
PhAMA
Innovative Medicines for Malaysia
1ST NATIONAL
BIO-THERAPEUTICS
CONGRESS – PUTTING PATIENT FIRST
22 NOVEMBER 2014

Globalization of Biosimilars

Dr. Paul Cornes

PhAMA

1ST NATIONAL BIO-THERAPEUTICS

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

Dr Paul Cornes,
Consultant Oncologist,
Bristol Haematology& Oncology Centre

Comparative Outcomes Group

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

European School of Oncology
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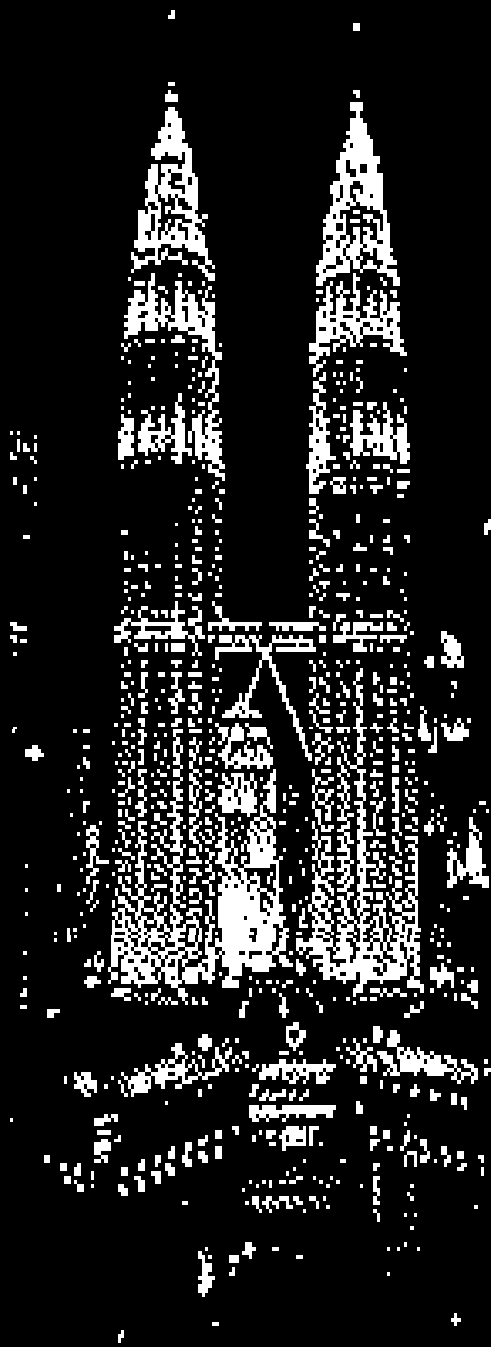
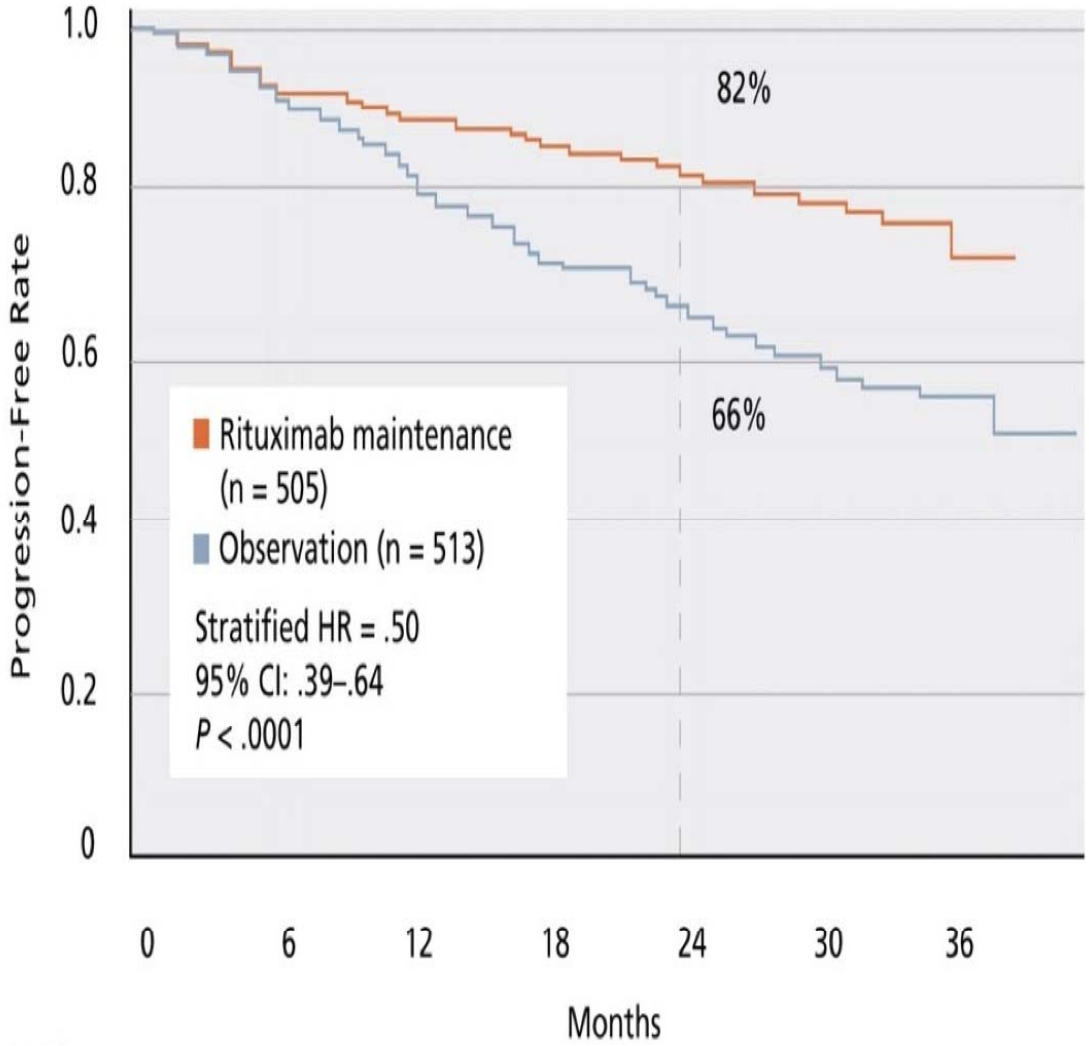


