1ST NATIONAL BIO-THERAPEUTICS CONGRESS — PUTTING PATIENT FIRST

22 NOVEMBER 2014
Globalization of Biosimilars

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
Globalization of Biosimilars

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Comparative Outcomes Group

ESO Task Force Advisory Board on Access to Innovative Treatment in Europe

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Monoclonals in cancer - lymphoma

- Rituximab
- Monoclonal Biologic drug against malignant white blood cells
- Halves the chance of lymphoma relapse

Question

- A patient is part way through a course of treatment with rituximab for diffuse B-cell lymphoma – She is responding without unexpected toxicity
- Your patient tells you that her son in India has been able to source “biosimilar rituximab” at a fraction of the Malaysian price.
- She asks if she can use this for her remaining treatment cycles?

- Do you? – please choose your best response:

1. Refuse – as the patient is part way through treatment and switching is not advised by Malaysian Guidelines
2. Refuse – because this drug is not licensed by the Malaysian National Pharmaceutical Control Bureau (NPCB)
3. Agree – but worry there is no data to support this change
Globalization of Biosimilars

- Question
  - Global cost problems
  - Terminology for biologic copy drugs
  - Rules for biosimilars
  - Evidence for safety
    - Regulatory
    - Post marketing surveillance
  - Observational studies of non-innovator copy drugs
- Question Revisited
I am very fortunate to work with international colleagues
There is a cost to cancer

- Cancer has the most devastating economic impact of any cause of death in the world.
- WHO: Cancer world's top killer since 2010
- The total economic impact of premature death and disability from cancer worldwide was $895 billion in 2008.
- Cancer causes the highest economic loss of all of the 15 leading causes of death worldwide.
- 16.7 percent of all 'healthy' years lost in the European Union.
- 83 million years of “healthy life” lost due to death and disability from cancer in 2008.

There is a cost to cancer

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16.7 percent of all 'healthy' years lost in the European Union

83 million years of "healthy life" lost due to death and disability from cancer in 2008.

Sorting out the funding for cancer will be the model used to manage other medical conditions.

Middle income countries face a considerable burden of cancer

Cancer related deaths and burden of disease grouped by income per capita

(2004)

### Malaysia

<table>
<thead>
<tr>
<th>Income level</th>
<th>GDP (current US$)</th>
<th>Population, total</th>
</tr>
</thead>
<tbody>
<tr>
<td>East Asia &amp; Pacific (developing only)</td>
<td>$312.4 billion 2013</td>
<td>29.72 million 2013</td>
</tr>
<tr>
<td>Upper middle income</td>
<td></td>
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Middle income countries face a challenge

- More cancer and Less drugs

low and middle income countries account for 61% of the world’s burden of cancer, yet only account for 5% of anti-cancer drug sales.

worldwide map of healthcare expenditure in 2008, according to World Health Organization (WHO).

Worldwide comparison of healthcare expenditure in 2010, according to the OECD.

- Malaysian success in cost-effective care may help guide 112 poorer countries to improve.
- Malaysia performs very well with 1/5th the spend.
- OECD spend average $3,268 ppp.
- Ranked 80th country for health spending.

Inescapable truth: some treatments we cannot afford.

Worldwide comparison of healthcare.

- The UN Development Programme has called Malaysia a "model for other developing countries".

- With a dual system in place administering heavily subsidised primary care to all citizens and a private sector delivering specialty services to those who can afford it, average life expectancy has risen to 74 years.

- The Economist, April 2014

Commercial drug development requires a return on investment

- Bayer CEO MarjinDekkers quoted at the December 3, 2013 FT Event, regarding Indian compulsory license of Sorafenib - Nexavar

  “we did not develop this product for the Indian market, let's be honest. I mean, you know, we developed this product for western patients who can afford this product, quite honestly”
Sir Andrew Dillon, chief executive of the National Institute for Health and Care Excellence, said --

“the NHS would never be able to afford every drug capable of making a difference to patients.”
Access is driven by affordability

- The use of trastuzumab (expressed in mg/case of breast cancer) in France, Poland, Russia, the UK, Sweden and Hungary 1999–2009.
Cost and access:
A survey of Oncologists - USA

- Even in the wealthiest countries there are barriers to accessing the best treatment

- A third of US Oncologists would offer more trastuzumab to breast cancer patients if a lower cost biosimilar was available!

