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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

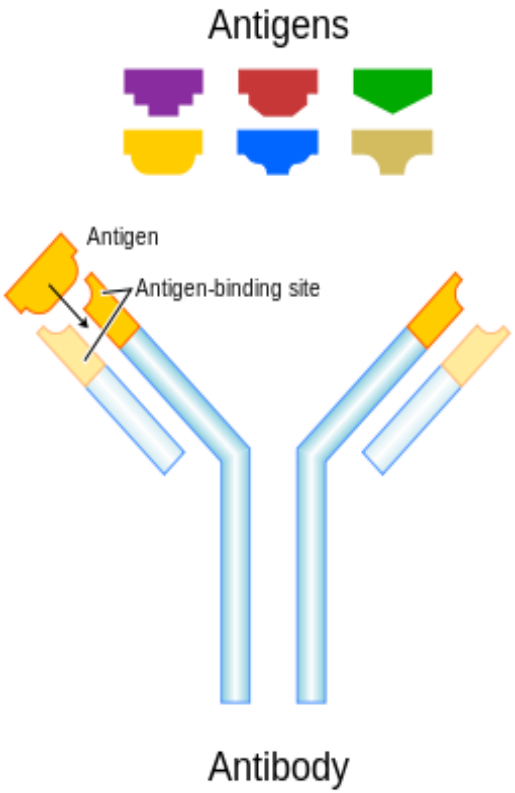
2. Produced by recombinant DNA

- 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 ie. Erythropoetin, growth hormone, biosynthetic human insulin and its analogues

2. Produced by recombinant DNA

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;

Main category	Type	Application	Mechanism/Target	Mode
Anti-inflammatory	**infliximab**	• Rheumatoid arthritis • Crohn's disease • Ulcerative colitis • Ankylosing spondylitis	Inhibits TNF-α	chimeric
	adalimumab	• Rheumatoid arthritis • Crohn's disease • Ulcerative colitis • Ankylosing spondylitis	Inhibits TNF-α	humanized
	basiliximab	• Acute rejection of renal	Inhibits IL-2 on activated T-cells	chimeric

Examples of clinically important monoclonal antibodies;

Main category	Type	Application	Mechanism/Target	Mode
Anti cancer	**gemtuzumab**	• Relapsed acute myeloid leukemia	Targets myeloid cell surface antigen CD33 on leukemia cells	humanized
	alemtuzumab	• B cell leukemia	Targets an antigen CD52 on T- and B-lymphocytes	humanized
	rituximab	• Non Hodgkin's lymphoma	Targets phosphoprotein CD20 on B lymphocytes	chimeric
	trastuzumab	• Breast ca with HER2/neu overexpression	Targets the HER2/neu (erbB2) receptor	humanized
	nimotuzumab	• Approved in squamous cell carcinomas, Glioma	EGFR inhibitor	humanized
	cetuximab	• Approved in squamous cell	EGFR inhibitor	chimeric

Examples of clinically important monoclonal antibodies;

Main category	Type	Application	Mechanism/Target	Mode
Anti-cancer and anti-viral	**bavituximab**	• Cancer, viral infections	Immunotherapy targets phosphatidylserine	chimeric
	palivizumab	• RSV infections in children	Inhibits an RSV fusion (F) protein	humanized

Main category	Type	Application	Mechanism/Target	Mode
Other	**abciximab**	Prevent coagulation in coronary angioplasty	Inhibits the receptor Gpllb on platelets	chimeri

