BIOSIMILARS - WHAT YOU NEED TO KNOW

Dr David Newby
BPharm GradDIpEpi PhD
Associate Professor
Discipline of Clinical Pharmacology
School of Medicine and Public Health

Objectives

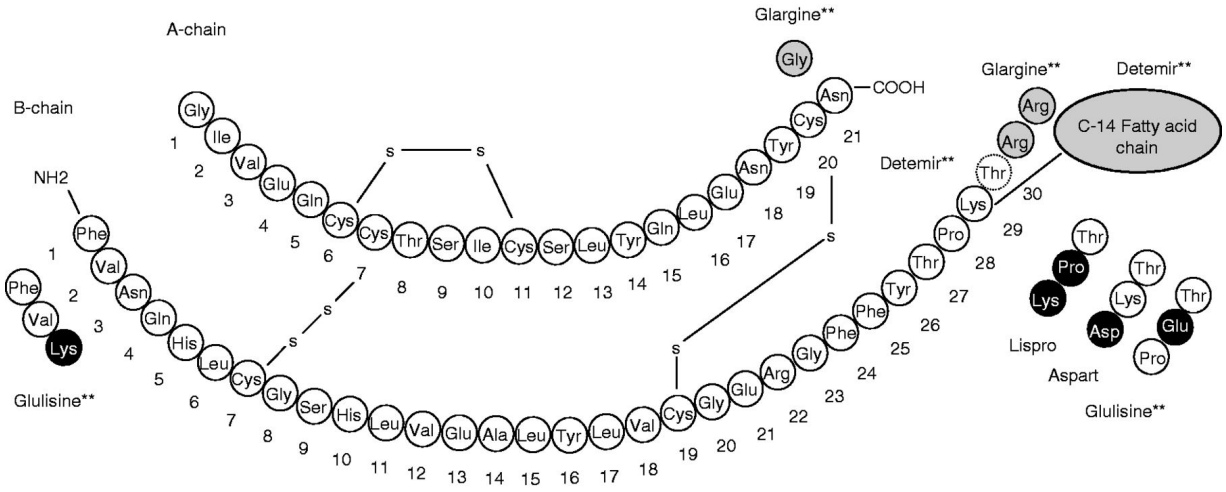
- Describe the difference between biologicals and small molecules
- Discuss the difference between biosimilars and generics
- Discuss why are biosimilars important to healthcare systems
- Discuss the terms Interchangeability, substitutability and ‘switching’ and the importance for biosimilars

Biologicals

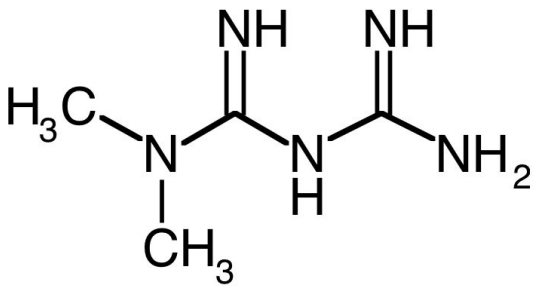
- History of over 100 years
  - First connected with diphtheria antitoxin 1895
- No clear single definition
  - Originally vaccines predominantly
  - Insulin and heparin
  - Monoclonal antibodies, fusion proteins (along with other proteins, toxins and radionucleotides) and recombinant proteins, growth factors, anti- and pro-angiogenic factors, and expression vectors generating proteins in situ
- TGA differentiates ‘biologicals’ from medicines made using biological or biotechnology processes
  - Latter referred to as biological medicines and regulated as pharmaceuticals

Biological medicines versus small molecule drugs

- Complex mixtures with large molecular weights



Insulins MW 5808 Da



Metformin MW 129 Da

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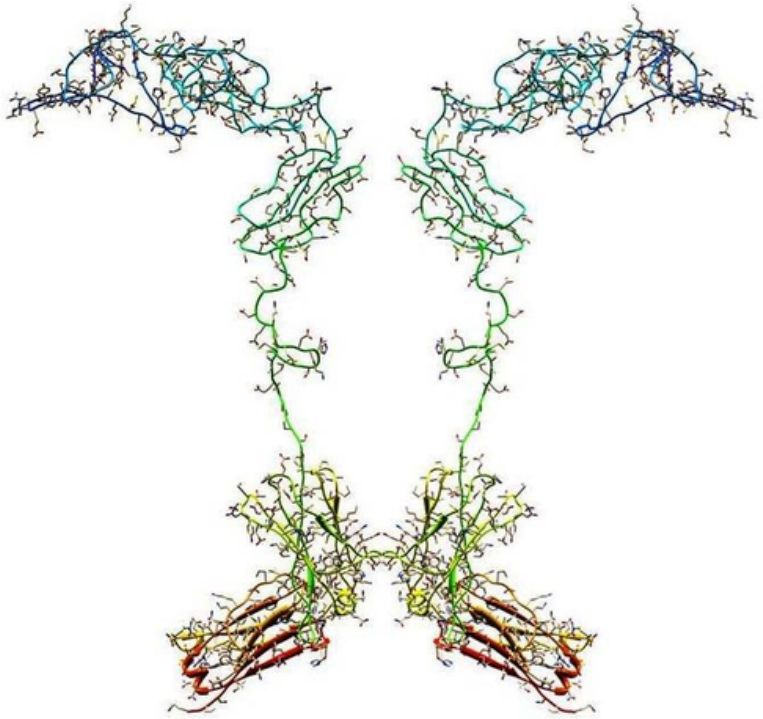
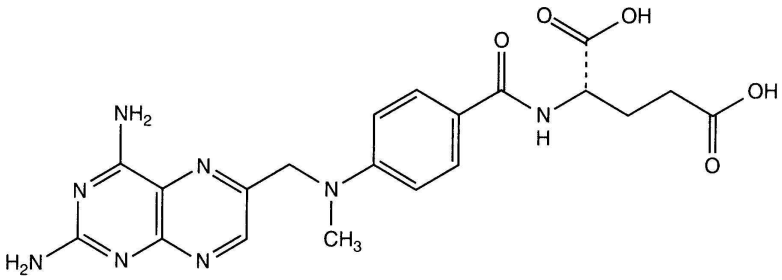