Monoclonals in cancer - lymphoma



- **Rituximab**
- **Monoclonal Biologic drug against malignant white blood cells**
- **Halves the chance of lymphoma relapse**
  - Prima trial reviewed at http://www.medscape.com/viewarticle/722470

http://www.jnccn.org/content/8/Suppl_6/S-1/F3.large.jpg

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 "biosimilarrituximab" at a fraction of the Malaysian price.**
- **She asks if she can use this for her remaining treatment cycles?**

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

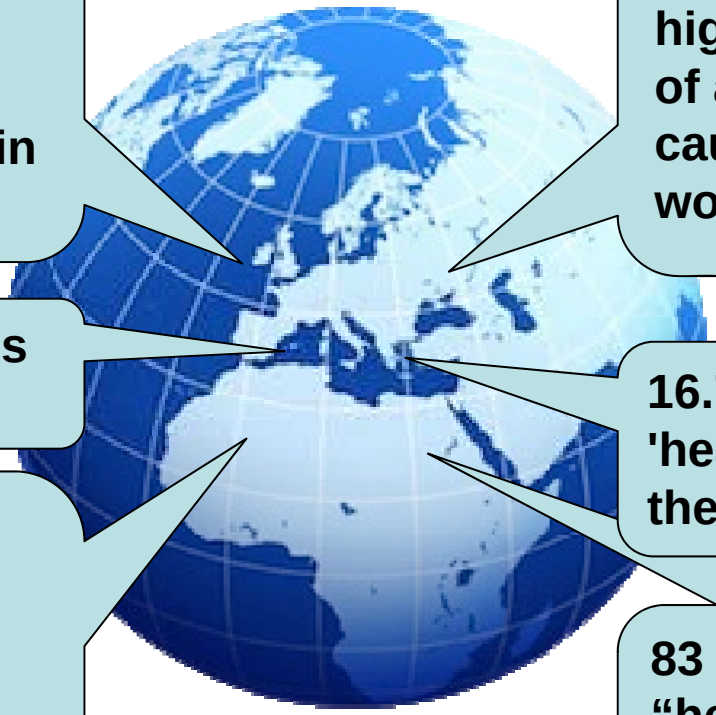
- Question Revisited

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.

Cancer causes the highest economic loss of all of the 15 leading causes of death worldwide



WHO: Cancer world's top killer since 2010

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

The total economic impact of premature death and disability from cancer worldwide was $895 billion in 2008.

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

www.usatoday.com/news/health/2008-12-09-cancer_N.htm
http://www.cancer.org/acs/groups/content/@internationalaffairs/documents/document/acspc-026203.pdf

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

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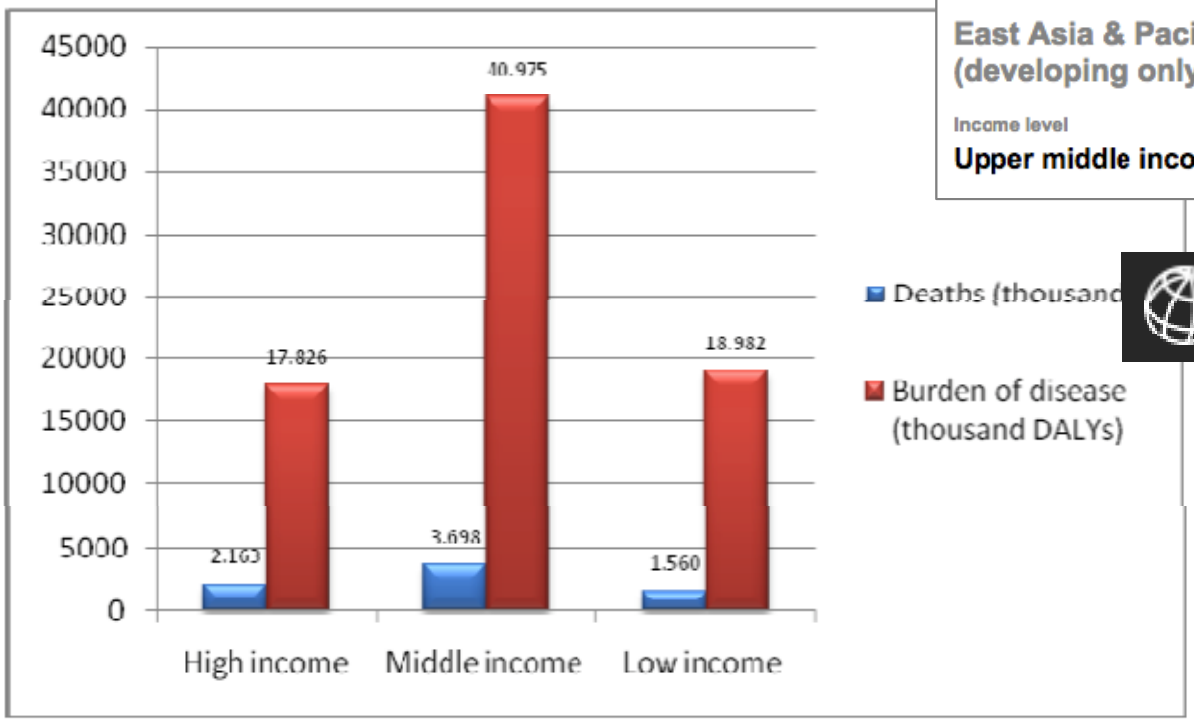
www.usatoday.com/news/health/2008-12-09-cancer_N.htm
http://www.cancer.org/acs/groups/content/@internationalaffairs/documents/document/acspc-026203.pdf