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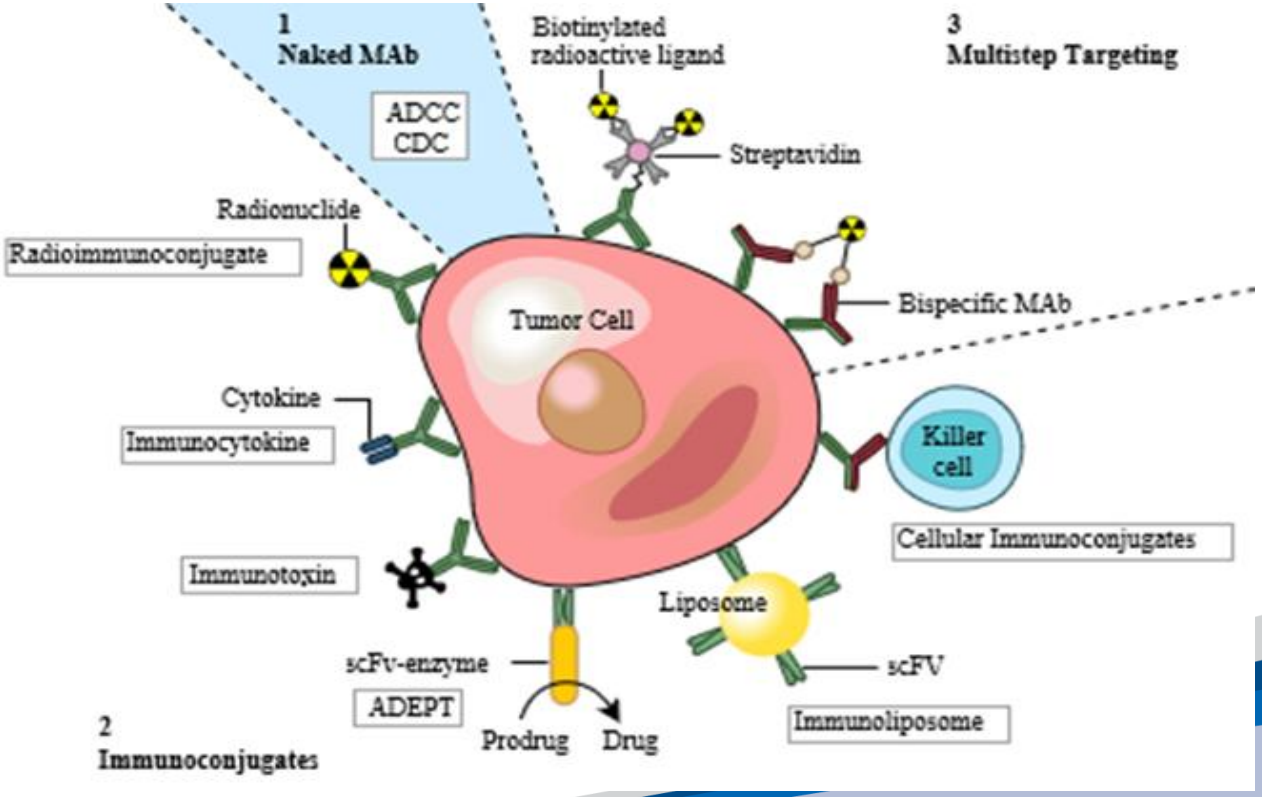
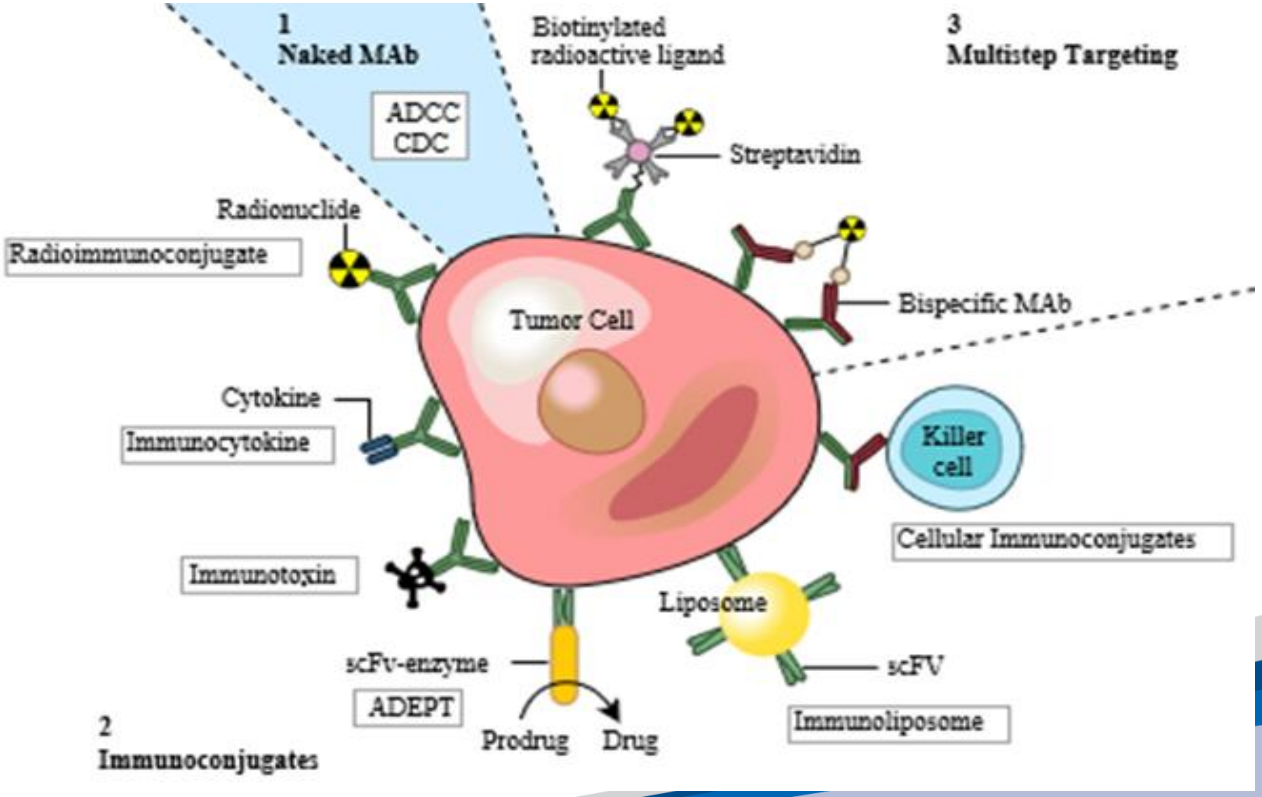
Applications of Monoclonal antibody treatment