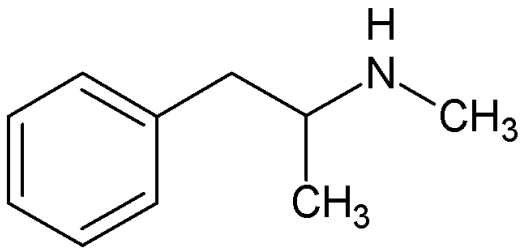
Etanercept MW 149,000 Da



Methotrexate MW 454 Da

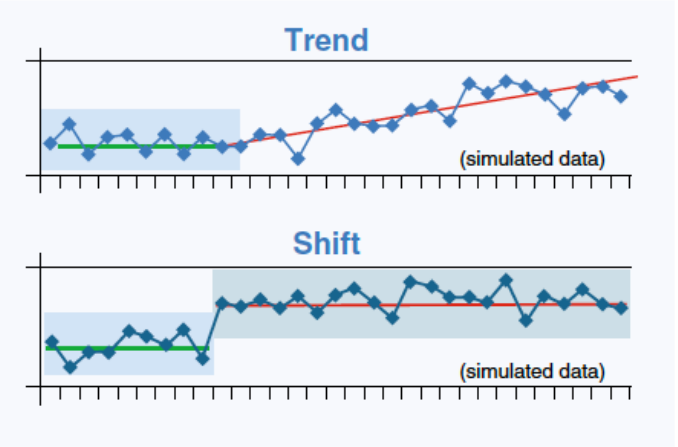
Biological medicines versus small molecules

- Complex manufacturing



Biological medicines versus standard pharmaceuticals

- Almost impossible to ensure identical copies[1]
  - **Drift:** unintended deviations caused by the manufacturing process
    - Can be a trend or sudden change
  - **Evolution:** intentional change in manufacturing to improve the product
- Poor stability − light, heat, etc
- Given parenterally
- Often immunogenic



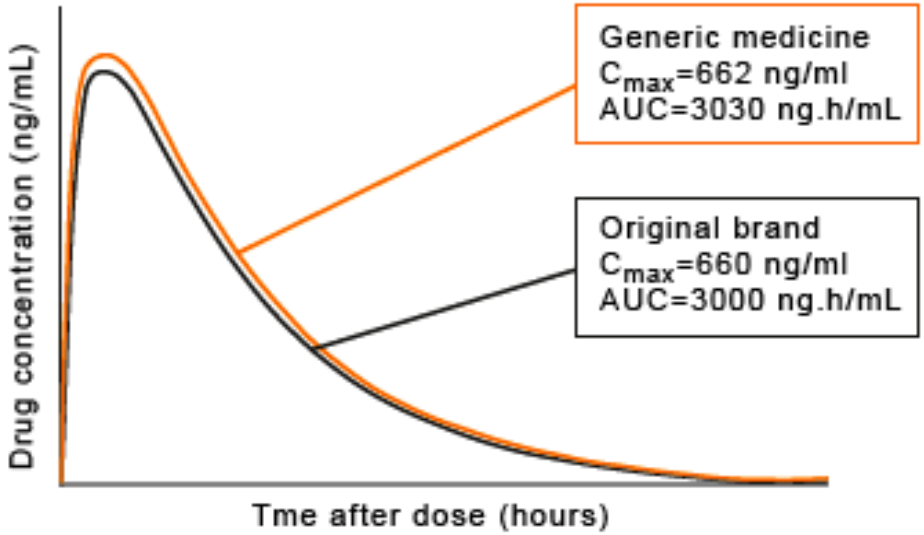
1. Ramanan S, Grampp G. Drift, evolution, and divergence in biologics and biosimilars manufacturing. BioDrugs. 2014 Aug 1;28(4):363-72.

Biosimilars versus generics

- Generics
  - TGA definition:
    - has the same quantitative composition of therapeutically active substances, being substances of similar quality to those used in the registered medicine or previously registered medicine; and
    - has the same pharmaceutical form; and
    - is bioequivalent; and
    - has the same safety and efficacy properties
  - Rely on originator for safety and efficacy
  - Bioequivalence
    - Similar plasma concentrations of active ingredient
      - C_{max}, T_{max}, and AUC

Bioequivalence analysis - a hypothetical bioequivalence study[1]

Mean concentration-time curves for two brands of a drug after single oral doses



The original brand:generic medicine ratio for AUC is 0.99 (90% CI 0.91 to 1.04) and for C_{max} is 0.99 (90% CI 0.92 to 1.07).

- To be bioequivalent, the 90% confidence intervals (90% CI) for the ratio of each pharmacokinetic parameter, C_{max} and AUC, must lie within the range 0.8-1.25
- Generally <10% difference; US study showed average difference ~3.5%[2]

1. Frequently asked questions about generic medicines. Aust Prescr 2007;30:41-3. Available: https://www.nps.org.au/australian-prescriber/articles/frequently-asked-questions-about-generic-medicines
2. Davit BM, Nwakama PE, Buehler GJ, Conner DP, Haidar SH, Patel DT, Yang Y, Yu LX, Woodcock J: Comparing Generic and Innovator Drugs: A Review of 12 Years of Bioequivalence Data from the United States Food and Drug Administration. Ann Pharmacother. 2009, 43 (10): 1583-1597. 10.1345/aph.1M141

Biosimilars

- Other terminology:
  - “similar biological medicine” (EU)
  - “similar biotherapeutic product” (WHO)
  - “subsequent entry biologics” (Canada)