Middle income countries face a considerable burden of cancer

Cancer related deaths and burden of disease grouped by income per capita (2004)



Malaysia

East Asia & Pacific (developing only)

GDP (current US$) $312.4 billion 2013

Income level: Upper middle income

Population, total: 29.72 million 2013

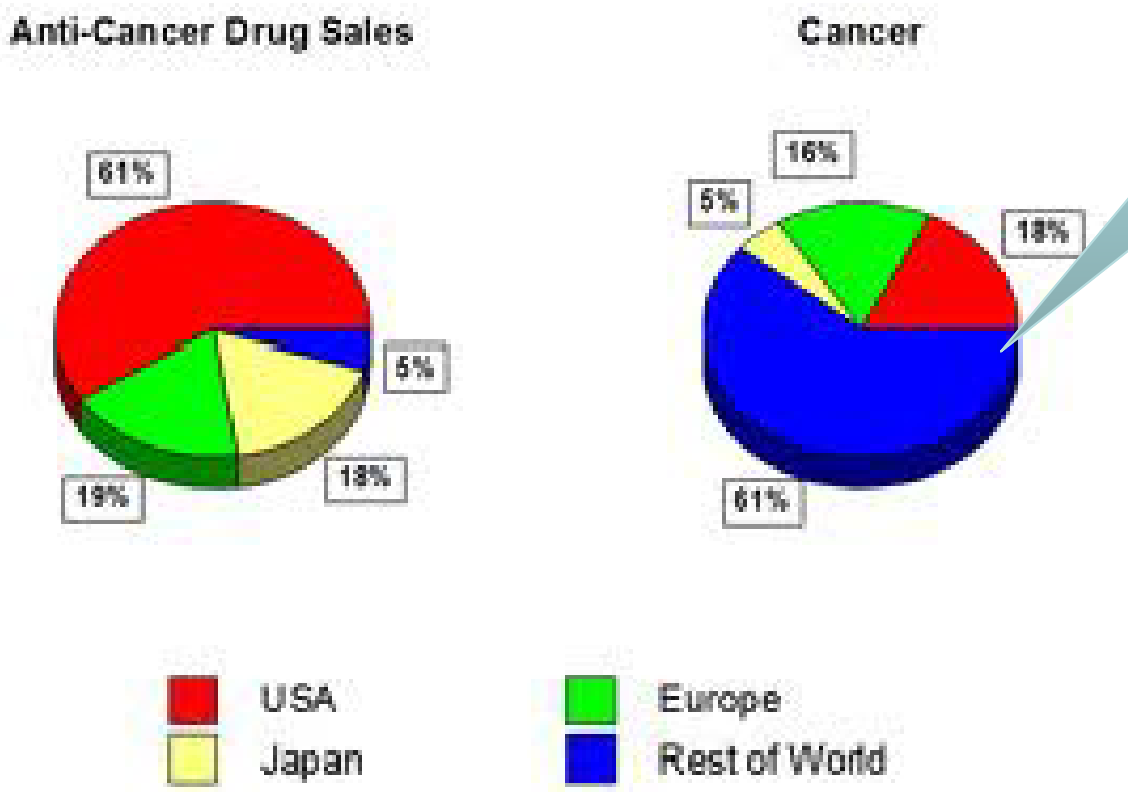
THE WORLD BANK IBRD • IDA

Source: World Health Organisation, The Global Burden of Disease: 2004 update. WHO 2008.

Kanavos P et al. The role of funding and policies on innovation in cancer drug development. Report for the European Cancer Research Managers Forum. LSE September 2009.

