1ST NATIONAL BIO-THERAPEUTICS CONGRESS — PUTTING PATIENT FIRST

22 NOVEMBER 2014
Biosimilars - Interchangeability and Substitution

Dr. Paul Cornes
Dr Paul Cornes
Conflict of interest

- Salary received:
  - United Kingdom National Health Service

- Honoraria received:
  - Roche
  - Janssen
  - Sandoz
  - Lilly
  - European Generics Association
  - Teva
  - Hospira
Biosimilars - Interchangeability and substitution

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Biosimilars - Interchangeability and substitution

Strive not to be a success, but rather to be of value
Question 1

- You are part way through a course of treatment with infliximab for rheumatoid disease - The patient is responding without serious toxicity
- Your pharmacy colleagues tell you that the next treatment is likely to come from a new purchase of biosimilar infliximab (approved for use by the EMEA)

Do you? – please chose your best response:

1. Refuse – as the patient is part way through treatment and switching is not advised by Malaysian Guidelines
2. Agree – but worry there is no data to support this change
3. Agree to the switch – as no excess adverse events are expected
Question 2

- You are part way through a course of dose dense chemotherapy for breast cancer – supported by Filgrastim GCSF to prevent neutropaenia. The patient is responding without serious toxicity.
- The patient will transfer mid-way through treatment to stay with her family in another area. Your colleague tells you that in their hospital, they use only biosimilar Filgrastim (approved for use by the EMEA and Malaysian Regulators).

Do you? – please chose your best response:

1. Refuse – the patient is part way through treatment and switching is not advised by Malaysian Guidelines
2. Agree – but worry there is no data to support this change
3. Agree to the switch – as no excess adverse events are expected
Biosimilars - Interchangeability and substitution

- Questions
  - Why have we been worried?
  - Terminology
  - Rules
  - Evidence for safety
    - Regulatory
  - Observational studies of substitution & switching
    - Originator to Originator
    - Originator to Biosimilar
  - RCTs of switching
- Questions Revisited
Biosimilars may share primary DNA and amino acid sequence with originators

- But with
  - Different vectors to transform host cells
  - Different Cell Banks
  - Different cell culture medium
  - Different culture vessels - “Bioreactors”
  - …..

- Different tertiary structure could result
  - Which could alter the functionality or safety of the drug

What might make physicians hesitate?

- Immunogenicity

- A protein can be modified in many ways:
  - side chains can be added,
  - protein misfolding makes different tertiary structure
  - degradation by oxidation or deamidation

Different patented manufacturing processes may invariably lead to structural differences in the final product.

Unlike classical generics, biosimilars are not *identical* to their originator products.

“Highly similar but not identical”

- Is not new to biotechnology

- Natural proteins come in a spectrum of isoforms

Example – Multiple Isoforms of Human Erythropoietin

Human serum EPO (65 ng). Two-dimensional gel electrophoresis of human serum EPO. IEF was carried out by using IPG strips with a pH gradient of 3 to 6. SDS-PAGE was performed in 12% gels followed by immunoblotting
“Highly similar but not identical”

- Is not new to biotechnology
- Natural proteins come in a spectrum of isoforms

“Highly similar but not identical”

- Is not new to biotechnology
- Natural proteins come in a spectrum of isoforms

Protein variation in products marketed internationally as epoetin alpha

Multiple different isoforms of proteins naturally occur

E is the original reference product

Unregulated copy drugs bought in Asia and South America

Immunogenicity from small manufacturing changes

- **Eprex®** (epoetin alfa)

- Two production changes made....
  1. uncoated rubber stoppers used in the syringe
  2. a new stabiliser added

- Several hundred patients developed anti-epoetin antibodies
  - these neutralised both endogenous erythropoietin and injected epoetin,
  - and stopped the bone marrow making red cells with development of profound anaemia
  - leading to some fatalities
Time-course of PRCA