- “a version of an already registered biological medicine that has a demonstrable similarity in physicochemical, biological and immunological characteristics, efficacy and safety, based on comprehensive comparability studies” (TGA)

Biosimilars

- Evaluation involves:
  - Quality
    - physicochemical and biological qualities are compared
  - Nonclinical
    - dosing and animal studies to detect any differences between the biosimilar and reference product
  - Clinical
    - tested in humans in a **clinical trial to demonstrate comparable effectiveness** and safety to the reference product

Safety concerns with biosimilars

- Immune related reactions
  - Anti-drug antibodies
    - Reduced effectiveness
    - Increased adverse effects
- Many factors influence immunogenicity
  - Patient-related
    - Age (e.g. young and old)
  - Disease-related
    - activated immune systems in chronic infections or autoimmune disease
    - Previous exposure to similar proteins as treatments
  - Administration-related
    - IV less than IM or SC
    - Short-term less than long-term
    - Continuous less than intermittent
  - Product-related
    - Impurities, degradation products

Evidence of immunogenicity

- Mixed results
- Etanercept
  - SB4 vs originator etanercept[1]
  - Lower incidence of Anti-drug antibodies (ADAs) with SB4 (0.7% vs 13.1%)
  - Lower incidence of injection site reactions with SB4 (3.7% vs 17.2% $p<0.001$)
- Infliximab
  - CT-P13 vs originator infliximab[2]
  - Lower ADAs with CT-P13 at week 14 (9% vs 11%) but more at 30 weeks (27% vs 23%)
  - Infusion related reactions slightly lower with CT-P13 (3.9% vs 4.9%)

1. Emery P, Vencovský J, Sylwestrzak A, Leszczyński P,Porawska W, Baranauskaite A, et al. A phase III randomised,double-blind, parallel-group study comparing SB4 withetanercept reference product in patients with activerheumatoid arthritis despite methotrexate therapy.Ann Rheum Dis 2015 Jul 6
2. Park W, Hrycaj P, Jeka S, Kovalenko V, Lysenko G, Miranda P, Mikazane H, Gutierrez-Ureña S, Lim M, Lee YA, Lee SJ. A randomised, double-blind, multicentre, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study. Annals of the rheumatic diseases. 2013 May 16:annrheumdis-2012.

Evaluation of the safety of biosimilars

- Design
  - Parallel comparisons in naïve patients
    - equivalence study not non-inferiority
  - Cross-over comparisons: originator → biosimilar
- Duration
  - Chronically administered → 1 year follow up
  - Shorter if favourable profile for originator

- Issues
  - Rare events still not detected pre-marketing → strong post marketing surveillance needed
    - Need to identify specific brands
  - Extrapolation to multiple indications – theoretical??
  - Multiple switching → increased immunogenicity?

Other issues with biosimilars versus generics

- No agreed naming convention
  - FDA proposes 4 letter suffix of random letters
    - Originator: filgrastim-sndz (manufaturer: Sandoz)
    - First biosimilar: filgrastim-dyyb (manufacturer: Celltrion)
  - WHO proposing similar
  - Criticism that has no connection to the product will be difficult to remember
  - TGA initially proposed a suffix starting with ‘sim’ followed by three letters
    - e.g. infliximab-simfam
  - TGA now dropped the suffix
    - Requires unique brand name
    - Cannot include the active ingredient in the brand name

Growth in biologicals - 2005

Table F (b): Top 10 drugs by prescription counts—2005

Drug	PBS/RPBS	Guild Survey	Total Community use
1 ATORVASTATIN	8,511,407	22,461	8,533,868
2 SIMVASTATIN	6,317,388	11,854	6,329,242
3 AMOXYCILLIN	2,428,534	2,553,406	4,981,940
4 PARACETAMOL	4,583,476	146,112	4,729,588
5 OMEPRAZOLE	4,312,024	11,177	4,323,201
6 SALBUTAMOL	2,992,123	1,174,721	4,166,844
7 ATENOLOL	3,257,148	894,745	4,151,893
8 CODEINE with PARACETAMOL	2,638,838	1,399,925	4,038,763
9 IRBESARTAN	3,181,629	599,277	3,780,906
10 CEFALEXIN	2,163,066	1,567,362	3,730,428

Australian Statistics on Medicine 2004/5: http://www.pbs.gov.au/info/statistics/asm/asm-2004-05

Growth in biologicals - 2005

Table G (b): Top 10 drugs by cost to Australian Government—2005

Drug	PBS/RPBS DDD/1000/DAY	PBS/RPBS Scripts	Cost to Australian Government ($AUS)
1 ATORVASTATIN	106.617	8,511,407	$574,426,634
2 SIMVASTATIN	57.404	6,317,388	$400,703,647
3 OMEPRAZOLE	20.092	4,312,024	$202,379,149
4 SALMETEROL and FLUTICASONE	.	2,823,361	$198,963,992
5 ESOMEPRAZOLE	12.845	3,353,864	$192,732,358
6 CLOPIDOGREL	8.033	2,058,272	$173,060,819
7 OLANZAPINE	2.949	728,248	$156,019,723
8 PRAVASTATIN	13.815	2,052,758	$126,981,644
9 PANTOPRAZOLE	11.281	2,663,692	$126,406,633
10 ALENDRONIC ACID	8.93	2,223,785	$126,177,262

- Total spending ~ $2.3B

Growth in biologicals - 2015

Table C: Top 10 drugs by prescription counts, 2015

Drug	PBS/RPBS	Under co-payment	Total
ATORVASTATIN	7,634,687	2,922,825	10,557,512
ROSUVASTATIN	6,667,654	2,764,678	9,432,332
ESOMEPRAZOLE	7,184,175	1,684,090	8,868,265
PARACETAMOL	7,003,988	361,643	7,365,631
PANTOPRAZOLE	4,618,171	1,738,738	6,356,909
PERINDOPRIL	4,005,504	2,114,337	6,119,841
AMOXYCILLIN	2,377,339	3,487,319	5,864,658
CEFALEXIN	2,851,477	2,753,113	5,604,590
METFORMIN HYDROCHLORIDE	3,570,613	1,585,270	5,155,883
AMOXYCILLIN with CLAVULANIC ACID	2,256,829	2,810,399	5,067,228