Middle income countries face a challenge

- **More cancer and Less drugs**

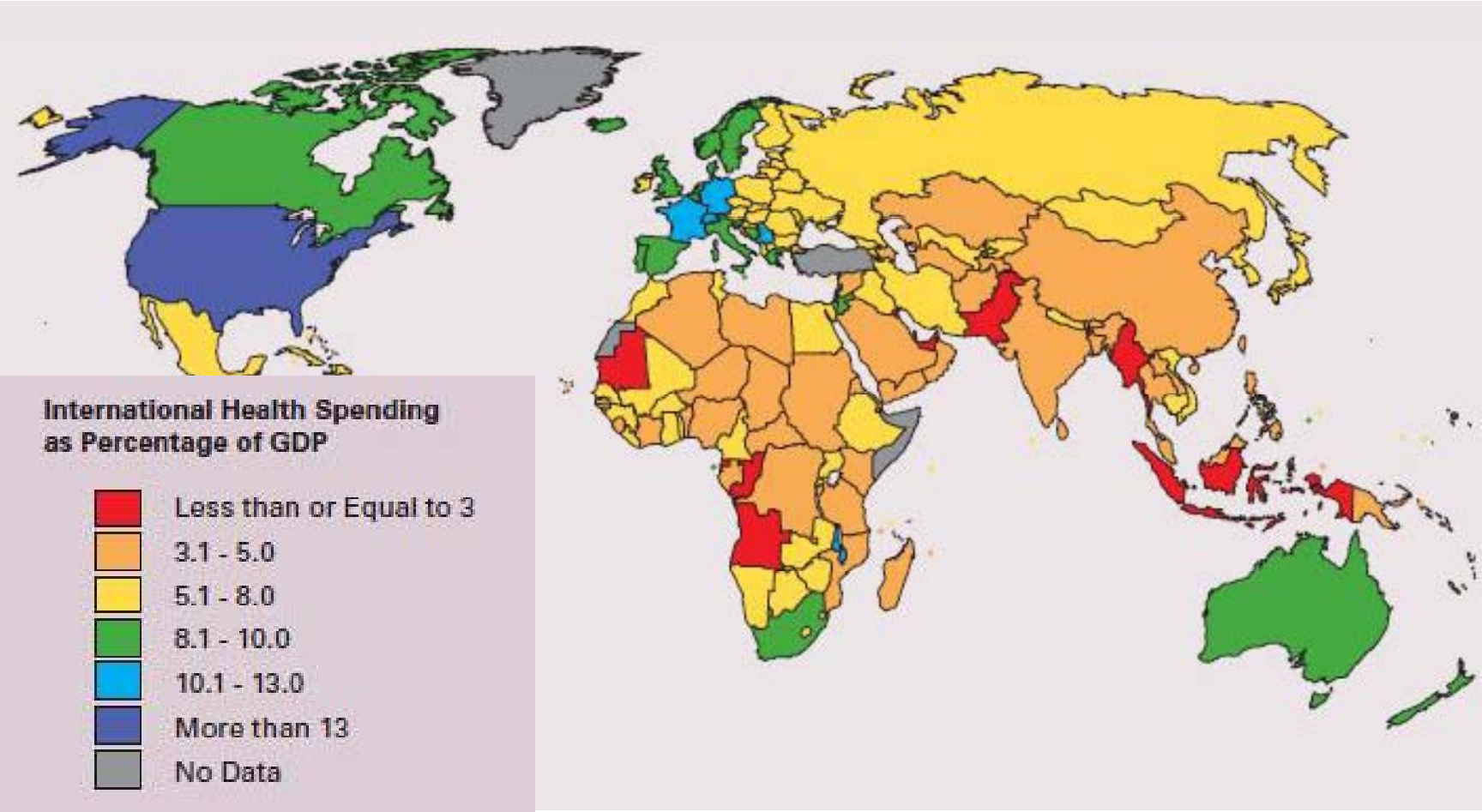


low and middle income countries account for 61% of the world's burden of cancer,

yet only account for 5% of anti-cancer drug sales.

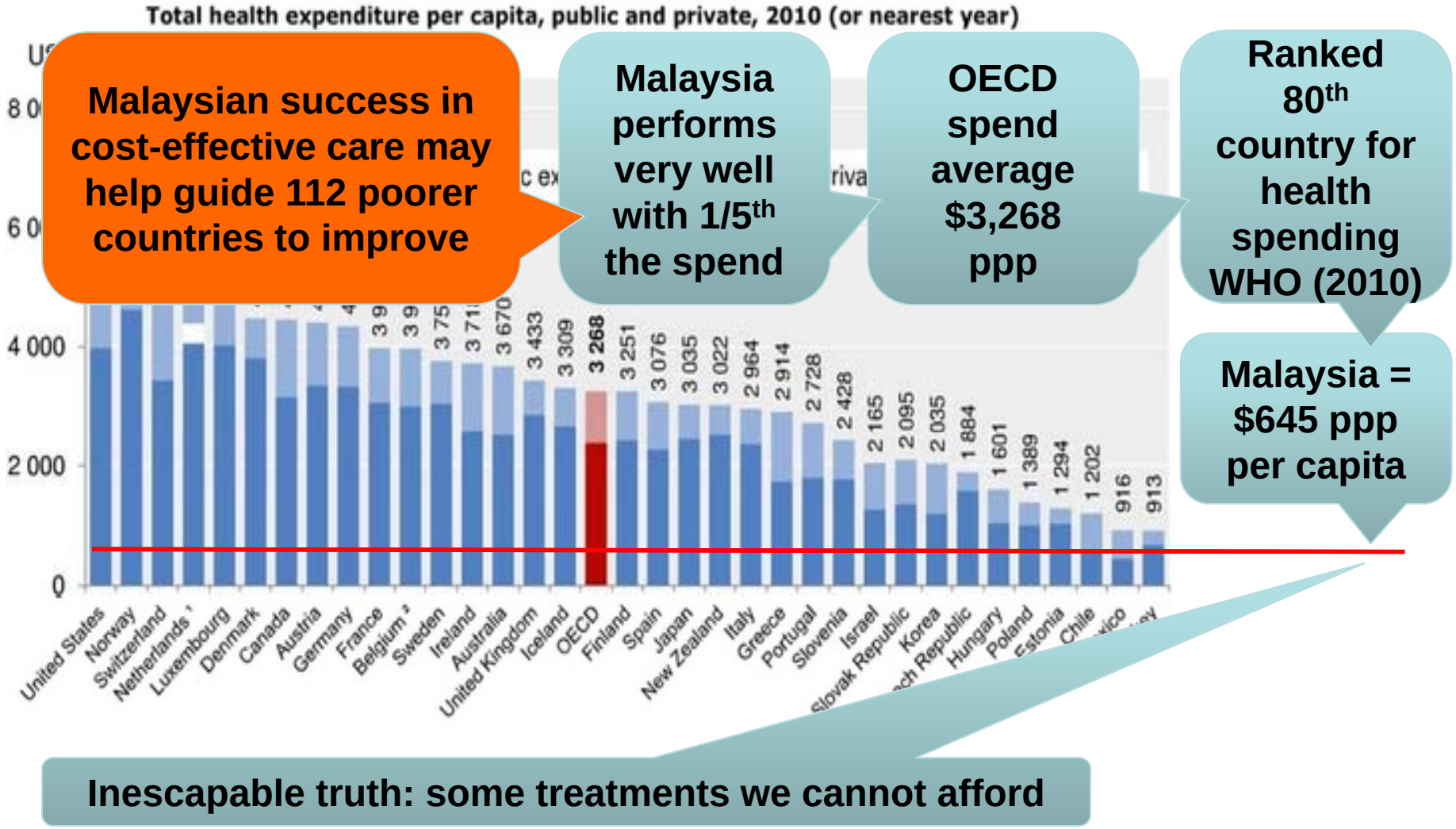
The International Network For Cancer Treatment and Research Statistics>http://www.inctr.org/about-inctr/statistics/. Accessed Sept 29, 2014