- **Cancer treatment -** ADEPT, antibody directed enzyme prodrug therapy



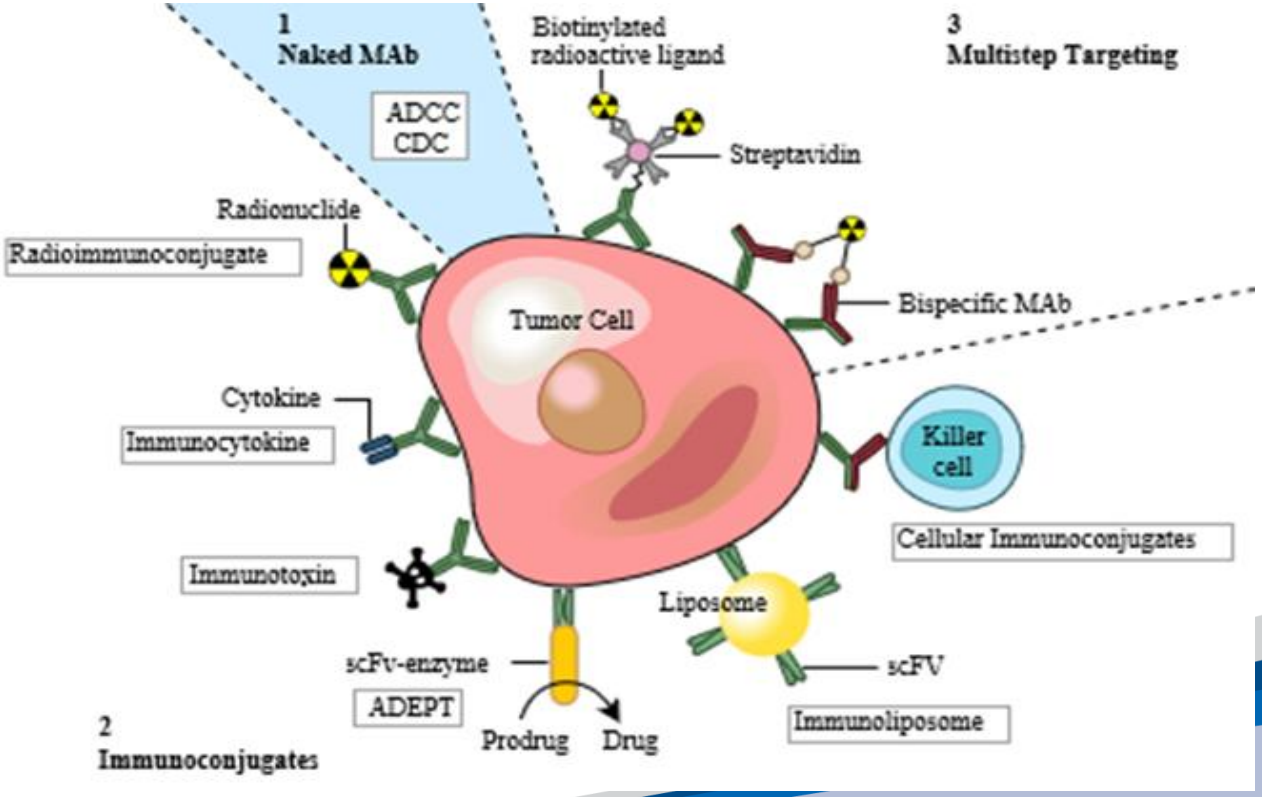
Applications of Monoclonal antibody treatment