Worryingly - this took 5 years and several hundred patients harmed to discover

New formulation introduced

New formulation withdrawn

All cases of PRCA

Cases associated with 1 make of epoetin

Ref: Kuhlmann M. Lessons learned from biosimilar epoetins and insulins. British Journal of Diabetes & Vascular Disease 2010 10: 90
Safety of biosimilar medicines: “EU DRA Vigilance”

- New EU pharmacovigilance legislation came into force in July 2012
  - legal obligation for the systematic tracking of medicines from manufacturer to patient
  - puts biosimilars in the same class as new substances
  - this means that manufacturers must include a ‘black symbol’ in the product information

EMEA: 2 weekly reports on any new drug or indication or if safety worries

IF YOU SEE SOMETHING, SAY SOMETHING.

BE SUSPICIOUS OF ANYTHING UNATTENDED.
Tell a cop, an MTA employee or call 1-888-NYC-SAFE.

YellowCard
Helping to make medicines safer
mhra.gov.uk/yellowcard
How good is the new vigilance system?

- EUDRA – Vigilance
  - 2,108,742 unique ADR reports
  - 439,971 biologic ADRs

- A total of 13,790 biopharmaceuticals (9,759 suspected) for which a biosimilar has been approved in the EU were identified in EV.

- For 90.4% of these biopharmaceuticals and 96.2% of the suspected biopharmaceuticals, the product was clearly identifiable.

Neutralizing antibodies to epoetin alfa triggered by soluble tungsten

- **Amgen Study:**
  - Tungsten pins are used to form the needle cavity in glass pre-filled drug syringes
  - 1,200 °C used to melt glass is sufficient to release some tungsten from the metal moulding pin
Neutralizing antibodies to epoetinalfa triggered by soluble tungsten

- Protein aggregates in biologic drugs stimulate immune responses.
- 2 cases from 337 in a trial of subcutaneous epoetin developed neutralizing antibodies
- A small number of individual syringes in 2 product batches were found to contain unusually high levels of aggregation & soluble tungsten
  - Tungsten induced denaturation and aggregation of the epoetin
  - Increasing the potential for immunogenicity

Not all drugs are equal – your drug regulatory authority is crucial

International copies of docetaxel compared for
- Activity
- Impurities

Key
- Acceptable
- Unacceptable
- Original reference drug

All EMEA approved generics were safe and active

Biosimilars - Interchangeability and substitution

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- Questions Revisited
Definitions

“We have really everything in common with America nowadays except, of course, language.”

Oscar Wilde, 1887

Ref: Oscar Wilde. The Canterville Ghost (1887)
Definitions: interchangeable & substitutable

- interchangeable
  - A product is interchangeable with another if both products are used and approved for the same indication.

- substitutable
  - Two products can be substitutable with each other if they can both be used in lieu of each other during the same treatment period.

And so – in theory, be substituted by a pharmacist.

Definitions: interchangeable & substitutable

USA: US Food and Drug Administration (FDA) does have the authority to designate two sorts of follow-on biologic drugs after patent expiry

1. “biosimilar”
2. “Interchangeable biosimilar”
Definitions: interchangeable & substitutable

FDA Definition of Interchangeability

Interchangeability means that the biologic product is biosimilar to the U.S.-licensed reference biological product and can be expected to produce the same clinical result as the reference product in any given patient.

- For a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product will not be greater than the risk of using the reference product without such alternation or switch.

- Interchangeable biological products may be substituted at the pharmacy level without the intervention of a healthcare provider.

FDA. Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations. URL: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm41162014
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- Interchangeable biological products may be substituted at the pharmacy level without the intervention of a healthcare provider.

This power is not an EMEA or European Union issue. The decision is delegated to member countries of the E.U.


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- **Interchangeable** biological products may be substituted at the pharmacy level without the intervention of a healthcare provider.

This also explains why there can be so much confusion between the terms “interchangeable” “substitution” and “switchable”.