Australian Statistics on Medicines 2015: http://www.pbs.gov.au/info/news/2016/09/aus-statistics-on-medicines-2015

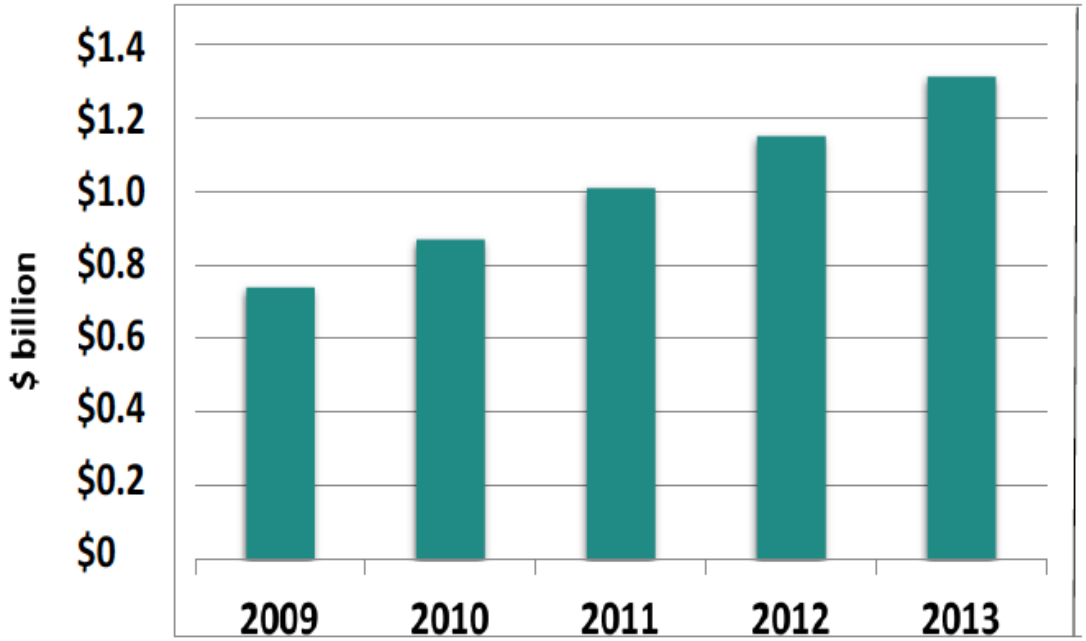
Growth in biologicals - 2015

Drug	DDD/1000/Pop	Scripts	Total Cost
ADALIMUMAB	0.60	185,246	329,711,021
ESOMEPRAZOLE	24.85	7,184,175	229,567,718
RANIBIZUMAB		137,201	213,608,450
AFLIBERCEPT		132,792	208,351,224
SALMETEROL and FLUTICASONE		3,081,584	204,998,295
ROSUVASTATIN	36.13	6,667,654	202,920,536
ETANERCEPT	0.32	95,800	168,593,840
PREGABALIN	6.75	2,958,702	161,937,157
INSULIN GLARGINE	7.61	359,843	150,832,113
RITUXIMAB		45,996	147,655,378

- Total spending ~$2b
- Spending on biologics ~$1.2b (60%)

Growth in biologics

Figure 1: Expenditure on biological medicines in Australia (Source: IMS, March 2014)



- 65 biologics funded on the PBS
- Approximately 15% of total PBS spending
- Grown 75% in 5 years (15% annually)
- Compound growth expected to be 22% by 2021

Why are biosimilars important?

- Generic medicines have been the biggest single way of reducing costs of small-molecule medicines

	Atorvastatin 20mg x 30 DPMQ
April 2010	$58.00
April 2012	$50.31
April 2014	$23.59
April 2016	$14.17
April 2017	$13.18

Reference pricing and F1/F2

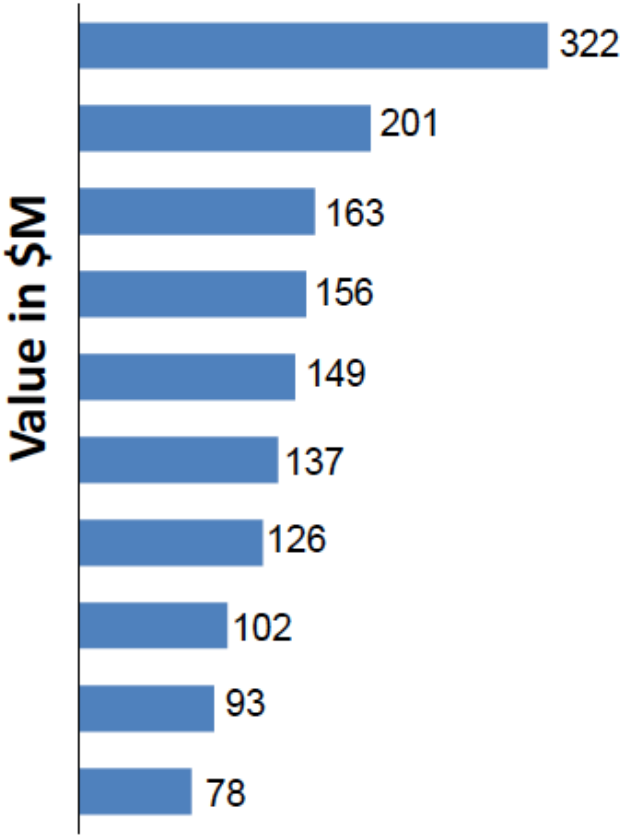
- Underpins the generic pricing

- Two ‘Formularies’ on the PBS
  - Designated by legislative instrument
  - F1: Originator brands
  - F2: Multiple brands or where in a therapeutic group and one member moves to F2

