Overview

1. Value of biologics
2. Biologics 101
3. Drug Development
4. Biosimilars
5. Patient Programs
6. Plan Sponsor Considerations
Value of biologics
Specialty (biologic) drugs

- 22% of drug spend
- 1.2% of claims
- Avg cost per Rx is $1,240 [vs $46 for other drugs]
- 13.3% per year increase [vs 4.2% decrease for other drugs]
- 55% of new drug approvals
- 64% of pipeline drugs
- Est. to be 25-30% of spend in 2017

*Express Scripts Canada 2012 Drug Trend Report*
New treatments put rheumatoid arthritis in remission

Janice Lloyd, USA TODAY  5:24 p.m. EST December 18, 2012

New treatments for rheumatoid arthritis lead to remission in 75% of patients.

John Hardin reflects on the 525-mile scenic bike ride he took along the West Coast with Tracie Seimon and her husband in October. They started in San Francisco, headed south to Los Angeles and rode eight hours a day for eight straight days.

Not exactly what he pictured when Hardin met Seimon two years ago. She was 37 and turned to Hardin, a prominent rheumatologist in New York, for help. Other physicians had not been able to diagnose the cause behind a crippling pain that started in her feet, spread to other joints and was accompanied by swelling, fatigue and fever.

“New treatments for rheumatoid arthritis lead to remission in 75% of patients”

“People who begin treatment within two years of the disease appearing can expect to have low or moderate disease activity with the new treatments, rather than merely relief from symptoms”
Biologics 101
Types of drugs

A drug can be:

1. **Chemically produced** (synthetic, chemical or small molecule drug)

2. **Biologically produced** (biologic)
Size & Complexity – Small Molecule Drugs & Proteins

<table>
<thead>
<tr>
<th>Size</th>
<th>Small Molecule Drug</th>
<th>Large Molecule Drug</th>
<th>Large Biologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>~3000 atoms</td>
<td>hGH</td>
<td>IgG Antibody</td>
</tr>
<tr>
<td>21 atoms</td>
<td></td>
<td></td>
<td>~25,000 atoms</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Complexity</th>
<th>Bike</th>
<th>Car</th>
<th>Business Jet</th>
</tr>
</thead>
<tbody>
<tr>
<td>~20 lbs</td>
<td>~3000 lbs</td>
<td></td>
<td>~30,000 lbs (without fuel)</td>
</tr>
</tbody>
</table>
Manufacturing

Chemical Drug Laboratory

- Produced by chemical or semi-synthetic synthesis
- Significant latitude to change manufacturing process to yield same final organic molecule
- Chemicals and solvents can be changed if measured accurately
Manufacturing

- Produced by living cells (animal, bacteria, yeast)
- “The product is the process”
- Product consistency, quality, and purity require that manufacturing process remains the same over time
- Living systems (cells) “programmed” to produce biologics are sensitive to minor changes in manufacturing process
- Small process differences can significantly affect
  - nature of finished biologic
  - way it functions in the body
How is a Biologic Made? A Living Process

1. Biologic medicines are typically made in **living organisms** mainly by genetically engineering DNA

2. The **DNA is introduced into cells** and a particular cell line is selected for expansion

3. The **cell line is expanded** in bioreactors

4. The **biologic drug** is then **isolated** and **purified** using sophisticated technology

5. Formulation Fill and Finish

6. Refrigeration, Storage and Transport

---

Biotechnology manufacturing is complex, using living organisms to create the product.
Seemingly minor differences can lead to products with different characteristics.

With wine the difference is in the flavor. With biologics, differences could be efficacy or safety.
Chemical Drugs

- Simple chemical ingredients
- Uniform, predictable structure and easy to characterize
- Defined chemical process
- Penetrates cell membrane (outer layer of cell)
- Relatively stable in GI system (e.g., stomach and intestines) therefore suitable for oral administration
Biologics

- Large, complex proteins
- Heterogeneous and difficult to characterize
- Expressed in biological system
- Do not penetrate cell membrane (outer layer of cell)
- Not very stable in GI system (e.g., stomach and intestines) therefore IV administration or injection is often used.
Drug Development
Drugs are fairly specific!

