on health system from complications due to disease (rotavirus, shingles, pneumococcal disease)



# Predictive Genetic Markers

- Combination of genomics with therapy (biologic & pharma)
- Marriage of predictive genetic markers with therapeutic treatment will increase the value of treatment intervention.
- Selection of therapy for a patient with the greatest efficacy and lowest probability of side-effects.
  - Herceptin: Patients with HER2 over-expression
  - Vectibix & Erbitux: Markers for who should NOT receive
- On the Horizon
  - Identification of high and low responders for new & existing therapeutics
  - Design therapies for specific populations



# Therapeutic Vaccines

- A therapy that stimulates the immune system to heighten the response to an existing disease state (Cancer, HIV, HCV, Alzheimers)
- Increased survival rates, fewer side-effects and more treatment options for difficult diseases
- Therapeutic Vaccines in Development
  - Provenge® - immunotherapy for prostate cancer (BLA)
  - Stimuvax® - stimulate immune response against specific cancer cells (phase III)
  - HCV – Reduction in viral load following stimulation of immune system (phase II)



# New Therapeutic Platforms

- siRNA: Silencing the genes that are the underlying cause of disease (high cholesterol, cancer, AMD)
- Cell Therapy: cultured cells that can replace damaged tissues (cartilage, burns)
- Stem Cell Stimulation to repair damaged neurons, from stroke, MS, trauma
- New delivery technologies that reduce the burden of administration



# Subsequent-Entry Biologics



# A Few Words on Subsequent-Entry Biologics

- A subsequent entry biologic (SEB) is a biologic drug that would enter the market subsequent to, and 'similar' to an innovator product authorized for sale in Canada. A subsequent entry biologic relies in part on prior information regarding safety and efficacy that is deemed relevant due to the demonstration of similarity to the reference biologic drug. (*Health Canada Guidance*)
- SEBs are also referred to as BIOSIMILARS, FOLLOW-ON PROTEIN PRODUCTS, and FOLLOW-ON BIOLOGICS