- A move to F2 causes an automatic price reduction and subsequent price reductions

Patent expiry of biologics

The 'wave' of patent expiries



	Expiry
Adalimumab (Humira)	2020
Ranibizumab (Lucentis)	2018
Etanercept (Enbrel)	Expired
Rituximab (Mabthera)	Expired
Trastuzumab (Herceptin)	Expired
Insulin Glargine (Lantus)	Expired
Infliximab (Remicade)	Expired
Insulin Aspart (Novomix, Novorapid)	2017
Bevacuzimab (Avastin)	2020
Pegfilgrastim (Neulasta)	2017

Skerritt J. What's trending in medicine regulation/ presentation to ARCS, January 2017. Available: https://www.tga.gov.au/sites/default/files/tga-presentation-arcs-seminar-sydney-24-january-2017.pdf

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Impacts of introducing biosimilars

- Budget impact estimates for infliximab in Eastern Europe in 2014[1]
  - Two scenarios:
    - Only able to start new patients on biosimilar (S1)
    - Able to switch between originator and biosimilar (S2)
  - Estimated savings of €15.3 million over the first 3 years (S1) increasing to € 20 million (S2)
  - Estimated to allow an additional 1,205 and 1,790 patient could be treated in S1 and S2, respectively

- RAND Corporation[2]
  - Estimates savings of US$1b to U$108b over 10 years

- All based on economic modeling

1. Brodszky V, Baji P, Balogh O, Pentek M. Budget impact analysis of biosimilar infliximab (CT-P13) for the treatment of rheumatoid arthritis in six Central and Eastern European countries. Eur J Health Econ [Internet]. 2014 May [cited 2015 Feb 2];15 Suppl 1:S65-71. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4046087
2. The Cost Savings Potential of Biosimilar Drugs in the United States. https://www.rand.org/content/dam/rand/pubs/perspectives/PE100/PE127/RAND_PE127.pdf

Interchangeable vs substitutable

- FDA can designate as “biosimilar biological product” or “interchangeable biological product”

- FDA definition of “interchangeable”
  - “biosimilar product can be **expected to produce the same clinical result** as the reference product in any given patient, and, for a biological that is administered more than once, that **the risk of alternating or switching** between use of the biosimilar product and the reference product is **not greater than the risk of maintaining the patient on the reference product**”

- TGA does not designate a biosimilar as ‘interchangeable’

- PBS and interchangeable
  - Section 101 (3BA) National Health Act
  - “If the Committee is of the opinion that a **drug or medicinal preparation should be made available**…the Committee must, in its recommendation…**specify whether** the drug or medicinal preparation and another drug or medicinal preparation **should be treated as interchangeable on an individual patient basis**.”

Interchangeable vs substitutable

- Substitutable on the PBS
  - 'a' flagging
  - Insulin glargine first considered on PBS
    - Received a positive recommendation → company chose not to list

- Generated significant controversy → consumer hearing with PBAC in July 2015[1]
  - decisions about substitution should occur in the therapeutic relationship between the prescriber and the patient with the patient giving informed consent
  - concerned that pharmacy **level substitution would be automatic** and may entail risks for patients.
  - concern that substitution of particular drugs may entail **use of a different drug delivery system**, which could lead to confusion for self-administered drugs (e.g. insulin)
  - Ability to **track biosimilars** versus originator for post marketing surveillance

1. CONSUMER HEARING – BIOSIMILAR MEDICINES 7 JULY 2015:: www.pbs.gov.au/consumer-hearing-record-on-biosimilars-2015

Studies about substitution − small molecules

- Australian study looking at substitution of small-molecule generics found nearly 50% have no change over 12 months and a further 34% have a single change[1]
  - Factor most likely to increase odds of multiple substitutions was the number of pharmacies attended (OR=1.29) → this is not likely with biosimilars due to the cost → pharmacies stock for regular clients
  - Study was done in 2005 → pre-price disclosures and so incentives to substitute much greater
- More recent study (2008) has indicated an increasing trend for substitution with 10-14% having 3 or more switches[2]
  - Younger (<50) more likely to swap multiple times

1. Kalisch, L. M., Roughead, E. E., & Gilbert, A. L. (2009). Pharmaceutical brand substitution in Australia: identifying factors associated with having multiple brand substitutions. International Journal of Pharmacy Practice, 17(6), 339-344.
2. Ortiz M, Simons LA, Calcino G. Generic substitution of commonly used medications: Australia-wide experience,2007–