Half of Oncologists in Brazil & Mexico

Four out of 5 of Oncologists in Russia

Cost and access: A survey of Oncologists - USA

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More than 90,000 women in Europe are diagnosed with HER2 positive breast cancer every year

only 1,500 women in the whole of India received trastuzumab for breast cancer in 2012

The world needs access to cheaper highly effective biologic drugs

"245 biopharma companies and institutes now developing or already marketing biosimilars throughout the world"

But many are not “biosimilars” as the WHO, FDA or EMEA would define them

They are often poorly regulated copy drugs
Why would patients accept less tested or regulated drugs?

The countries with the least access to nationally funded drugs have the lowest wages with which to buy them.
The countries with the least access to nationally funded drugs have the lowest wages with which to buy them.

- That is where cheaper copy drugs fit in.

  Are they safe?
  Are they effective?
  Where can we access the drug information and product characteristics?
Multiple versions of recombinant human epoetin are available worldwide

- Biologic copy versions of Epoetin Alfa (Numbered I to VIII) – compared with original branded Eprex (E) by Isoelectric focusing gel separation

Multiple isoforms of the protein exist even with the original drug

These are NOT “Biosimilars”

Many of the copy drugs show significant variation in structure
Multiple versions of recombinant human epoetin are available worldwide

- Biologic copy versions of Epoetin Alfa (Numbered I to VIII) – compared with original branded Eprex (E) by Isoelectric focusing gel separation

Multiple isoforms of the protein exist even with the original drug

These are NOT “Biosimilars”

BIOSIMILAR W.H.O. – “A biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product”

Biologic copy drugs are NOT “Biosimilars”:

- Biologic copy drugs are NOT biosimilars:
  - “Biosimilar” is a specific term introduced by the European Medicines Agency to describe a follow-on biologic drug regulated by the EMEA drug development pathway

In contrast to non-EMEA regulated copy drugs, Biosimilars show highly similar structure

Globalization of Biosimilars

- Question

- Global cost problems
- Terminology for biologic copy drugs
- Rules for biosimilars
- Evidence for safety
  - Regulatory
  - Post marketing surveillance
- Observational studies of non-innovator copy drugs

- Question Revisited
A new classification of Biologic drugs

- **Biologics**
  - **Originals**
    - True Innovator
    - Biobetter
  - **Non-originales**
    - Biosimilars
    - Non original Biologics
  - **Non-Originals**
    - New Drug & Novel Target
    - Same target but modified drug
    - Highly similar
    - Less similar or less tested copy

CLASSIFICATION OF BIOLOGICS - adapted from IMS Health report -
A new classification of Biologic drugs

- **True Innovator**: Scientific evolution. Phase 0, 1, 2, 3 and 4 trials required by EMA
- **Biobetter**: Better efficacy, safer, easier administration, longer shelf life, etc. Phase 0, 1, 2 (?not always), 3 & 4 trials required by EMA
- **Biosimilars**: Clinically equivalent and comparable to originators. Phase 0, 1, 3 and 4 trials required by EMA
- **Non original Biologics**: Copy drugs developed outside Europe and USA – registration often based on basic chemical similarity and very limited clinical trial data

A new classification of Biologic drugs: Examples

- **Biologics**
  - **Originals**
    - True Innovator
      - Eylea
  - **Noniginals**
    - Biobetter
    - Biosimilars
    - Non original Biologics
      - Pegasys
      - Inflectra
      - Reditux

CLASSIFICATION OF BIOLOGICS - adapted from IMS Health report -
Globalization of Biosimilars

- Question
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  - **Rules for biosimilars**
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- Question Revisited
Defining a biosimilar

- The World Health Organization:

  - A biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product.

A new classification of Biologic drugs

Biosimilars: Clinically equivalent and comparable to originators. Phase 0, 1, 3 and 4 trials required by EMA.
Malaysia played a key role in creating the WHO standards for regulating biosimilars.

- 2007 WHO drafting group
- 2008 WHO draft WHO/BS/08 .2101
- 2008 WHO Expert Committee on Biological Standardisation (ECBS)
- WHO consultation meeting: 2009 Canada
- 2009 WHO revision
- Safety assessment of SBPs was as a critical component for licensing and post-marketing surveillance
- Malaysia is one of the countries to present its experience for national requirements
- Approved by WHO Expert Committee on Biological Standardization, October 2009

WHO standards for naming biosimilars

WHO Consultation in Korea in 2010

Agreed only medicinal products authorized on the basis of a full comparability package involving quality, non-clinical and clinical aspects, should be called “bio-similars”

Alternative WHO Names: “Similar Biotherapeutic Products”, “Subsequent Entry Biologics”, “Follow On Biologics”

copy products appropriately licensed by other pathways are called “non-innovator biological products”

Approved by WHO Expert Committee on Biological Standardization, October 2009

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Is it a biosimilar?