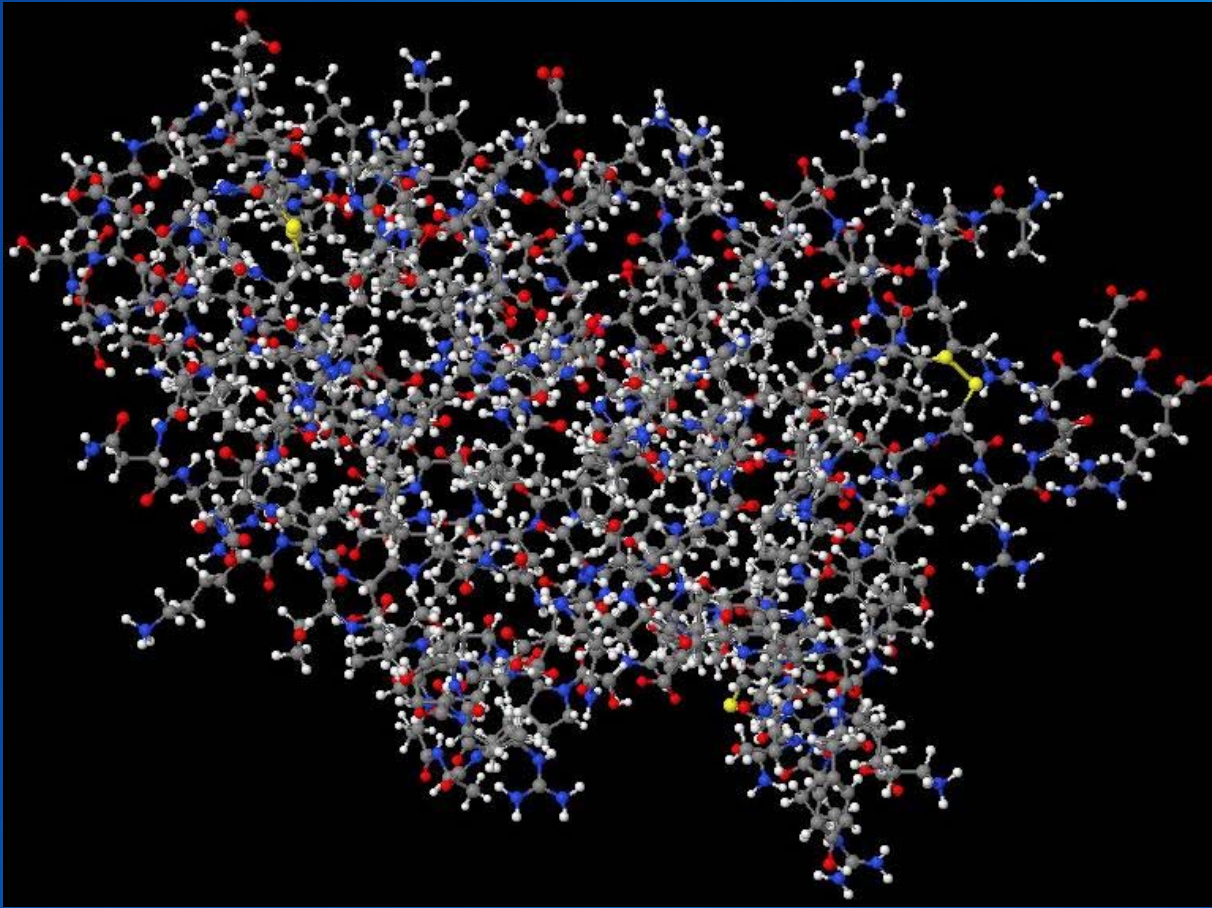
# SEBs and Generic Pharmaceuticals

## What Are The Differences?

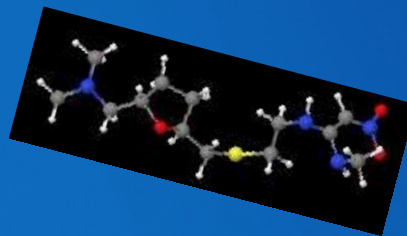
- Health Canada Guidance Document:
  - Generic drugs are pharmaceutical drugs, while Subsequent Entry Biologics are biologic drugs.
  - Subsequent Entry Biologics are approved using the new drug submission pathway, while generic drugs are approved using the abbreviated new drug submission pathway.
  - A Subsequent Entry Biologic is also not substitutable with its reference product and will always require clinical trials to support their approval.”
  - Unlike generic drugs, a Subsequent Entry Biologic is not declared pharmaceutical or bioequivalent to its reference drugs.



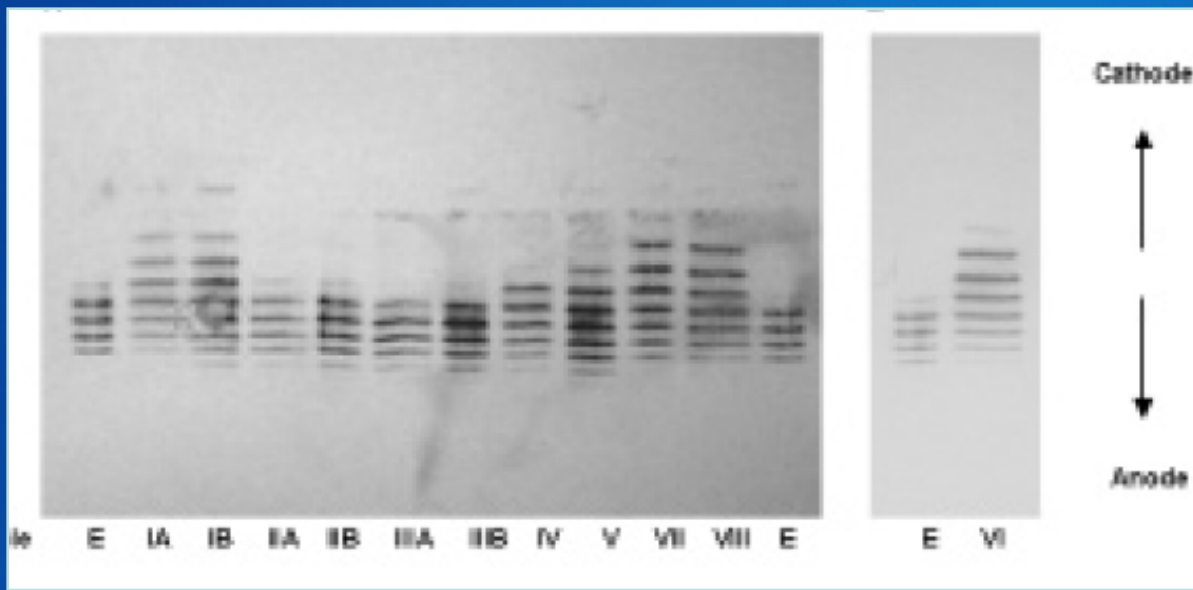
epoetin



ranitidine



# Comparisons of epoetin alfa show they are not equivalent to Eprex®



Sample	Concentration (IU/ml)	Country*
IA	2,000	Korea
IB	4,000	Korea
IIA	2,000	Korea
IIB	10,000	Korea
IIIA	2,000	Korea
IIIB	10,000	Korea
IV	2,000	Argentina
V	10,000	Argentina
VI	4,000	India
VII	10,000	China
VIII		China

## Authors Conclusions

- “quality of biopharmaceuticals from these sources is questionable”
- “physicochemical characterisation of these products does not prove that their clinical quality is inferior”
- “The establishment of clear guidelines for follow-up biologics by regulatory agencies in the USA and Europe, such as FDA and EMEA, can protect patients in these markets by ensuring that only high-quality biopharmaceutical products gain market approval”



# Cornerstones of Health Canada Guidance

- SEBs are not “generic” biologics.
- High standard for determination of similarity.
  - Full Chemistry and Manufacturing Data Required
- Clinical trials will always be required with a preference for “equivalency trials”
- No declaration of bioequivalence.
- Requirement for Post-Market Surveillance/Risk Management Plan equivalent to a new biologic.
- Once approved an SEB is regulated like any other new biologic therapeutic.