PBAC considerations in ‘a’ flagging

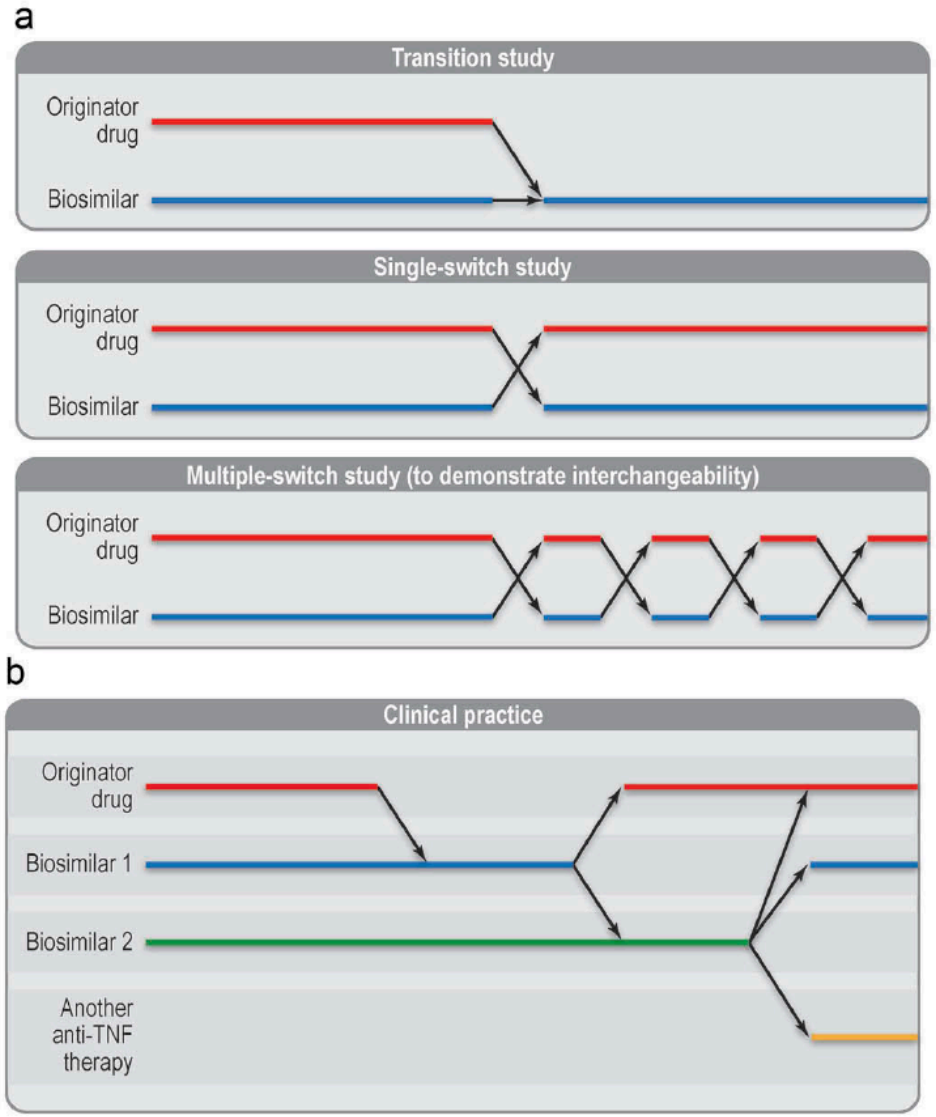
- Each will be considered on a case-by-case basis
- Key principles:
  - There should be evidence that the biosimilar was safe and effective in treatment-naïve patients initiating on the biosimilar product;
  - There should be no evidence (data) that there was significant differences in clinical effectiveness or safety compared with the reference (originator) medicine;
  - There was no evidence that identified populations where the risks of using the biosimilar medicine was disproportionately high;
  - The evidence should support equal safety and effectiveness when switching between the reference (originator) medicine and the biosimilar medicine; and,
  - Whether the TGA has deemed a medicine to be biosimilar with the reference (originator) medicine.

FDA and Interchangeability

- Recently updated (January 2017)[1]
- “FDA anticipates that data and information acquired from a switching study or studies will be useful in assessing the risk, in terms of safety and diminished efficacy, of alternating of switching between the products”

1. https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm537135.pdf

Switching trials with biosimilars



Faccin F, Tebbey P, Alexander E, Wang X, Cui L, Albuquerque T. The design of clinical trials to support the switching and alternation of biosimilars. Expert Opinion on Biological Therapy. 2016 Dec 1;16(12):1445-53.

Switching studies - infliximab

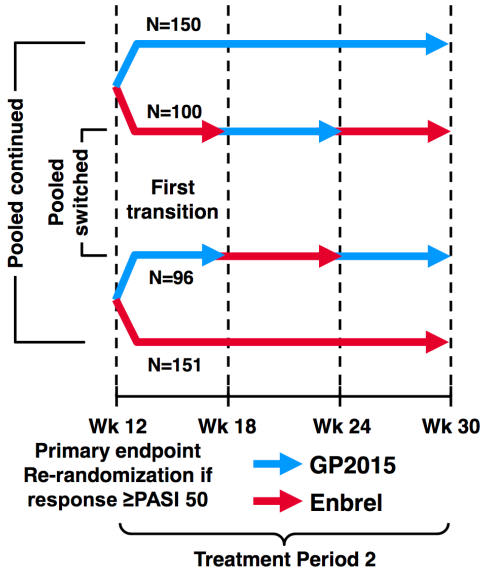
- Extension study of PLANTERA[1]
  - CT-P13 vs Remicade®
  - Extension to 52 week RCT → extended to 102 weeks with patients on Remicade® switched to CT-P13 at 52 weeks

	Patients positive for ADAs and NAbs (n, %)		
Time point	**Maintenance group* (n=159)**	**Switch group† (n=143)**	**p Value**
Extension study period			
Week 78 ADAs	71 (44.7)	66 (46.2)	0.82
NAbs	71 (100.0)	64 (97.0)	
Week 102 ADAs	64 (40.3)	64 (44.8)	0.48
NAbs	64 (100.0)	64 (100.0)	
ADA persistency (n/N‡, %)			
Sustained ADAs	73/91 (80.2)	74/92 (80.4)	1.00
Transient ADAs	18/91 (19.8)	18/92 (19.6)	1.00