Intas launches rituximab biosimilar, Mabtas in India

Intas Pharmaceuticals, has recently declared that, they began to sell Mabtas, biosimilar rituximab in the Indian market.

The company’s subsidiary Intas Bio Pharma was already selling some biosimilars, including G-CSF, Pegylated G-CSF and also erythropoietin with their own brands. Now, with a recent update, they declared that, a biosimilar version of Roche/Genentech’s Rituxan/Mabthera is being marketed in India.

We have to note once again that, this product is not developed in accordance with global biosimilar guidelines and like Reditux, which was developed by Dr. Reddy’s, it is launched in India first.

It is NOT just a copy biologic drug with chemical similarity

We have to note once again that, this product is not developed in accordance with global biosimilar guidelines and like Reditux, which was developed by Dr. Reddy’s, it is launched in India first.
What is NOT a biosimilar - Example

- Rituximab copy drugs are marketed outside the EU and USA
- One product, “Reditux” is a monoclonal antibody targeting CD20, used in DLBCL, will drop WBCs and is described as a “biosimilar” in publications from the companies employees.
- It is chemically different to Rituximab
- Its clinical evidence for registration was a 17 patient single arm study
  - In 16 patients for whom the data was available, pre-treatment mean B lymphocyte count which was 121/ul (range:1.5–410.5) dropped to a mean of 9.9/ul (range:0.3–62.3) after the first cycle and remained in that range for the rest of treatment period.

Indian “Similar Biologics” Guidelines 2012
Indian “Similar Biologics”

- Over 40 biologics are marketed in India and more than half of these, 25 in total, are “biosimilars”.
- A further 25 biosimilars are in their final stages of development (in 2012).
- 2012 sales include:
  - 16 brands of Epoetin
  - 14 brands of GCSF

- Phase III trials with a minimum of 100 patients are mandatory for establishing bioequivalence in India.
Indian “Similar Biologics”

- Where are the trial data?

Search of Clinical Trials Registry for completed trials – keyword “biosimilar” found (Sept 14, 2014)
- Only 10 in total
- 1 completed study
  - Registered on: 06/09/2013 = CTRI/2013/09/003963 - For etanerceptvsbiosimilaretanercept
- 4 in recruitment phase
Biologic copy drugs: Terminology matters

WHO/RRA BT_DRAFT/24 January 2014
ENGLISH ONLY

REGULATORY EXPECTATIONS AND RISK ASSESSMENT FOR BIOTHERAPEUTIC PRODUCTS

Scientific Principles to Consider

NOTE:
This document has been prepared for the purpose of inviting comments and suggestions on the proposals contained therein, which will then be considered by the Expert Committee on Biological Standardization (ECBS). Publication of this early draft is to provide information about the proposed WHO document on Regulatory Expectations and Risk Assessment for Biotherapeutic Products to a broad audience and to improve transparency of the consultation process.

Names used for biosimilars include:

- ‘follow-on biologic’,
- ‘subsequent entry biologic’,
- ‘similar biotherapeutic product’,
- ‘similar biological medicinal product’,
- ‘biogeneric’,
- ‘me-too biologic’,
- ‘non-innovator biologic’

Biologic copy drugs: Terminology matters

Names used for biosimilars include:

- ‘follow-on biologic’,
- ‘subsequent entry biologic’,
- ‘similar biotherapeutic product’,
- ‘similar biological medicinal product’,
- ‘biogeneric’,
- ‘non-innovator biologic’

An even greater problem is that all of these terms have in some cases been used to refer to products which are not biosimilars according to the EU/WHO definitions and have not been evaluated using the comparability approach which is essential if the guidelines are followed.

Confusion over terminology is not just a potential concern for patient safety and efficacy but ‘biosimilars’ leads to misconceptions which arise from misleading published reports on apparent problems with ‘biosimilars’.

Biologic copy drugs: Terminology matters

  - Describes EpoetinWepox™ (Wockhardt Limited, India) as a biosimilar
  - no evidence it was approved using the comparability approach required in EMA or WHO biosimilarity guidelines.