Drugs work on one receptor in a disease pathway
Potential drug targets for cancer

- **Growth factors** (e.g., EGF, amphiregulin TGF-α)
- **Hormones** (e.g., bombesin)
- **Nuclear receptors** (e.g., oestrogen)
- **Survival factors** (e.g., IGF1)
- **Anti-growth factors** (e.g., TGF-β)
- **Death factors** (e.g., FasL)
- **Cytokines** (e.g., ILs, IFNs)
Disease pathways

Drugs
Upcoming Biologic Patent Expiries

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Remicade</td>
<td>Enbrel</td>
<td>Thyrogen</td>
<td>Fabrazyme</td>
<td>Rituxan</td>
<td>Tysabri</td>
<td>Xolair</td>
<td>Oncia</td>
</tr>
<tr>
<td></td>
<td>Avonex</td>
<td>Erbitux</td>
<td>Campath</td>
<td></td>
<td></td>
<td>Vectibix</td>
<td>Avastin</td>
</tr>
<tr>
<td></td>
<td>Cerezyme</td>
<td>Eprex</td>
<td>Synagis</td>
<td></td>
<td></td>
<td>Rituxan</td>
<td>Herceptin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aranesp</td>
<td></td>
<td></td>
<td></td>
<td>Pegasys</td>
<td>Lucentis</td>
</tr>
</tbody>
</table>

**Patents**

- Inventor has the exclusive right to manufacture and sell an invention for a stipulated period of time
- Once a patent expires information becomes public and can be used to produce a generic copy of the patented product
- 20 year patent countdown for a new medicine usually begins with the filing of the first patent (e.g., discovery)
New Drug Discovery & Development

High-risk research: more than $1 billion over 10-15 years
Market exclusivity following approval: 8-10 years

Drug discovery Preclinical Clinical trials Regulatory review Scale-up to manufacturing Market exclusivity

Pre-discovery

Pre-discovery

Drug discovery Preclinical Clinical trials Regulatory review Scale-up to manufacturing Market exclusivity

High-risk research: more than $1 billion over 10-15 years Market exclusivity following approval: 8-10 years

Cash Flow—You do the math...

- **20 years** Patent length
- **10-15 years** Between discovery and new medicine brought to market
- **5-9 years** Patent life remaining when medicine comes to market
- **One in 10,000** Molecules becomes a medicine
- **$1 billion** Average cost to a new medicine
Biosimilars or Subsequent Entry Biologics (SEB)
Health Canada definition: “An SEB is a biologic drug that enters the market subsequent to a version previously authorized in Canada, and with demonstrated similarity to a reference biologic drug.”\textsuperscript{1}

\textbf{Biosimilars are similar...} \hspace{0.5cm} \textbf{....but not identical to the original medicine}

\textsuperscript{1} Health Canada Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs), 2010/03/05
Interchangeability in Canada

Two regulatory hurdles

1. Health Canada Approval—bioequivalency
2. Provincial Regulations—interchangeability
# Health Canada Approval

<table>
<thead>
<tr>
<th>Synthetic Drugs</th>
<th>Biologics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Generic Drug</strong></td>
<td><strong>Subsequent Entry Biologics</strong></td>
</tr>
<tr>
<td>• Abbreviated New Drug Submission to Health Canada</td>
<td>• New drug submission pathway to Health Canada</td>
</tr>
<tr>
<td>• Demonstrate the drug’s bio-equivalence with a Canadian reference brand product.</td>
<td>• Require clinical trials</td>
</tr>
<tr>
<td>• Tests conducted on potency, purity and stability of the new drug</td>
<td>• Full Chemistry and Manufacturing Data Required</td>
</tr>
<tr>
<td>• Health Canada declares bio-equivalence to the brand drug product</td>
<td>• Not declared pharmaceutical or bioequivalent to reference drugs.</td>
</tr>
<tr>
<td></td>
<td>• Requirement for Post-Market Surveillance/Risk Management Plan equivalent to a new biologic.</td>
</tr>
<tr>
<td></td>
<td>• Regulated like any other new biologic</td>
</tr>
</tbody>
</table>
Re: Interchangeability / Substitutability of Subsequent Entry Biologics (SEBs)

Dear Provincial/Territorial Drug Plan Directors:

This letter is intended to bring to your attention Health Canada's responses to inquiries regarding SEBs and interchangeability/substitutability.

Health Canada has recently finalized a guidance document that is expected to facilitate the federal drug regulatory approval process for subsequent entry biologics (SEBs). An SEB is a biologic drug that enters the market subsequent to a version previously authorized in Canada, and with demonstrated similarity to a reference biologic drug. It 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 and which influences the amount and type of original data required.