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



Ref: worldwide map of healthcare expenditure in 2008, according to World Health Organization (WHO). URL: http://www.ezega.com/news/NewsDetails.aspx?Page=news&NewsID=2059. Accessed Nov 20, 2014

Worldwide comparisonof 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 WHO (2010)

Malaysia = $645 ppp per capita

Inescapable truth: some treatments we cannot afford

Ref: OECD 2010 health data. WHO ranking;
http://en.wikipedia.org/wiki/List_of_countries_by_total_health_expenditure_%28PPP%29_per_capita. Accessed Nov 21, 2014

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.***

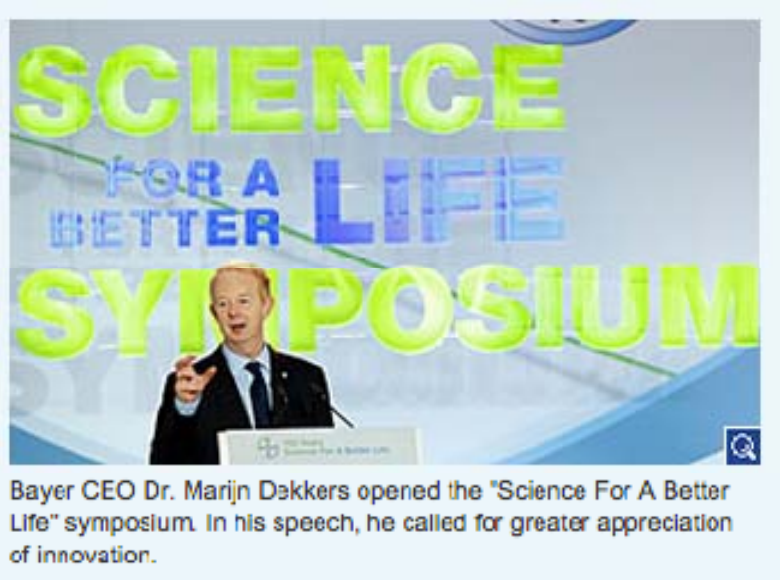
- **The Economist, April 2014**

Ref How sustainable is Malaysian healthcare? The Economist, April 11th 2014. URL: http://www.eiu.com/industry/article/1991716983/how-sustainable-is-malaysian-healthcare/2014-04-11#. Accessed Nov 6, 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"***



Bayer CEO Dr. Marijn Dekkers opened the "Science For A Better Life" symposium. In his speech, he called for greater appreciation of innovation.

Knowledge Ecology International

Attending and mending the knowledge ecosystem

Home » Blogs » Claire Cassedy's blog

Transcript of Bayer CEO Marjin Dekkers quote at the December 3, 2013 FT Event, regarding India compulsory license of Nexavar

View | What links here

Submitted by Claire Cassedy on 7. February 2014 - 9:25

On January 21, 2014, Ketaki Gokhale of Bloomberg published a story in Businessweek on disputes over drug patents. The story closed with a rather sinister quote attributed to Bayer CEO Marijn Dekkers, "We did not develop this medicine for Indians. We developed it for Western patients who can afford it." The comment in question was made by Dekkers at a December 3, 2013 event hosted by the Financial Times, titled "Buffering the Pharma Brand: Restoring Reputation, Rebuilding Trust." The article and particularly Dekkers' quote caught the attention of health advocates and went viral in the health policy community.

A little over a week later, Ryan Chittum of the Columbia Journalism Review published an article, complaining that Gokhale had "misquoted" Dekker's comments. Bloomberg reviewed the quote, which had been paraphrased, and updated the article, to read.

Ref - Claire Cassedy. Transcript of Bayer CEO MarjinDekkers quote at the December 3, 2013 FT Event, regarding India compulsory license of Nexavar. Knowledge Ecology International. February 7, 2014. http://keionline.org/node/1924. Accessed Oct 30, 2013. Bayer AG's "Science For A Better Life" Symposium - How Scientists See Future Research Trend. BNC. November 20, 2013. URL: http://www.bnc.bayer.com/bayer/bnci.nsf/id/How-Scientists-See-Future-Research-Trends. Accessed Oct 30, 2014

Access is driven by affordability

Politics & Policy

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Africa Asia-Pacific Europe Latin America & Caribbean Middle East & North Africa UK US &

August 22, 2014 3:28 pm

Drug cost watchdog chief calls for honesty with public

By Andrew Ward and Sarah Neville Author alerts

Politicians and health officials must be more honest with the public about the tough choices facing the NHS in an era of austerity, the head of the UK's drug cost watchdog has urged.