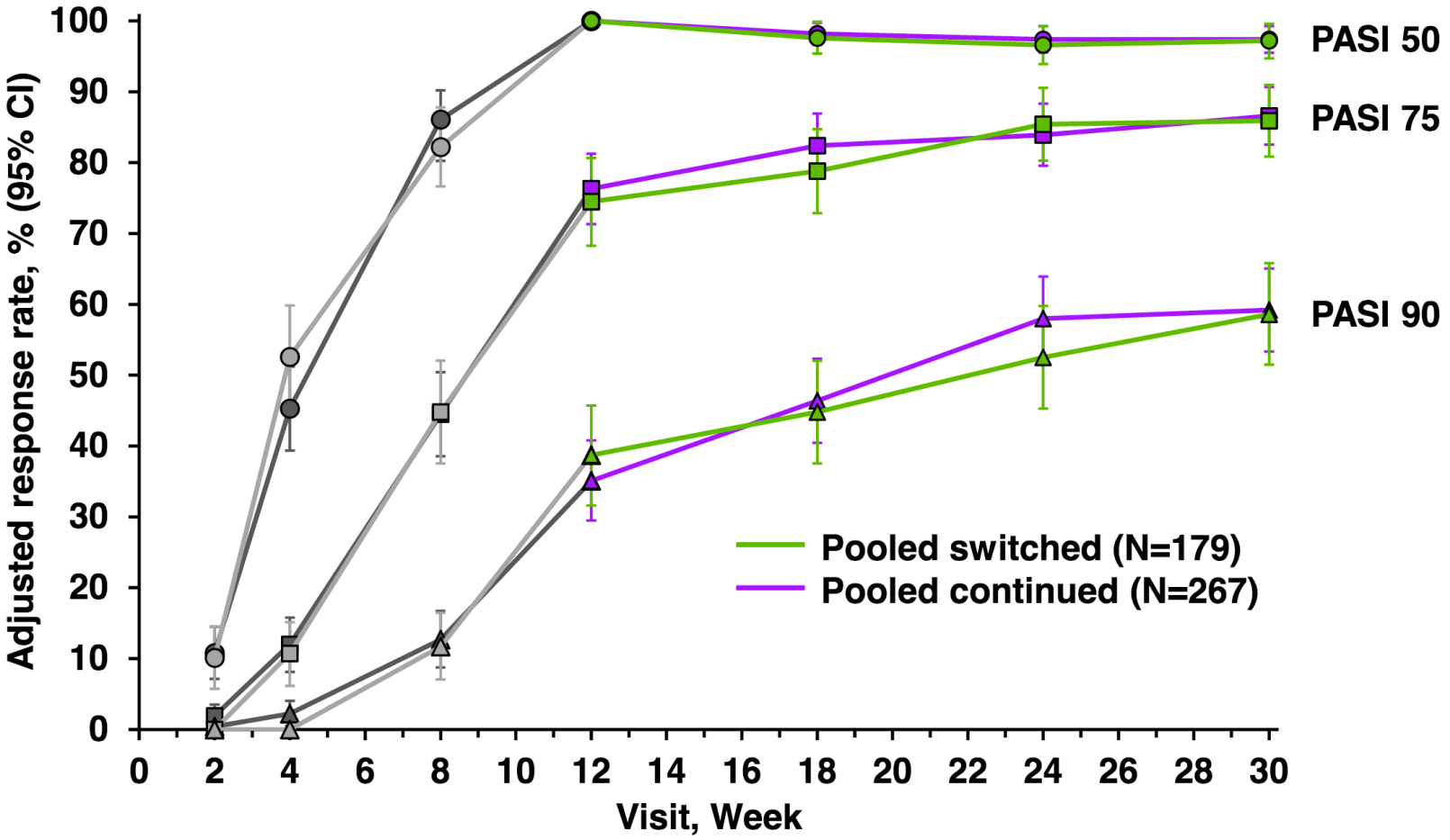
1. Yoo DH, Prodanovic N, Jaworski J, Miranda P, Ramiterre E, Lanzon A, Baranauskaite A, Wiland P, Abud-Mendoza C, Oparanov B, Smiyan S. Efficacy and safety of CT-P13 (biosimilar infliximab) in patients with rheumatoid arthritis: comparison between switching from reference infliximab to CT-P13 and continuing CT-P13 in the PLANETRA extension study. Annals of the rheumatic diseases. 2017 Feb 1;76(2):355-63.

Switching studies

- NOR-SWITCH
  - Sponsored by the Norwegian government
  - Seen by many as a pivotal trial for switching with infliximab
  - 52-week, randomised, double-blind, parallel study involving 6 different indications for infliximab
  - Still a single switch!
  - Preliminary results only
    - ADA detected 7.1% Remicade® vs 7.9% Remsima™
- GP15-302[1]
  - Comparison of biosimilar etanercept (GP2015) to Enbrel®
  - All patients had psoriasis
  - Phase 2 had switches every 6 weeks



1. https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM513088.pdf



- PASI=Psoriasis Area and Severity Index
- Immunogenicity at 30 weeks (patients with ADA)
  - GP2015 0 (0%)
  - Enbrel® 5 (1.7%)

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Summary of switching of biosimilars

- Post-market experience and single switch trials so far have not indicated significant risks

- Unanswered questions:
  - Are risks different for different underlying conditions?
  - How long do we need studies to be to feel confident?
  - How to balance need for evidence with access to affordable biosimilars?

Other rumored proposed policy initiatives to increase uptake of biosimilars

- Mandatory prescribing by international non-proprietary name (INN)
- Mandatory prescribing of biosimilars for treatment naïve patients
- Loosening Authority restrictions for biosimilars
- Reduced co-payments for biosimilars

Pharmacists role with biosimilars

ETANERCEPT

Source: General Schedule

Body System: ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS > IMMUNOSUPPRESSANTS > IMMUNOSUPPRESSANTS

▸ Note

▸ ⚠ Authority Required

Code & Prescriber	Medicinal Product Pack (Name, form & strength and pack size)	Max qty packs	Max qty units	No. of repeats	DPMQ	Max Safety Net	Max price to consumer
9087G (MP)	ETANERCEPT ETANERCEPT Injections 50 mg in 1 mL single use pre-filled syringes, 4, 1 (PI, CMI)	1	1	3	$1048.77	$38.80	$38.80

Available brands
Brenzys
Enbrel

INFLIXIMAB

Source: S100 HSD Private

Body System: ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS > IMMUNOSUPPRESSANTS > IMMUNOSUPPRESSANTS

