Biologicals – cost or benefit: ethical dilemma?

By Dr JL Makkink – SAMA conference 20 September 2015
Disclaimer:

- Although I’m the Medical advisor at POLMED, the views and/or opinions presented here today are solely those of the presenter and do not necessarily represent those of POLMED.
Discussion points:

1. What is a “Biological?”
2. Major kinds of biopharmaceuticals
3. Major classes of biopharmaceuticals
4. Applications of mAbs
5. Biosimilars in Biopharmaceuticals
6. Commercialization
7. SEP of Biopharmaceuticals
8. Health Economic evaluation process
Discussion points

9. Clinical outcomes
10. Biopharmaceuticals in PMBs
11. Values in Medical Ethics
12. HTA decision making process
13. Pitfalls in funding process
What is a “Biological” product?

- **Definition** - A biopharmaceutical, also known as a biologic medical product or biologic, is any medicinal product manufactured in, extracted from, or semisynthesized from biological sources.
- Different from chemically synthesized pharmaceuticals
- They are isolated from natural sources—human, animal, or microorganism.
Major kinds of biopharmaceuticals include:

- Blood factors (Factor VIII and Factor IX)
- Thrombolytic agents (tissue plasminogen activator)
- Hormones (insulin, glucagon, growth hormone, gonadotrophins)
- Haematopoietic growth factors (Erythropoietin, colony stimulating factors)
- Interferons (Interferons-α, -β, -γ)
- Interleukin-based products (Interleukin-2)
- Vaccines (Hepatitis B surface antigen)
- Monoclonal antibodies (Various)
- Additional products (tumour necrosis factor, therapeutic enzymes)
Major classes of biopharmaceuticals

1. Extracted from living systems
2. Produced by recombinant DNA
3. Vaccines
4. Gene therapy
1. Extracted from living systems

- Some of the oldest forms of biologics are extracted from the bodies of animals, and other humans, examples include;
  - Whole blood and other blood components
  - Organs and tissue transplants
  - Stem cell therapy
  - Antibodies for passive immunization (e.g., to treat a viral infection)
  - Some biologics that were previously extracted from animals, such as *insulin*, are now more commonly produced by recombinant DNA.
Blood plasma is a type of biopharmaceutical directly extracted from living systems.
2. Produced by recombinant DNA

- In most cases, the term "biologics" is used more restrictively for a class of therapeutics that are produced by means of biological processes involving recombinant DNA technology.
- The medications are usually one of three types:
  a) Substances that are (nearly) identical to the body's own key signalling proteins i.e. Erythropoetin, growth hormone, biosynthetic human insulin and its analogues
b) Monoclonal Antibodies - These antibodies are "custom-designed" (using hybridoma technology or other methods. Including enzyme induction, inhibition of cell proliferation, enhancement of immune effector cells such as macrophages and cytotoxic T lymphocytes) and can therefore be made specifically to counteract or block any given substance in the body, or to target any specific cell type. Examples of such monoclonal antibodies for use in various diseases are given in the table below;
Immunoglobulin

Each antibody binds to a specific antigen; an interaction similar to a lock and key.
Examples of clinically important monoclonal antibodies;

<table>
<thead>
<tr>
<th>Main category</th>
<th>Type</th>
<th>Application</th>
<th>Mechanism/Target</th>
<th>Mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-inflammatory</td>
<td>infliximab</td>
<td>• Rheumatoid arthritis</td>
<td>Inhibits TNF-α</td>
<td>chimeric</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Crohn’s disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Ulcerative colitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Ankylosing spondylitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>adalimumab</td>
<td>• Rheumatoid arthritis</td>
<td>Inhibits TNF-α</td>
<td>humanized</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Crohn’s disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Ulcerative colitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Ankylosing spondylitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>basiliximab</td>
<td>• Acute rejection of renal transplant</td>
<td>Inhibits IL-2 on activated T-cells</td>
<td>chimeric</td>
</tr>
</tbody>
</table>
### Examples of clinically important monoclonal antibodies:

<table>
<thead>
<tr>
<th>Main category</th>
<th>Type</th>
<th>Application</th>
<th>Mechanism/Target</th>
<th>Mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti cancer</td>
<td>gemtuzumab</td>
<td>Relapsed acute myeloid leukemia</td>
<td>Targets myeloid cell surface antigen CD33 on leukemia cells</td>
<td>humanized</td>
</tr>
<tr>
<td></td>
<td>alemtuzumab</td>
<td>B cell leukemia</td>
<td>Targets an antigen CD52 on T- and B-lymphocytes</td>
<td>humanized</td>
</tr>
<tr>
<td></td>
<td>rituximab</td>
<td>Non Hodgkin’s lymphoma</td>
<td>Targets phosphoprotein CD20 on B lymphocytes</td>
<td>chimeric</td>
</tr>
<tr>
<td></td>
<td>trastuzumab</td>
<td>Breast cancer with HER2/neu overexpression</td>
<td>Targets the HER2/neu (erbB2) receptor</td>
<td>humanized</td>
</tr>
<tr>
<td></td>
<td>nimotuzumab</td>
<td>Approved in squamous cell carcinomas, Glioma</td>
<td>EGFR inhibitor</td>
<td>humanized</td>
</tr>
<tr>
<td></td>
<td>cetuximab</td>
<td>Approved in squamous cell</td>
<td>EGFR inhibitor</td>
<td>chimeric</td>
</tr>
</tbody>
</table>
Examples of clinically important monoclonal antibodies;

<table>
<thead>
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<th>Mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-cancer and anti-viral</td>
<td>bavituximab</td>
<td>• Cancer, viral infections</td>
<td>Immunotherapy targets phosphatidylserine</td>
<td>chimeric</td>
</tr>
<tr>
<td></td>
<td>palivizumab</td>
<td>• RSV infections in children</td>
<td>Inhibits an RSV fusion (F) protein</td>
<td>humanized</td>
</tr>
</tbody>
</table>

<table>
<thead>
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</tr>
</thead>
<tbody>
<tr>
<td>Other</td>
<td>abciximab</td>
<td>Prevent coagulation in coronary angioplasty</td>
<td>Inhibits the receptor Gpllb on platelets</td>
<td>chimeri</td>
</tr>
</tbody>
</table>
Applications of Monoclonal antibody treatment

- **Cancer treatment** - ADEPT, antibody directed enzyme prodrug therapy
Applications of Monoclonal antibody treatment

- **Cancer treatment** - ADCC, antibody dependent cell-mediated cytotoxicity
Applications of Monoclonal antibody treatment

- Cancer treatment - CDC, complement dependent cytotoxicity
Applications of Monoclonal antibody treatment

- **Cancer treatment** - scFv, single-chain Fv fragment
Major classes of biopharmaceuticals

3. **Vaccines** - Many vaccines are grown in tissue cultures

4. **Gene therapy** - Viral gene therapy involves artificially manipulating a virus to include a desirable piece of genetic material
Commercialization

• New molecule – patent 20 yrs
• Less than 5 years to recover investment costs
• The total number of patents granted for biopharmaceuticals has risen significantly since the 1970s
• In 1978 the total patents granted was 30
• This had climbed to 15,600 in 1995, and by 2001 there were 34,527

Commercialization

• Global market for Biologicals estimated at $41 billion
• has been growing at an impressive compound annual growth rate of 21% over the previous five years.
• over one third of all pipe-line products in active development are biopharmaceuticals
• this segment is set to continue outperforming the total pharmaceutical market and could easily reach US$100 billion by the end of this decade.
Large-scale production

Biopharmaceuticals may be produced from:
- microbial cells (e.g., recombinant E. coli or yeast cultures)
- mammalian cell lines
- plant cell cultures

in bioreactors of various configurations, including photo-bioreactors.

- Important issues of concern are cost of production, microbial contamination (by bacteria, viruses, mycoplasma)
Biosimilars in Biopharmaceuticals

- expiration of numerous patents for blockbuster biologics between 2012 and 2019
- interest in biosimilar production, i.e., follow-on biologics, has increased
- Compared to small molecules that consist of chemically identical active ingredients, biologics are vastly more complex
Biosimilars in Biopharmaceuticals

• Due to their heterogeneity and the high process sensitivity, neither originators nor follow-on manufacturers produce reliably constant quality profiles over time.

• Thus, biosimilars require a different regulatory framework compared to small-molecule generics.

• The filing pathway requires more testing than for small-molecule generics, but less testing than for registering completely new therapeutics.
Biosimilars in Biopharmaceuticals

Why is this relevant?
Biosimilars in Biopharmaceuticals

COST!!
Regulation

• In the United States, biologics are regulated by the FDA's Center for Biologics Evaluation and Research

• In SA – MCC

• Approval may require several years of clinical trials, including trials with human volunteers.