Throughout the SEB policy development process Health Canada has been asked by external stakeholders whether an SEB can be used interchangeably with its reference biologic drug; whether an SEB is automatically substitutable with its reference biologic drug; and whether an SEB is therapeutically substitutable with its reference biologic drug.

In response to these stakeholder inquiries, Health Canada has stated the following:

- SEBs are not "generic" biologics. Authorization of an SEB is not a declaration of pharmaceutical or therapeutic equivalence to the reference biologic drug.

Stakeholders have also recommended that, as the federal regulator of drug products, Health Canada should review data that supports therapeutic interchangeability and make a recommendation as to whether this can be done safely and effectively by physicians.

In response to this recommendation, Health Canada has stated the following:

- Specialized clinical studies can be used to support therapeutic interchangeability, however, these studies are not usually done and their relevance may not be long-lasting. Over time, as sponsors of the SEB and the reference biologic drug make their own independent manufacturing changes, differences could be introduced that affect the drug products. For this reason, Health Canada does not support automatic substitution of a SEB for its reference biologic drug and recommends that physicians make only well-informed decisions regarding therapeutic interchange.

If you have questions or concerns regarding Health Canada's position as it has been expressed here, please contact us at:

OTTU-PIC BP0IC-2HC-SG-CC CA
Special Projects Unit,
Office of Policy and International Collaboration
Biologics and Genetic Therapies Directorate
Health Canada
Address Locator # 0792
200 Tunney's Pasture Drive
tOttawa ON, K1A 0K9

Telephone: 613-940-4736
Fax: 613-992-316

For more information about SEBs please refer to the following documents (available on the Health Canada website):

- Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs)
- Questions & Answers To Accompany the Final "Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs)"

Yours sincerely,

Dr. Elwyn Griffiths
Director General

Cc: Federal/Provincial Relations Division, Strategic Policy Branch, Health Canada
Office of Pharmaceuticals Management Strategies, Strategic Policy Branch, Health Canada
• SEBs are not “generic biologics. Authorization of an SEB is not a declaration of pharmaceutical or therapeutic equivalence to the reference biologic drug.

• Health Canada does not support automatic substitution of a SEB for its reference biologic and recommends that physicians make only well-informed decisions regarding therapeutic interchange.
## Summary

<table>
<thead>
<tr>
<th>Synthetic Drugs</th>
<th>Biologics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Generic Drug</strong></td>
<td><strong>Subsequent Entry Biologics (SEB)</strong></td>
</tr>
<tr>
<td>1. Health Canada determines bio-equivalency between generic and brand name drug</td>
<td>1. Health Canada will not declare bio-equivalency between SEB and brand name drug</td>
</tr>
<tr>
<td>2. Provincial government regulations determine rules for pharmacist ability to substitute generic drug for brand name drug.</td>
<td>2. Provincial government regulations will likely not permit pharmacist to substitute SEB for brand name drug without consulting physician.</td>
</tr>
<tr>
<td>3. In most provinces pharmacist permitted to substitute generic for brand name drug without consulting physician.</td>
<td>3. In order for the SEB to be dispensed, the physician will have to specifically prescribe SEB.</td>
</tr>
</tbody>
</table>
Biosimilar Pricing

• Unlike generics, biosimilar manufacturers have to appropriately invest in clinical development, manufacturing and post-approval safety monitoring programs similar to that of innovators\(^1,2\)

• Because of this development investment, cost savings achievable for biosimilars may not be as large as for generics\(^3\)

• To make high quality biosimilar medicines, the likely cost saving in comparison to innovator medicines is 10-30%\(^4\)

“...compared to chemical molecules, the savings expected are less prominent due to the high costs involved in the development of biosimilars.”\(^3\)

Impact to Private Plans

SEBs are not “generic biologics”

Due to different:
- Complexity in structure
- Manufacturing process
- Clinical requirements
- Authorization process
- Prescribing
- Pharmacist interchange

- SEBs likely won’t generate the same savings associated with the introduction of traditional generic drugs
We’ve got a positive latitude.
When it comes to winemaking, climate plays a starring role. And a region’s climate depends on its latitude.