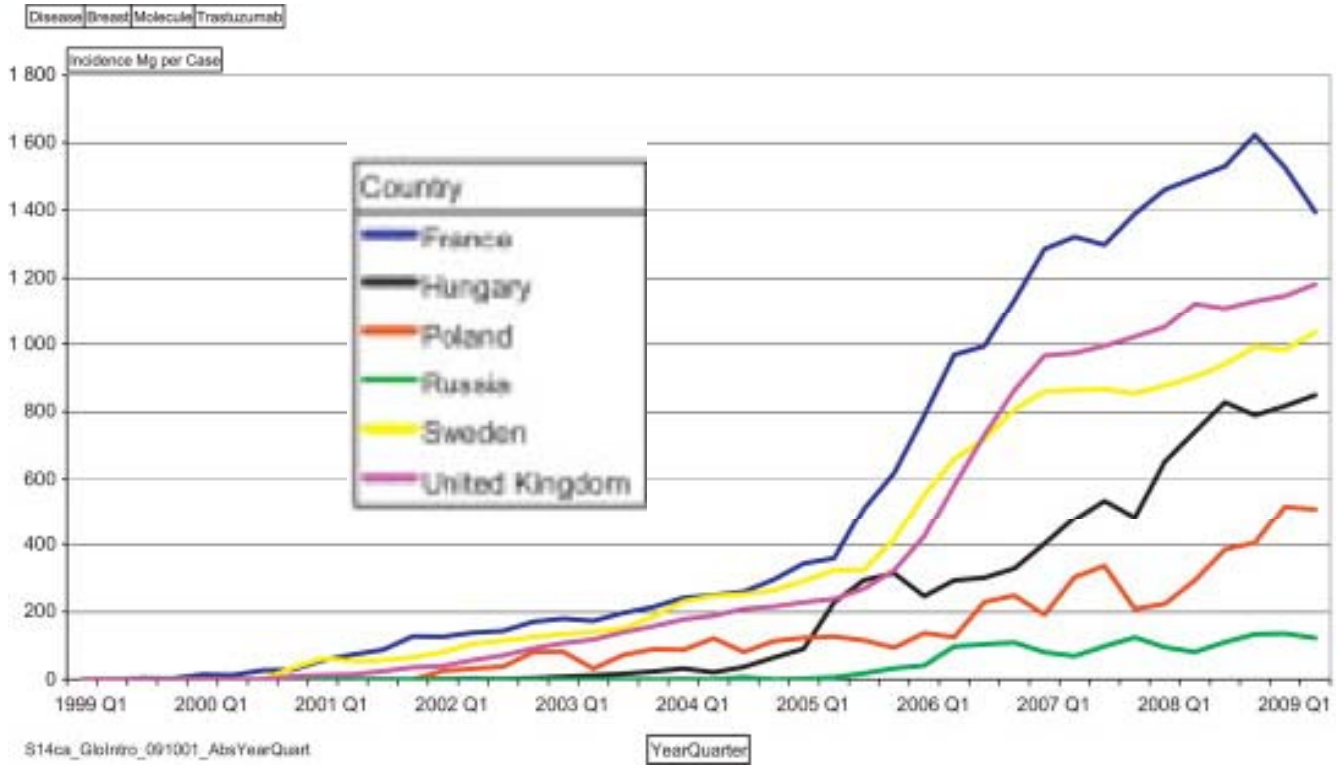
Amid a row over its rejection of life-extending cancer medicines, Sir Andrew Dillon, chief executive of the National Institute for Health and Care Excellence, said the NHS would never be able to afford every drug capable of making a difference to patients.

- **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."***

Ward A, Neville S. Drug cost watchdog chief calls for honesty with public. FT.com August 22, 2014 3:28 pm.http://www.ft.com/cms/s/0/c62145a6-2896-11e4-8bda-00144feabdc0.html#axzz3BQtnSrsu. Accessed Aug 25, 2014

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.**



Journal of Cancer Policy 2014 2, 45-62DOI: (10.1016/j.jcpo.2014.01.003)

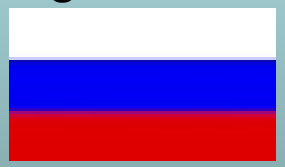
Cost and access:
A survey of Oncologists - USA

- **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!**
  - Lammers, PE et al. Barriers to the use of trastuzumab for HER2+ breast cancer and the potential impact of biosimilars: A physician survey in the United States and emerging markets. J ClinOncol 32:5s, 2014 (suppl; abstr 610)

Half of Oncologists in Brazil & Mexico

Four out of 5 of Oncologists in Russia



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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

Lammers, PE et al. Barriers to the use of trastuzumab for HER2+ breast cancer and the potential impact of biosimilars: A physician survey in the United States and emerging markets. J ClinOncol 32:5s, 2014 (suppl; abstr 610) Roche abandons Herceptin patents in India. Pharmafile Published on 19/08/13 at 11:48am. URL: http://www.pharmafile.com/news/180576/roche-abandons-herceptin-patents-india. Accessed Nov 21, 2014

The world needs access to cheaper highly effective biologic drugs

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Over 700 biosimilars now in development worldwide: report

WORLD NEWS | SEPTEMBER 30, 2014

LYNNE TAYLOR

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More than 700 follow-on biologic therapies are currently in development, and they are expected to account for around a quarter of the $100 billion-worth of sales stemming from off-patent biologic drugs by the end of this decade, according to new research.