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*FDA. Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations. URL: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm41162014*
Definitions: interchangeable & substitutable

- **interchangeable**
  - A product is interchangeable with another if both products are used and approved for the same indication.

  You could substitute the biosimilar drug in your protocols and expect no clinically meaningful difference in outcomes.

- **Substitutable / USA “Interchangeable”**
  - Two products can be substitutable with each other if they can both be used in lieu of each other during the same treatment period.

  Implies – that the batch to batch variation of the original product is similar to its differences with the biosimilar drug.

  Switching does not then increase risks. Either could be used during the same course of treatment for an individual patient.

Interchangability

- US FDA is very keen to develop “interchangeable biosimilars”
  - interchangeable approval requires extensive additional clinical testing beyond that required for biosimilars.
  - In return for this additional expense, the first approved interchangeable version of any reference biologic is rewarded with one year of exclusivity, during which the FDA cannot approve any additional interchangeables for that biologic.

Ref:
Biosimilars - Interchangeability and substitution

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Interchangeability

- By definition, when a Biosimilar has been approved for an indication by your regulatory authority
  - It is interchangeable with the reference product

- Which means you could use either drug and expect no clinically meaningful differences to occur
Substitution

- The EMEA can approve biosimilars for the EU
- But the issue of substitution is in the hands of member states of the EU

More than 12 countries across Europe have introduced rules to prevent automatic substitution of biological medicines by biosimilars.

2014: France has passed a law to permit automatic substitution

2014: USA has passed a law to permit interchangeability & switching mid-treatment

Substitution

- The WHO issue guidelines for biosimilar regulation
- But the issue of substitution is in the hands of member states of the WHO

Malaysian guidelines of 2011 prevent automatic substitution of biological medicines by biosimilars at pharmacy level.

2014: France has passed a law to permit automatic substitution

2014: USA has passed a law to permit interchangeability & switching mid-treatment

Automatic substitution

- EMA and WHO
  - automatic substitution by pharmacist is not an EMA or WHO power
  - France has proposed it

- US - FDA
  - Will permit for “interchangeable biosimilars”
  - But not for “biosimilars”

- Malaysia
  - Advises against automatic substitution

Biosimilars - Interchangeability and substitution

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Manufacturing changes are frequent in biologic drugs over time

- Example: every single biologic agent used in rheumatology has had a manufacturing change – some had >35 changes

Martina Weise and 4 other members of the Biosimilars Working party of the EMEA wrote:

‘It is fair to say that the current, widely used biologicals are not, after several changes to their original manufacturing process, anymore identical to the original version at the time of marketing authorisation’

C Schneider, Ann Rheum Dis March 2013 Vol 72 No 3


“..the “similar but not identical” paradigm of biosimilars appears to fuel uncertainties about [biosimilars]. However, this principle is not new to biotechnology; even consecutive batches of originator products are never identical to each other...this is normal and is why adequate controls on batch consistency have to be imposed.”

- Weise et al. Blood 2012; 120: 5111-5117
Manufacturing changes are frequent in biologic drugs over time

Relative content of the individual isoforms of originator Darbepoetin before and after a manufacturing change
pre-change (n = 18) batches, post-change (n = 4) batches

Figure 1 Comparison of the pre- and post-change Aranesp batches measured by capillary zone electrophoresis. (a) Relative content of the individual isoforms of the pre-change (n = 18) and the post-change (n = 4) batches. (b) Representative electropherograms; peaks are labeled with the isoform number.

Manufacturing changes are frequent in biologic drugs over time

- Example of darbepoetin changes
  1. Re-establishment of master cell bank
  2. Modification of the vector used to produce the antigen/source material, incl. new master cell bank
  3. Change from roller bottle (RB) manufacturing process to a more scaleable high throughput (HT) process using cells in suspension
  4. Change of cell culture medium

Change was rated as “Replacement of a biological substance or product of biotechnology with one of a slightly different molecular structure.