# An SEB Submission

## CMC

- Drug substance
    - Manufacture
    - Characterisation
    - Control
    - Reference standard
    - Container
    - Stability
  - Drug product
    - Description
    - Development
    - Manufacture
    - Control
    - Reference standard
    - Container
    - Stability
- + Comparability data
- + Analytical comparison with reference product

## Nonclinical

- Pharmacology
  - Primary pharm.
  - Secondary pharm.
  - Safety pharm.
  - Interactions
- Pharmacokinetics
  - ADME
  - Interactions
- Toxicology
  - Single dose
  - Repeat dose
  - Genotoxicity
  - Carcinogenicity
  - Reproduction
  - Local tolerance

## Clinical








- Pharmacology
- Pharmacokinetics
  - Single dose
  - Repeat dose
  - Special populations
- Efficacy and safety
  - Dose finding
  - Schedule finding
  - Pivotal
    - Indication 1
    - Indication 2
    - Indication 3
    - Indication 4
- Post-marketing studies
  - Safety in larger population
  - Lack of efficacy in other indications
  - Immunogenicity

# Eleven Biosimilar Approvals In Europe to Date:

For 6 biologics plus; 2 rejected; 3 withdrawn

Trade Name	Common Name International Nonproprietary Name	Biosimilar Sponsor(s)	Reference Product	Decision	Decision Date
Omnitrope®	somatropin	Sandoz	Genotropin®	Approved	April 12, 2006
Valtropin®	somatropin	BioPartners	Humatrope®	Approved	April 24, 2006
Alpheon®	Interferon alfa-2a	BioPartners	Roferon-A®	Rejected	June 28, 2006
“Sandoz EPO” Abseamed® Epoetin alfa Hexal Binocrit®	epoetin alfa	Sandoz Hexal Medice	Eprex®	Approved	Aug. 28, 2007
“Hospira EPO” Silapo® Retacrit®	epoetin zeta	Hospira Stada	Eprex®	Approved	Dec. 18, 2007
Insulin Rapid Marvel	Soluble Insulin	Marvel	Humulin®	Withdrawn	Jan. 16, 2008
Insulin Long Marvel	Isophane Insulin	Marvel	Humulin®	Withdrawn	Jan. 16, 2008
Insulin 30/70 Mix Marvel	Biphasic Insulin	Marvel	Humulin®	Withdrawn	Jan. 16, 2008
Biferonex	Interferon beta 1-a	BioPartners	Avonex®	Rejected	Feb 19, 2009
“Teva G-CSF” Tevagrastim® Ratiograstim® Filgrastim ratiopharm Biograstim®	filgrastim	Teva Ratiopharm Sandoz Arzneimittle	Neupogen®	Approved	Sept. 15, 2008

# Differential Profiles Between Biosimilar and Reference Products

	1988	1997	2001	2007	2007	2008	2007 <b>Withdrawn 2009</b>
<b>Lead Manufacturer</b>							
<b>INN</b>	Epoietin α	Epoietin β	Darbepoetin α	Epoietin α	methoxy polyethylene glycol-epoietin β	Epoietin ζ	Epoietin δ
<b>Half life</b>	Short	Short	Long	Short	Long	Short	Short
<b>Oncology approval</b>	• CIA (weight based dosing)	• CIA (Fixed dosing)	• CIA (Fixed dosing)	• CIA (weight based dosing)	X	• CIA (weight based dosing)	X
<b>Renal approval</b>	• (Pre-)Dial. (IV/SC)	• (Pre-)Dial. (IV/SC)	• (Pre-)Dial. (IV/SC)	• (Pre-)Dial. (IV)	• (Pre-)Dial. (IV/SC)	• (Pre-)Dial. (IV)	• (Pre-)Dial. (IV/SC)
<b>Surgery approval</b>	• ADP • Elective s.	• ADP	X	• ADP • Elective s.	X	• ADP	X
<b>Dosage IE</b>	1k–40k	500–30k	1.8k–60k	1k–10k	500–100k	1k–40k	2k–20k

Source: Derived from product EPAR, EMEA, 2009

# Key Messages

- Biologics provide therapies for previously untreated or poorly treated diseases
- Biologic therapies are an important part of the health care system but still a small portion of overall prescriptions
- New advances in genomics and immunology and new therapeutic platforms will enhance the value of biotech therapies
- SEBs will provide additional therapeutic choices but are not generic replacements for biologics.



# For More Information on Health Biotechnology

[www.biotech.ca/en/what-biotech-is/health.aspx](http://www.biotech.ca/en/what-biotech-is/health.aspx)

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