- **Cancer treatment -** ADCC, antibody dependent cell-mediated cytotoxicity



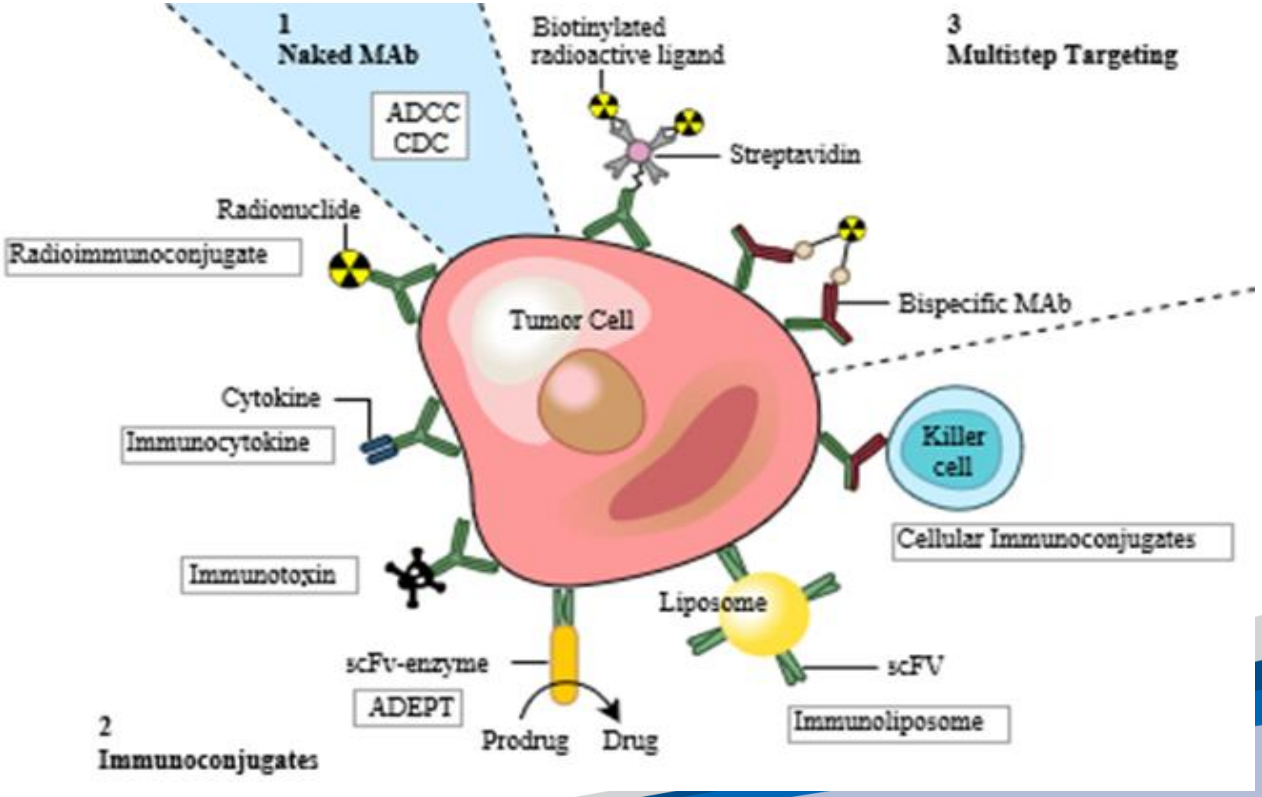
Applications of Monoclonal antibody treatment