▸ Note

▸ ⚠ Authority Required

Code & Prescriber	Medicinal Product Pack (Name, form & strength and pack size)	Max qty packs	Max qty units	No. of repeats	DPMQ	Max Safety Net	Max price to consumer
10057H (MP)	INFLIXIMAB infliximab 100 mg injection, 1 vial (PI, CMI)	1	1	1	$604.86	$38.80	$38.80

Available brands
Inflectra
Remicade

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PSA position statement - biosimilars

- The patient's health is the prime consideration and any decision to substitute one brand for another should not place the patient at risk
- Substitution may only occur after consultation with and agreement of the patient and not when the 'no brand substitution' box is crossed
- Given the paucity of long-term data pharmacist should contribute to ongoing monitoring of efficacy and safety
- Pharmacists play a pivotal role in educating patients about biosimilars
- Pharmacists should play a pivotal role in pharmacovigilance of biosimilars

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DON'T GIVE PHARMACISTS POWER OVER BIOSIMILARS: AUSTRALIAN RHEUMATOLOGY ASSOCIATION

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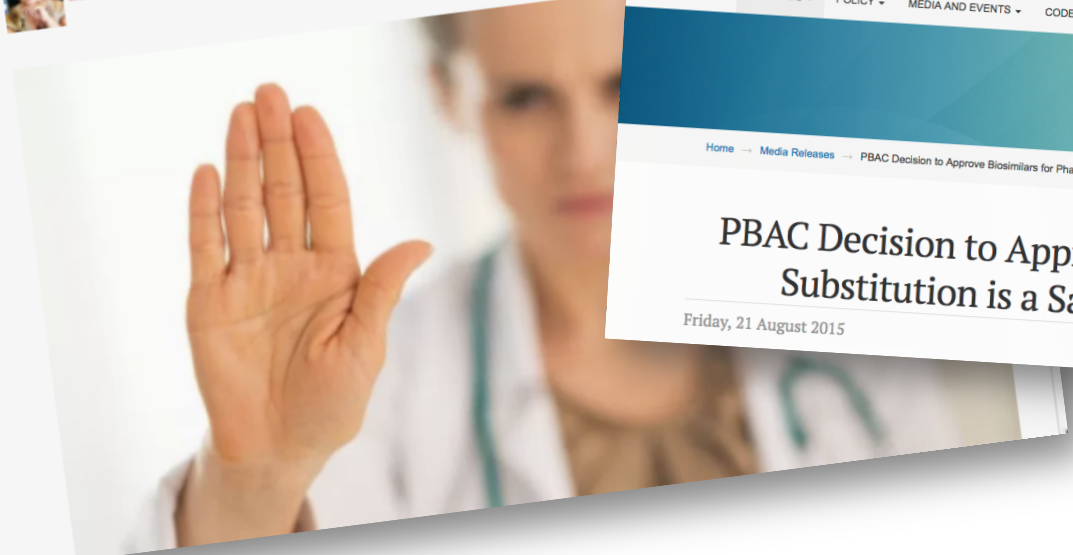
MEGAN HAGGAN — 23/06/2015



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PBAC Decision to Approve Biosimilars for Pharmacy Substitution is a Safety Concern for Patients

Friday, 21 August 2015

Media Release

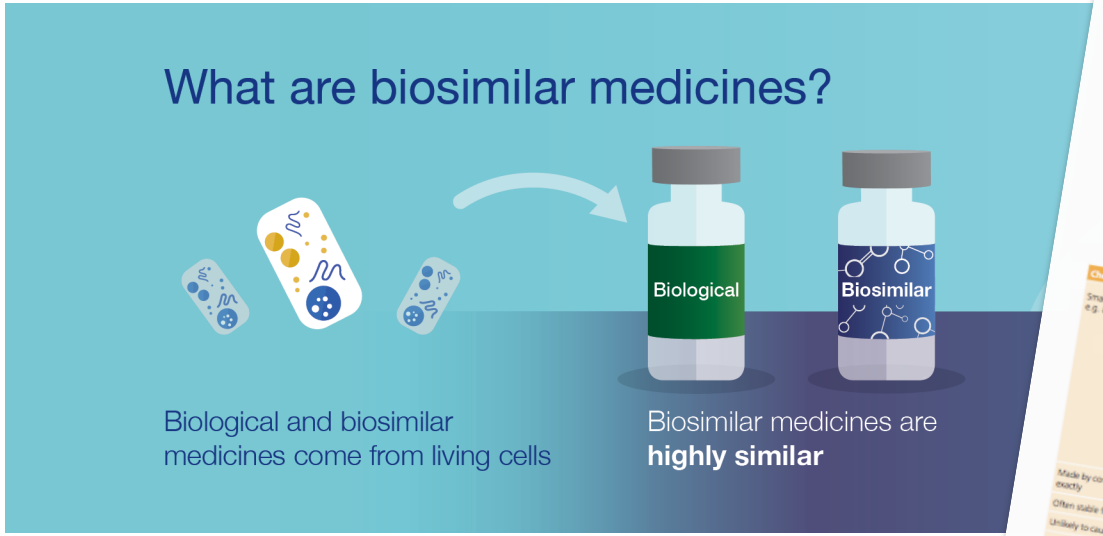
THE UNIVERSITY OF NEWCASTLE AUSTRALIA

Key messages about biosimilars

- Biosimilars will play an important role in ensuring access to affordable treatments
- Need to carefully balance the unknown issues of safety from swapping and changing with encouraging the use of biosimilars
- Pharmacists will play a pivotal role in advising patients to enable informed decisions about substitution
- Pharmacists will play an important role in Pharmacovigilance for these new agents

More information and fact-sheets

- Department of Health Biosimilar Awareness Initiative
- http://www.health.gov.au/internet/main/publishing.nsf/Content/biosimilar-awareness-initiative



THANK YOU

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DISCUSSION

A presentation to company name
1 March 2007