• Even after the drug is released, it will still be monitored for performance and safety risks.
## Costs: SEP of Biopharmaceuticals in SA

<table>
<thead>
<tr>
<th>Proprietary Name</th>
<th>Active Ingredients</th>
<th>Strength Unit</th>
<th>Dosage Form</th>
<th>SEP</th>
<th>Unit Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reopro</td>
<td>Abciximab</td>
<td>10 mg/5ml</td>
<td>INJ</td>
<td>4,677.07</td>
<td>935.41</td>
</tr>
<tr>
<td>Humira 40 mg</td>
<td>Adalimumab</td>
<td>40 mg</td>
<td>INJ</td>
<td>8,809.60</td>
<td>5,506.00</td>
</tr>
<tr>
<td>Humira 40 mg</td>
<td>Adalimumab</td>
<td>40 mg/0.8ml</td>
<td>PED</td>
<td>8,809.59</td>
<td>5,505.99</td>
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<tr>
<td>Mabcampath</td>
<td>Alemtuzumab</td>
<td>10 mg/ml</td>
<td>INF</td>
<td>21,180.79</td>
<td>2,353.42</td>
</tr>
<tr>
<td>Mabcampath 30 mg/ml</td>
<td>Alemtuzumab</td>
<td>30 mg/ml</td>
<td>INF</td>
<td>22,893.16</td>
<td>7,631.05</td>
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<tr>
<td>Simulect</td>
<td>Basiliximab</td>
<td>20 mg</td>
<td>INJ</td>
<td>12,996.40</td>
<td>2,599.28</td>
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<tr>
<td>Avastin 400Mg 16Ml</td>
<td>Bevacizumab</td>
<td>100 mg/4ml</td>
<td>INF</td>
<td>15,319.46</td>
<td>957.47</td>
</tr>
<tr>
<td>Avastin 100Mg 4Ml</td>
<td>Bevacizumab</td>
<td>100 mg/4ml</td>
<td>INF</td>
<td>3,829.87</td>
<td>957.47</td>
</tr>
<tr>
<td>Erbitux 2Mg/ML</td>
<td>Cetuximab</td>
<td>2 mg/ml</td>
<td>INJ</td>
<td>2,897.69</td>
<td>2,897.69</td>
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</tbody>
</table>
## Costs: SEP of Biopharmaceuticals in SA

<table>
<thead>
<tr>
<th>Proprietary Name</th>
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<th>Strength</th>
<th>Unit</th>
<th>Dosage Form</th>
<th>SEP</th>
<th>Unit Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erbitux 5Mg/Ml</td>
<td>Cetuximab</td>
<td>5</td>
<td>mg/ml</td>
<td>INF</td>
<td>2,897.69</td>
<td>144.88</td>
</tr>
<tr>
<td>Zenapax 5Ml</td>
<td>Daclizumab</td>
<td>25</td>
<td>mg/5ml</td>
<td>INJ</td>
<td>3,717.57</td>
<td>743.51</td>
</tr>
<tr>
<td>Mylotarg</td>
<td>Gemtuzumab ozogamicin</td>
<td>5</td>
<td>mg</td>
<td>INJ</td>
<td>24,930.20</td>
<td>4,986.04</td>
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<tr>
<td>Simponi</td>
<td>Golimumab</td>
<td>50</td>
<td>mg/0.5ml</td>
<td>PFP</td>
<td>9,220.00</td>
<td>18,440.00</td>
</tr>
<tr>
<td>Zevalin</td>
<td>Ibritumomab Tiuxetan</td>
<td>1.6</td>
<td>mg/ml</td>
<td>VIA</td>
<td>181,288.84</td>
<td>45,322.21</td>
</tr>
<tr>
<td>Revellex 100 mg</td>
<td>Infliximab</td>
<td>100</td>
<td>mg/10ml</td>
<td>INJ</td>
<td>5,025.76</td>
<td>502.58</td>
</tr>
<tr>
<td>Yervoy 5mg/ml</td>
<td>Ipilimumab</td>
<td>5</td>
<td>mg/ml</td>
<td>INF</td>
<td>48,050.04</td>
<td>4,805.00</td>
</tr>
<tr>
<td>Yervoy 5mg/ml</td>
<td>Ipilimumab</td>
<td>5</td>
<td>mg/ml</td>
<td>INF</td>
<td>192,200.08</td>
<td>4,805.00</td>
</tr>
<tr>
<td>Tysabri</td>
<td>Natalizumab</td>
<td>20</td>
<td>mg/ml</td>
<td>INF</td>
<td>18,791.57</td>
<td>1,252.77</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
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<th>Unit Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>XOLAIR 150mg</td>
<td>Omalizumab</td>
<td>150 mg</td>
<td>INJ</td>
<td>4,863.28</td>
<td>4,052.73</td>
</tr>
<tr>
<td>Synagis 50 mg</td>
<td>Palivizumab</td>
<td>50 mg</td>
<td>INJ</td>
<td>7,539.11</td>
<td>7,539.11</td>
</tr>
<tr>
<td>Synagis 100 mg</td>
<td>Palivizumab</td>
<td>100 mg/ml</td>
<td>INJ</td>
<td>12,195.14</td>
<td>12,195.14</td>
</tr>
<tr>
<td>Lucentis® 10Mg/Ml Solution For Injection</td>
<td>Ranibizumab</td>
<td>10 mg/ml</td>
<td>INJ</td>
<td>7,353.00</td>
<td>31,969.57</td>
</tr>
<tr>
<td>Mabthera 100Mg 10Ml</td>
<td>Rituximab</td>
<td>100 mg/10ml</td>
<td>INF</td>
<td>6,728.85</td>
<td>336.44</td>
</tr>
<tr>
<td>Mabthera 500Mg 50Ml</td>
<td>Rituximab</td>
<td>100 mg/10ml</td>
<td>INF</td>
<td>16,822.22</td>
<td>336.44</td>
</tr>
<tr>
<td>Actemra 80</td>
<td>Tocilizumab</td>
<td>80 mg/4ml</td>
<td>INF</td>
<td>987.22</td>
<td>246.81</td>
</tr>
<tr>
<td>Actemra 200</td>
<td>Tocilizumab</td>
<td>200 mg/10ml</td>
<td>INF</td>
<td>2,468.04</td>
<td>246.81</td>
</tr>
<tr>
<td>Actemra 400</td>
<td>Tocilizumab</td>
<td>400 mg/20ml</td>
<td>INF</td>
<td>4,936.09</td>
<td>246.81</td>
</tr>
<tr>
<td>Herceptin</td>
<td>Trastuzumab</td>
<td>440 mg</td>
<td>INJ</td>
<td>24,290.91</td>
<td>1,156.71</td>
</tr>
</tbody>
</table>
Health economic evaluation