Related Links

Global biosimilars pipeline expands 40 in 12 months study.asp

Germany: "EU's most favourable market for biosimilars"

It is rare to see a new business segment emerge in any market, but this is what is happening within the biopharmaceutical development industry, with 245 biopharma companies and institutes now developing or already marketing biosimilars throughout the world, says the study, from Thomson Reuters BioWorld.

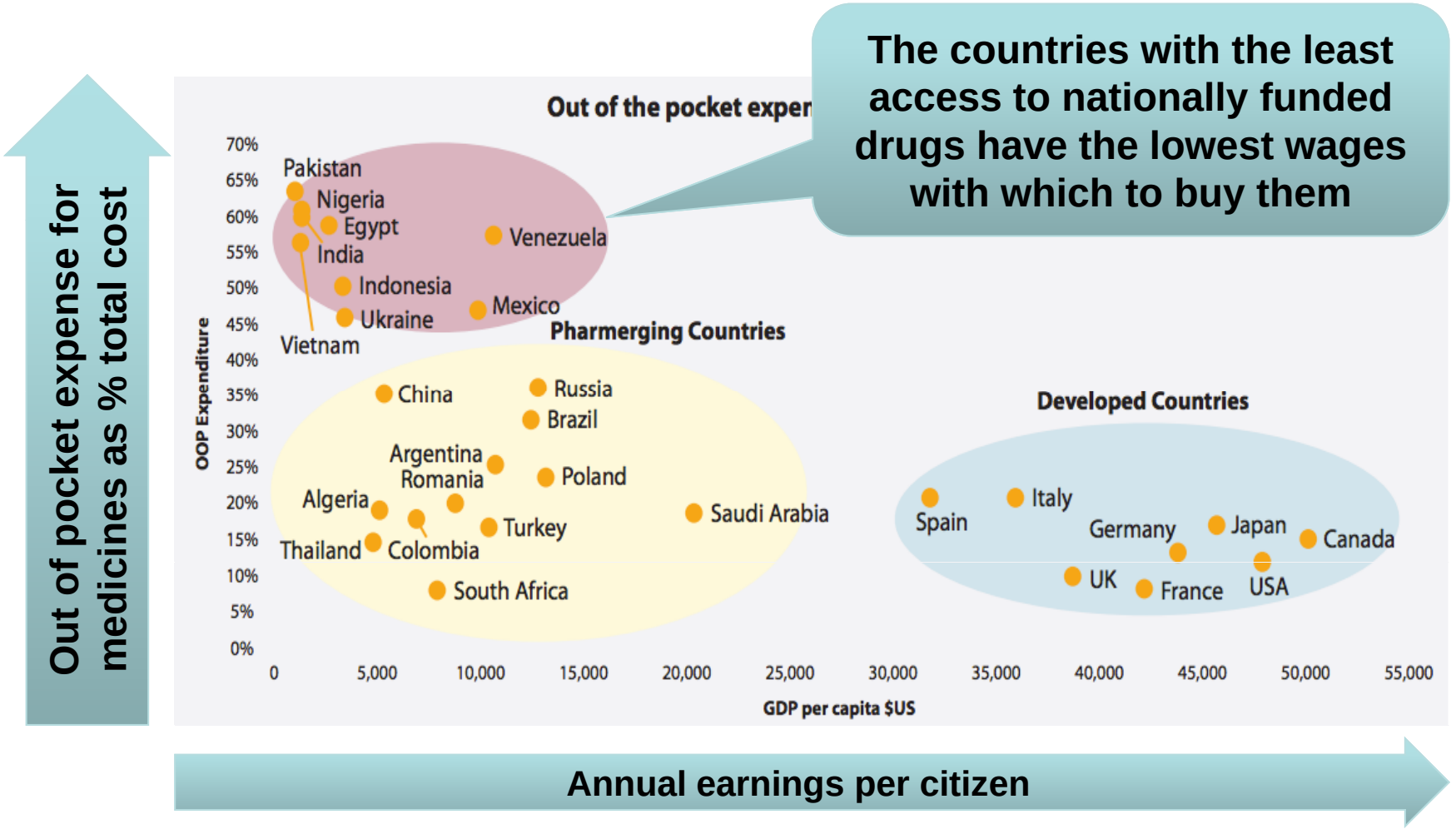
"245 biopharma companies and institutes now developing or already marketing biosimilars throughout the world"

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

They are often poorly regulated copy drugs

Taylor L. over 700 biosimilars now in development worldwide: report. Pharma Times digital September 30, 2014.http://www.pharmatimes.com/article/14-09-30/over_700_biosimilars_now_in_development_worldwide_report.aspx#ixzz3flma1lfd. Accessed Oct 6, 2014

Why would patients accept less tested or regulated drugs?