  - Describes an epidemic of pure red cell aplasia in Thailand
  - Associated with use of “biosimilar” epoetins
  - All were approved using the Thai process employed for chemical generics

Biologic copy drugs: Terminology matters

- Schellekens H, Combe C. Poster presented at: XLI ERA-EDTA Congress, Lisbon, Portugal, 15–18 May 2004

Looked at the isoform pattern of copies of epoetin-alfa bought in Korea, Argentia, India and China

None were developed by a recognised EMA or WHO Biosimilar pathway

Isoelectric focusing/Western Isoform distribution of 12 epoetins. Epoetinalfa (E) is the control.
Biologic copy drugs: Terminology matters

Biologic copy drugs: Terminology matters

- Then became Figure 3 in Kuhlmann M, and Covic A Nephrol. Dial. Transplant. 2006;21:v4-v8

![Fig. 3. Gel of EPO samples from 12 different manufacturers in Latin America and Asia [17].](image)
Biologic copy drugs: Terminology matters

- Then became a slide used in a presentation by Anna Harrington-Morozova at the Biosimilars Congregation meeting 2012

Ref
Biologic copy drugs: Terminology matters

- Then became figure 4 in an article by Aris R on Pharmaphorum

As a result many biosimilars are being developed in emerging markets. Unfortunately, due to lack of regulations, the products are not always of a quality that would be expected in the EU or US (figure 4).

Where the article describes the potential for poor quality biosimilars...

“which could create inferiority in patient care”
Terminology matters: Naming and Labeling.

WHO International Non-Proprietary Name (INN) policy has been:

1. biologics with identical amino acid sequences and no post-translational modifications should have the same INN.

2. biologics with different amino acid sequences (even one difference) should have different, related INNs.

3. biologics with the same amino acid sequences that differ in their post-translational modifications should have different, related INNs.

Terminology matters: Naming and Labeling.

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3. biologics with the same amino acid sequences that differ in their post-translational modifications should have different, related INNs.

Would this confuse us between highly regulated “biosimilars” and potentially low quality “non-innovator copy biologics”?

Proposed to have a random 4 digit suffix

Could batch labeling and recording be more important?

How different is “different” – original biologics vary tertiary structure over time with batch changes?

However, application for an INN is voluntary and not every developer of a biologic applies for an INN!

The US FDA refers to the United States Adopted Name (USAN) Council

- USAN assigns non-proprietary names in the U.S. and works closely with the WHO
  ......BUT......

- The FDA has said that while they seek global regulatory harmonization where possible, the U.S. will have to adopt a policy that is consistent with the authorizing statute and that works with U.S. medicines and health care systems

- The FDA is keen to develop “interchangeable biosimilars”

These will have passed FDA agreed trials to demonstrate the safety of substitution or switching during a single course of treatment

- The dispensing pharmacist will chose which version to dispense

This may require a similar INN to be allocated

- But the “NDC” National drug Code with batch data is more important for pharmacovigilance

Global Dis-Harmonization of Biosimilar Naming and Labeling.

EMA has not been directive about the naming of related, similar biologics

- because while the authority to approve biologics, including biosimilars, resides with the EMA,
- authority for naming and labeling resides with the regulators of individual member states.

This works in practice because the EUDRA-Vigilance programme is working well

>96% of adverse events reported can be matched to the brand of drug

Meta-analysis of Pharmacovigilance reports & trials shows no unexpected toxicity from biosimilars

Suggests that in Europe - there is no evidence that a unique INN will improve the effectiveness of pharmacovigilance

Some biosimilars have >300,000 patient years exposure

Pharmacovigilance: USA and EU

- After problems with Vioxx (100 million prescriptions) the ADR pharmacovigilance systems were redesigned

- FDA may determine Risk Evaluation and Mitigation Strategy (REMS) but this is not a requirement (FDAAA)
- Risk Minimization Action Plans (RiskMAPs) not mandatory in US but strongly advised at the time of filing, especially for NCE
- Risk management plan is mandatory in the EU
- A valid EU-RMP must
  - Section 1: Product Information
  - Section 2: Safety Specifications
  - Section 3: PVG Plan
- Section 4: Risk Minimisation Plan if needed

Pharmacovigilance: USA and EU

- AERS
- MedWatch Program (Voluntary and Mandatory)
- Optional Electronic Reporting
- NDA Annual Reports to FDA.
- Consumer Reports
- ‘Dear HCP’ Letters
- Expedited Reporting of all Class Action lawsuits

- Clinicians are encouraged, but not required, to report drug-related adverse events either to drug manufacturers or directly to the FDA

- NDA Periodic Reports quarterly during the first 3 years after the medicine is approved, and annual reports thereafter.