Biosimilars

- From a scientific and regulatory point of view, the active substance of the biosimilar is just another version of the active substance of the originator product.

- This is important to state since the same scientific principles that underlie the comparability exercise for the purpose of demonstrating similarity of a product before and after a change in manufacturing process also apply to the comparability exercise for the purpose of demonstrating biosimilarity.
  - European Medicines Agency, Committee for Medicinal Products for Human Use: Guideline on similar biological medicinal products (CHMP/437/04/Rev1).

Example of darbepoetin changes

- In addition to in-vitro binding studies – the manufacturer provided:
  1. Single dose PK study in male beagle dogs
  2. 4 week repeated (3x/week) tox study in beagles - For toxicity, PK, PD, Immunological measurements
  3. Phase I comparative PK study (randomized, 2-way, open-label, crossover, SC) with 2 single doses in 48 healthy volunteers
  4. Phase III comparative efficacy study (controlled, randomized, in 446 CKD haemodialysis patients, SC or IV, maintenance)
  5. Single arm safety study with HT (open label, in 1172 CKD patients)

The new version was approved based on demonstrated comparability of quality, non-clinical, and (limited) clinical data.

Example of rituximab changes

- Found a structural change in rituximab in batches sampled over time

Comparison of the different pre- and post-change batches of Rituxan/Mabthera

Relative amount of the G0 glycan of the pre-change (n = 13) and post-change (n = 11) batches

Example of rituximab changes

- Which was associated with a functional change in rituximab

The change led to a difference in potency of the drug measured by ADCC assay
Example of etanercept-Enbrel changes

**Figure 3** Comparison of the different pre- and post-change batches of Enbrel. (a) Relative amounts of basic variants of the pre-change \( n = 6 \) and the post-change \( n = 6 \) batches as measured by CEX. (b) Relative amount of the G2F glycan of the pre-change \( n = 25 \) and the post-change \( n = 9 \) batches. (c) Exemplary CEX chromatograms. (d) Exemplary glycan mapping chromatograms.
Variation in the production process is a normal occurrence in biologic drugs

- Christian K. Schneider, MD, is Senior Medical Officer at the Danish Medicines Authority.
- He is Chairman of the EMA's Committee for Advanced Therapies

“…The scientific principles of a change in manufacturing process of an originator mAb/cept molecule and the generation of a biosimilar are the same”

- Further references:
Quality of biosimilar medicines

- Brinks V, et al. Quality of original and biosimilar epoetin products. Pharm Res. Published online: 01 October 2010. Doi: 10.1007/s11095-010-0288-2
Quality of biosimilar medicines

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**Results** Tested EPO products differed in content, isoform composition, and potency.

**Conclusion** Of the tested products, the biosimilars have the same or even better quality as the originals. Especially, the potency of originals may significantly differ from the value on the label.
Biosimilar drugs rely on analytics to ensure similarity

- That technology has increased sensitivity enormously
- Example: Mass Spectrometry

<table>
<thead>
<tr>
<th>Year</th>
<th>Detection limit for peptides (pmol)</th>
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<tr>
<td>1990</td>
<td>100</td>
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<td>1993</td>
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<td>2008</td>
<td>0.0001</td>
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<tr>
<td>2011</td>
<td>0.00001</td>
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10 Million-fold increase

"In the USA, there is no public regulatory determination of comparability similar to the European Public Assessment Report, so physicians and patients may never know a manufacturing change has occurred. “

Biosimilars - Interchangeability and substitution

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Switching is frequent: Often between originator drugs!

- **22% of Italian patients switched epoetins in 18 months**
  - Only 2% were to biosimilars
- **14.4% of US patients switched epoetins in 5 years**
- **90% of paediatricians surveyed have switched a patient’s biologic drug to another brand**
- **1 in 5 patients in the Prospective Immunogenicity Surveillance Registry (PRIMS) switches epoetin brands in without reported complications**
Switching is frequent: Often between originator drugs!