• **Cost minimization**
  – Clinical outcomes similar
  – Difference in costs

• **Cost to benefit analysis**
  – costs and benefits are both valued in cash terms
  – “Input costs” vs “Output costs”

• **Cost effectiveness evaluation**
  – measures outcomes in 'natural units', such as mmHg, symptom free days, life years gained etc.
Clinical outcomes

• Trastuzumab (Herceptin) – in early and metastatic breast ca
• Anti TNF agents
  – RA
  – Crohn’s
  – Ulcerative colitis
  – Psoriatic arthritis
  – Ankylosing spondylitis
• Gaucher’s disease – lisosomal storage disease
• Hemophilia – Recombinant Factor VIII
• NICE, Cochrane reviews
PMBs and the Biopharmaceuticals

Where the treatment component of a category in Annexure A is stated in general terms “medical- or surgical management” it should be interpreted as referring to prevailing hospital based medical and surgical management for the condition.

Where significant differences exist between the Public and Private sector practices, the interpretation of the PMBs should follow the predominant Public hospital practice, as outlined in the relevant provincial or national public hospital clinical protocols.

Amendments to the PMBs with explanatory notes as published by the CMS Feb 2003.
Chronic disease list – treatment algorithms

- Crohn’s disease
- SLE
- Ulcerative colitis
- RA
Diagnostic Treatment pairs

- 270 conditions
- Predominantly what is available in the Public sector
Values in Medical Ethics

A common framework used in the analysis of medical ethics is the "four principles" approach postulated by Tom Beauchamp and James Childress in their textbook Principles of biomedical ethics.
Values in Medical Ethics

The four principles are:

a. **Respect for autonomy** - the patient has the right to refuse or choose their treatment.

b. **Beneficence** - a practitioner should act in the best interest of the patient.

c. **Non-maleficence** - "first, do no harm“

d. **Justice** - concerns the distribution of scarce health resources, and the decision of who gets what treatment (fairness and equality).

Values in Medical Ethics

- **Beneficence** - In the medical context, this means taking actions that serve the best interests of patients.

- **Non-maleficence** - The concept of non-maleficence is embodied by the phrase, "first, do no harm," that it is more important not to harm your patient, than to do them good. This is partly because enthusiastic practitioners are prone to using treatments that they believe will do good, without first having evaluated them adequately to ensure they do no (or only acceptable levels of) harm.
Current HTA decision making process

- Submission to funder by distributor/pharmaceutical company
- Evaluation by HTA experts/HE in Managed care organisation
  - General approach in current process
    1. Does it work?
    2. If so how well? (CEA, CBA, CM)
    3. Is it safe?
    4. Is it well tolerated?
    5. Are the benefits worth the risk?
General approach in current process continued

6. Is it available?
7. What does it cost?
8. Could it save money?
9. Are there alternative treatments?
10. If there are, how well do they compare?
11. Is the new treatment good value for money?
12. Can we afford it?
13. Does it fit with the public priorities?
Pitfalls in existing funding process

- Dr – patient relationship
- Third party payer
- Scheme rules, benefit limits
- Legislation (Medical Schemes’ Act.)
- Affordability
- Willingness to pay concept
- FFS environment
- Financial risk
Thank you!