Our vineyards are located in Niagara, on the 43rd parallel – the same parallel as Bordeaux, France, and Tuscany, Italy. So even though they’re sold in your local grocery store, our wines share the same beginnings, same taste and same quality as those world-class grapes.

Because really, it’s all in the latitude.
Patient Programs
Scenario 1

- Drug approved by Health Canada
- Infused drug not covered by hospital, provincial plan or cancer agency formulary
- Patients need a way to access medication with medical supervision
- Network of private infusion clinics to allow patients to receive infusions
Scenario 2

- Patients need specialized training or support to receive medication
- Current healthcare system cannot support additional services required
- Program created to provide support that patients and physicians need
Scenario 3

- Physicians and patients want to “sample” a new medication
- New biologic therapies require special handling and refrigeration—cannot be stored in physician’s office or patient’s home.
- Sample “card” provided for physician to give to patient.
Scenario 4

- Coinsurance of 20% on a $30,000 per year drug is $6,000
- Even with private coverage, the coinsurance is a barrier to access
- Program offers financial assistance for patient coinsurance.
Patient Assistance Program Components

1. Samples
2. Physician concierge
3. Patient training
4. Patient disease education
5. Reimbursement investigation/coordination
6. Risk management programs (required by Health Canada)
7. Infusion clinic management
8. Home infusions
9. Patient coaching and adherence
10. Arranging appointments with other necessary healthcare professionals
11. Coordination of tests needed before and after drug treatment
12. Coordination of patient appointments
13. Drug distribution
14. Drug dispensing
15. Patient Safety
16. Bridging
17. Online tools
18. Financial or co-pay assistance
19. Compassionate assistance
20. Financial support for additional expenses
Plan Sponsor
Considerations
## Are biologics the problem?

### 2011 Green Shield study
- 5% of plan members account for 43% of costs
- 20% of high-cost claimants account for 75% of costs
- 21% of the costs were for biologics
- 9% of high-cost claimants took biologics

### Chronic conditions
- Chronic conditions can be positively influenced through adoption of lifestyle changes that promote wellness and effective disease management
- Green Shield calls these claimants the “impactables.”

<table>
<thead>
<tr>
<th>% of high cost claimants</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>9%</td>
<td>Biologics</td>
</tr>
<tr>
<td>50%</td>
<td>Stomach disorders</td>
</tr>
<tr>
<td>51%</td>
<td>Depression</td>
</tr>
<tr>
<td>52%</td>
<td>High cholesterol</td>
</tr>
<tr>
<td>61%</td>
<td>Hypertension</td>
</tr>
</tbody>
</table>

Used with permission - Green Shield – “Don't let biologics be the fall guy” (The Inside Story July 2012)
Drug Coverage Philosophy?

1. Cover all drugs needed

2. Protection for significant illness and associated costs?
Appropriate Use

• Evidence based treatment
• As approved by Health Canada
• Clinical guidelines
• Recommended sequence
• Evaluate cost savings vs administrative and employee relations impact of the program

• Examine total value of treatment
  ➢ Drug cost
  ➢ Reduced absenteeism
  ➢ Increased productivity
  ➢ Avoid LTD
Summary

1. Value of biologics
2. Biologics 101
3. Drug Development
4. Biosimilars
5. Patient Programs
6. Plan Sponsor Considerations
Key Takeaways

1. Biologic drugs are different than synthetic drugs
2. Biosimilars or Subsequent Entry Biologics (SEBs) are not “generic biologics”
3. SEBs likely won’t generate the same savings associated with the introduction of traditional generic drugs
4. Biologics (biosimilars) and synthetic (generic) drugs differ in:
   - Complexity in structure
   - Manufacturing process
   - Clinical requirements
   - Authorization process
   - Prescribing
   - Pharmacist interchange
Key Takeaways

5. Plan Sponsors should be aware of or consider:
   - Infusion Confusion
   - Patient Programs
   - Case Management
   - Are biologics the problem?
   - Drug coverage philosophy
   - Appropriate use of biologic medications
   - Impact of plan designs on overall cost and plan members
Questions
and
Discussion
Specialty Drugs

1. Requirement for frequent dosage adjustments and intensive clinical monitoring
2. Need for intensive patient training and compliance assistance
3. Limited or exclusive product availability and distribution
4. Specialized product handling and/or administration requirements
5. Generally, cost more than $500 per month
   • Biologics are specialty drugs
   • Not all specialty drugs are biologics

Express Scripts Canada