- Cancer and haematology patients may have different brands of filgrastim (white cell growth factor) to prevent neutropeanic fever during different courses of chemotherapy

- EORTC guidelines endorse biosimilar use
Review of all published data on switching between originator and biosimilar

12,039 patients in 58 clinical trials

193 Post Authorisation Adverse event reports from EU DRA Vigilance

The safety of switching between therapeutic proteins

Hans C Ebbers, Michael Muenzberg & Huub Schellekens

†Utrecht University, Utrecht Institute for Pharmaceutical Sciences (UIPS), Department of Pharmaceutics, TB Utrecht, The Netherlands

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Human Growth Hormone – no safety signals

Epoetin – no safety signals

G-CSF – no safety signals

Review of all published data on switching between originator and biosimilar

12,039 patients in 58 clinical trials

193 Post Authorisation Adverse event reports from EU DRA Vigilance

- Human Growth Hormone – no safety signals
- Epoetin – no safety signals
- G-CSF – no safety signals

EMEA. Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues - Executive summary.
**PRCA**

- Natural incidence with epoetin-alfa was 1/100,000
  - 3 cases in first decade of Eprex Use
- After Eprex formulation change rose to 50/100,000

- Exposure to epoetin-alfa Binocrit reached 300,000 patient-years by February 2014
  - Approved 2007

**Strongly suggests that a similar association between PRCA and biosimilar epoetin-alfa is now very unlikely**
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Substitution & Switching

- There is a worry that switching between Innovator and Biosimilar drugs during a single cause of treatment could significantly increase the risks of adverse events.

- Trials to support switching may be crucial for the concerns of some physicians and patient groups.

- In the USA it may earn the registration as an “Inter-changable” biosimilar.
Substitution & Switching

- Plantera trial design: CTP13 Biosimilar vs originator reference

Substitution & Switching: Plantera trial

- **Response:** by ACR20/50/70

<table>
<thead>
<tr>
<th></th>
<th>Week 54</th>
<th>Week 78</th>
<th>Week 102</th>
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<td><strong>Arm 1</strong></td>
<td>Original</td>
<td>Biosimilar</td>
<td>Biosimilar</td>
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<tr>
<td><strong>Arm 2</strong></td>
<td>Biosimilar</td>
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## Substitution & Switching: Plantera trial

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<th>Week 78</th>
<th>Week 102</th>
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<tr>
<td>Arm 1</td>
<td>77.5%/50.0%/23.9%</td>
<td>78.2%/47.9%/29.6%</td>
<td>72.2%/48.3%/24.5%</td>
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<tr>
<td>Arm 2</td>
<td>76.8%/45.7%/21.9%</td>
<td>71.5%/48.3%/24.5%</td>
<td>71.8%/51.4%/26.1%</td>
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No difference

Substitution & Switching: Plantera trial

- Anti-drug antibodies present

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<tr>
<td>Arm 1</td>
<td>49.3%</td>
<td>49.6%</td>
<td>49.6%</td>
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<tr>
<td>Arm 2</td>
<td>49.1%</td>
<td>50.4%</td>
<td>46.4%</td>
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No difference

Substitution & Switching:

Phase III Study Comparing the Efficacy and Safety of EP2006 and Filgrastim (PIONEER)

This study has been completed.

Sponsor:
Sandoz

Information provided by (Responsible Party):
Sandoz

ClinicalTrials.gov Identifier:
NCT01519700

First received: January 13, 2012
Last updated: November 3, 2014
Last verified: November 2014

Purpose
The study will assess the efficacy of EP2006 compared to Filgrastim with respect to the mean duration of severe neutropenia during treatment with myelosuppressive chemotherapy in breast cancer patients.

Substitution & Switching - Pioneer

- Pioneer trial: GCSF for chemotherapy induced neutropaenia. During TAC chemotherapy for breast cancer

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<tr>
<th>Trial Arm</th>
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Randomise

Substitution & Switching - Pioneer

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Classic Biosimilar trial

Substitution & Switching - Pioneer

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Randomise

Pioneer has closed on the trials database: Results expected soon!