- Eudravigilance
- Mandatory electronic reporting
- Only include Medically Confirmed Reports
- Require QPPV
- Rapid Alert System EU, there are no harmonized rules for post-marketing studies.

- In the United Kingdom, reports of such events are actively solicited through the Prescription-Event Monitoring system, which surveys prescribers regarding any adverse experiences among the first 10,000 people who use a given drug.

- The European Medicines Evaluation Agency (EMEA) requires PSURs every 6 months for 2 years, annually for the 3 following years, and then every 5 years (at the time of renewal of registration).

Safety is all our responsibilities

No clinical trial could have been big enough to detect Pure red cell Aplasia (PRCA) with reformulated Epoetin-alfaEprex (50+/100,000 PYE Patient years exposure)

80 Million patients were treated with rofecoxib-Vioxx before the link to cardiac disease was certain

Pharmacovigilance: Malaysia

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  - **Observational studies of non-innovator copy drugs**

- Question Revisited
What is NOT a biosimilar - Example

- “Not Biosimilars” are called “non-comparable biologics” (NCB)
- This does not mean that they are not potentially active, effective or safe
  - However this is difficult to determine if the registration study is so limited
- Evidence for safety & effectiveness has then to come from the treatment in routine clinical use

**What is NOT a biosimilar - Example**

- “Not Biosimilars” are called “non-comparable biologics”

  The maker has gone into partnership with Merck to develop an EMA approved version


  Reditux was introduced in India in April 2007 at 50% of the original price in India, producing a 10-fold market expansion for the product.

Would Substitution or Switching be safe?

- Mabthera vs Reditux
  - Out of their study
  - 29 patients with DLBCL switched between Mabthera and Reditux

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- She asks if she can use this for her remaining treatment cycles?

- Do you? – please chose your best response:

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2. Refuse – because this drug is not licensed by the Malaysian National Pharmaceutical Control Bureau (NPCB)
3. Agree – but worry there is no data to support this change
IF YOU SEE SOMETHING, SAY SOMETHING.
BE SUSPICIOUS OF ANYTHING UNATTENDED.
Tell a cop, an MTA employee or call 1-888-NYC-SAFE.
All the first 3 patients treated by Dr O’Neil with cetuximab at Carolina’s Lineberger Comprehensive Cancer Center collapsed with anaphylaxis.

Nashville, Tennessee, was finding the same problem

The makers traced the doses:
- they had come from different batches.

when O’Neil spoke to oncologists from other areas of the country, they didn’t know what he was talking about.

A prominent colorectal oncologist in New York “thought we were lying or crazy,” O’Neil recalls.

Cetuximab reactions


<1% rate in Boston

22% rate of cetuximab reactions


IgE Antibodies Binding to Cetuximab in Sera from 76 Case Subjects and 462 Controls

Results are shown according to whether the treating physician reported a hypersensitivity reaction (HSR) to cetuximab or no HSR reaction.

Results are also shown for pretreatment serum samples from control subjects and from subjects who had not received cetuximab.

The horizontal lines indicate geometric mean values for the positive results.

Values with multiplication signs indicate the number of negative values for each symbol.
Hypersensitivity Reactions to Cetuximab Related to IgE Antibodies Against Oligosaccharides

Roxanne Nelson
March 12, 2008

March 12, 2008 — Hypersensitivity reactions to cetuximab (Erbitux) have been reported, and a significantly higher prevalence is found in the southeastern United States. In the March 13 issue of the New England Journal of Medicine, researchers report that severe hypersensitivity reactions to cetuximab appear to be associated with immunoglobulin (IgE) antibodies against galactose-alpha-1,3-galactose that were present before cetuximab therapy.

Using a recently developed assay, the researchers found IgE antibodies in serum samples obtained from both from patients and controls. The results showed IgE antibodies specific for the oligosaccharide galactose-alpha-1,3-galactose, which is present on the Fab portion of the cetuximab heavy chain.
The geographic distribution of these reactions reflects the regional high prevalence of both IgEAb and the tick, Amblyomma americanum.

Geographical distribution of cetuximab hypersensitivity reactions, O’Neil et al, JCO 2007

High Incidence Areas: Rocky Mountain Spotted Fever

IF YOU SEE SOMETHING, SAY SOMETHING.
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