- **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

(Patent applications Luke Foster. "Patenting in the Biopharmaceutical Industry—comparing the US with Europe". Archived from the original on 2006-03-16. Retrieved 2006-06-23.)

Commercialization

- Global market for Biologicals estimated at $41billion
- 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

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

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Costs: SEP of Biopharmaceuticals in SA

Proprietary Name	Active Ingredients	Strength	Unit	Dosage Form	SEP	Unit Price
Erbitux 5Mg/Ml	Cetuximab	5	mg/ml	INF	2,897.69	144.88
Zenapax 5Ml	Daclizumab	25	mg/5ml	INJ	3,717.57	743.51
Mylotarg	Gemtuzumab ozogamicin	5	mg	INJ	24,930.20	4,986.04
Simponi	Golimumab	50	mg/0.5ml	PFP	9,220.00	18,440.00
Zevalin	Ibritumomab Tiuxetan	1.6	mg/ml	VIA	181,288.84	45,322.21
Revellex 100 mg	Infliximab	100	mg/10ml	INJ	5,025.76	502.58
Yervoy 5mg/ml	Ipilimumab	5	mg/ml	INF	48,050.04	4,805.00
Yervoy 5mg/ml	Ipilimumab	5	mg/ml	INF	192,200.08	4,805.00
Tysabri	Natalizumab	20	mg/ml	INF	18,791.57	1,252.77

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Costs: SEP of Biopharmaceuticals in SA

Proprietary Name	Active Ingredients	Strength	Unit	Dosage Form	SEP	Unit Price
XOLAIR 150mg	Omalizumab	150	mg	INJ	4,863.28	4,052.73
Synagis 50 mg	Palivizumab	50	mg	INJ	7,539.11	7,539.11
Synagis 100 mg	Palivizumab	100	mg/ml	INJ	12,195.14	12,195.14
Lucentis® 10Mg/Ml Solution For Injection	Ranibizumab	10	mg/ml	INJ	7,353.00	31,969.57
Mabthera 100Mg 10Ml	Rituximab	100	mg/10ml	INF	6,728.85	336.44
Mabthera 500Mg 50Ml	Rituximab	100	mg/10ml	INF	16,822.22	336.44
Actemra 80	Tocilizumab	80	mg/4ml	INF	987.22	246.81
Actemra 200	Tocilizumab	200	mg/10ml	INF	2,468.04	246.81
Actemra 400	Tocilizumab	400	mg/20ml	INF	4,936.09	246.81
Herceptin	Trastuzumab	440	mg	INJ	24,290.91	1,156.71

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.

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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).

Gillon, R (1994). "Medical ethics: four principles plus attention to scope". British Medical Journal 309 (184). doi:10.1136/bmj.309.6948.184

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

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Thank you!