- Pioneer trial: GCSF for chemotherapy induced neutropenia. During TAC chemotherapy for breast cancer


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“switching” trial
Promotion of Switching and Substitution

- This is not within the power of the EMA or WHO to control
  - They delegate this to individual countries

- Some countries have legislated to promote this
  - Examples: USA & France

- Many countries have advised against “automatic substitution” by a pharmacist
  - So pharmacists will have to notify the prescribing physician if this is possible

Some medical societies have requested evaluation of this process
Norwegian Health department currently funds Infliximab (Remicade) for
  - rheumatoid arthritis, spondyloarthritis,
  - psoriatic arthritis, chronic plaque psoriasis
  - ulcerative colitis, Crohn's disease

Annual cost for a compliant patient was estimated at GBP 7580 (€12,226, 40,000 RM) in the UK

Infliximab Biosimilar costs 39% less than Remicade in Norway
  - It is the first choice Inflammatory Disease Modifying Biologic for the Norwegian NHS

Promotion of Biosimilars: Switching and Substitution

- The NOR-SWITCH Study:
  - Infliximab original vs Infliximab biosimilar (Remsima)
    - ClinicalTrials.gov Identifier: NCT02148640
  - Aim: RCT to assess the safety and efficacy of switching from Remicade to the biosimilar treatment Remsima in patients with rheumatoid arthritis, spondyloarthritis, psoriatic arthritis, ulcerative colitis, Crohn's disease and chronic plaque psoriasis

- Primary Outcome Measures:
  - Occurrence of disease worsening

NOR-SWITCH
ClinicalTrials.gov Identifier: NCT02148640

- Budget for 500 patients for a year:
  - 500 x 12,226 Euro a year per patient wholesale.
  - = 6.1 Million Euros (26 Million RM) a year
    - 500x12226 = 6113000

- Infliximab Biosimilar costs 39% less than Remicade in Norway
  - Budget impact if 50% of patients switched = 1.2 Million Euros
    - 250 x 12226 x 0.39 = 1192035

- Most patients take infliximab for 2 years, after 2 years, savings should be 2.4 M Euros/year recurring

- Why not invest that 2.4 M Euros / 20 M Norwegian Krone in a trial to switch 50% of patients on infliximab to a biosimilar that is 39% cheaper for 1 year?

Biosimilars - Interchangeability and substitution

- Questions
- Why have we been worried?
- Terminology
- Rules
- Evidence for safety
  - Regulatory
- Observational studies of substitution & switching
  - Originator to Originator
  - Originator to Biosimilar
- RCTs of switching
- Questions Revisited
Question 1

- You are part way through a course of treatment with infliximab for rheumatoid disease - The patient is responding without serious toxicity
- Your pharmacy colleagues tell you that the next treatment is likely to come from a new purchase of biosimilar infliximab (approved for use by the EMEA)

Do you?
1. Refuse – as the patient is part way through treatment and switching is not advised by Malaysian Guidelines
2. Agree – but worry there is no data to support this change
3. Agree to the switch – as no excess adverse events are expected
Question 2

- You are part way through a course of dose dense chemotherapy for breast cancer – supported by Filgrastim GCSF to prevent neutropaenia. The patient is responding without serious toxicity
- The patient will transfer mid-way through treatment to stay with her family in another area. Your colleague tells you that in their hospital, they use only biosimilar Filgrastim (approved for use by the EMEA and Malaysian Regulators)

Do you?

1. Refuse – the patient is part way through treatment and switching is not advised by Malaysian Guidelines
2. Agree – but worry there is no data to support this change
3. Agree to the switch – as no excess adverse events are expected
1ST NATIONAL BIO-THERAPEUTICS CONGRESS — PUTTING PATIENT FIRST

22 NOVEMBER 2014