Rickwood S et al. Biosimilars and non-original biologics. Insights for the coming decade of change. White paper - IMS Health 2013. http://www.imshealth.com/deployedfiles/imshealth/Global/Content/Healthcare/Life%20Sciences%20Solutions/Generics/IMSH_Biosimilars_WP.pdf. Accessed April 23, 2014

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

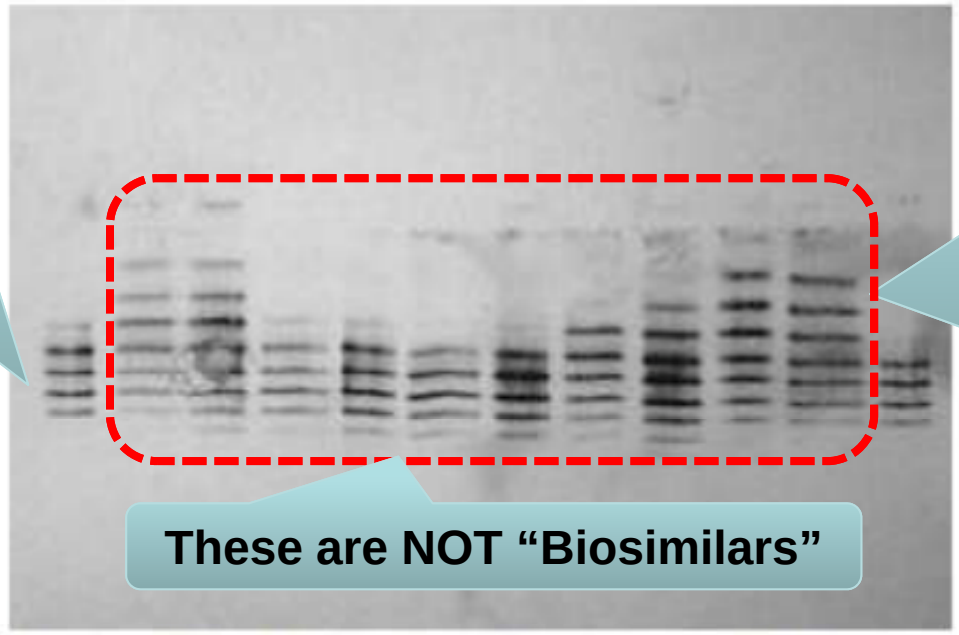
- That is where cheaper copy drugs fit in

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**
  - Schellekens H et al. Eur J Hosp PharmPract 2004;3: 43-7

Multiple isoforms of the protein exist even with the original drug



Many of the copy drugs show significant variation in structure

These are NOT "Biosimilars"

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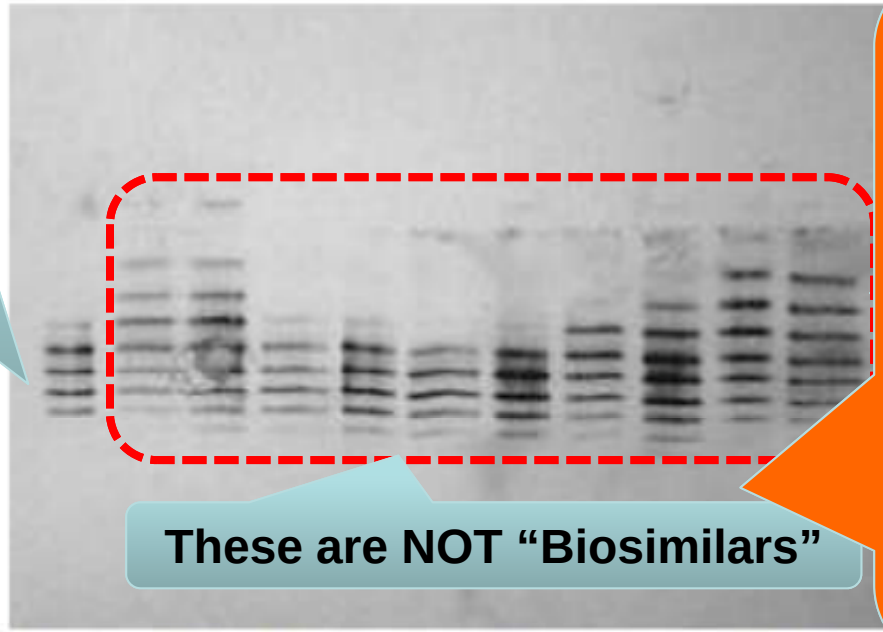
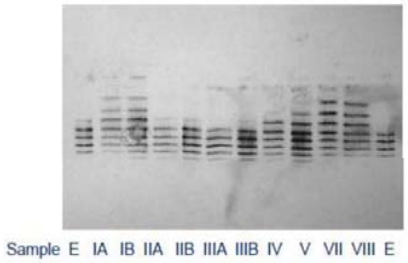


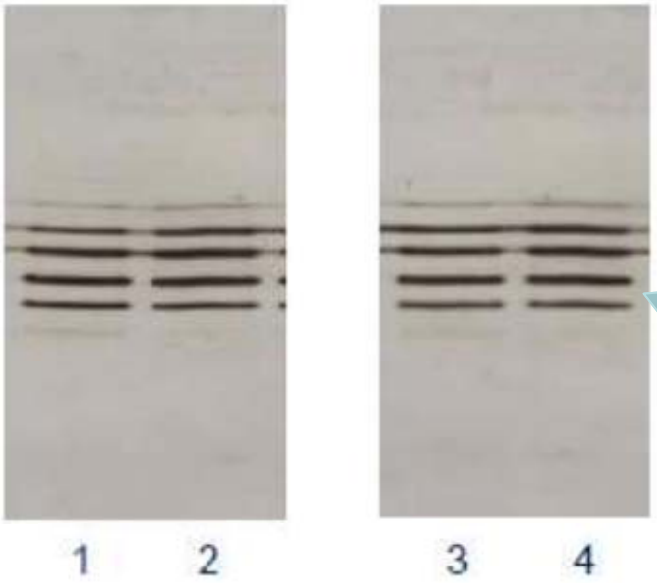
BIOSMILAR
W.H.O. –
"A biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product"

World Health Organization. Expert Committee on Biological Standardization. Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs). World Health Organization. [Online] October 23, 2009. http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf.

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

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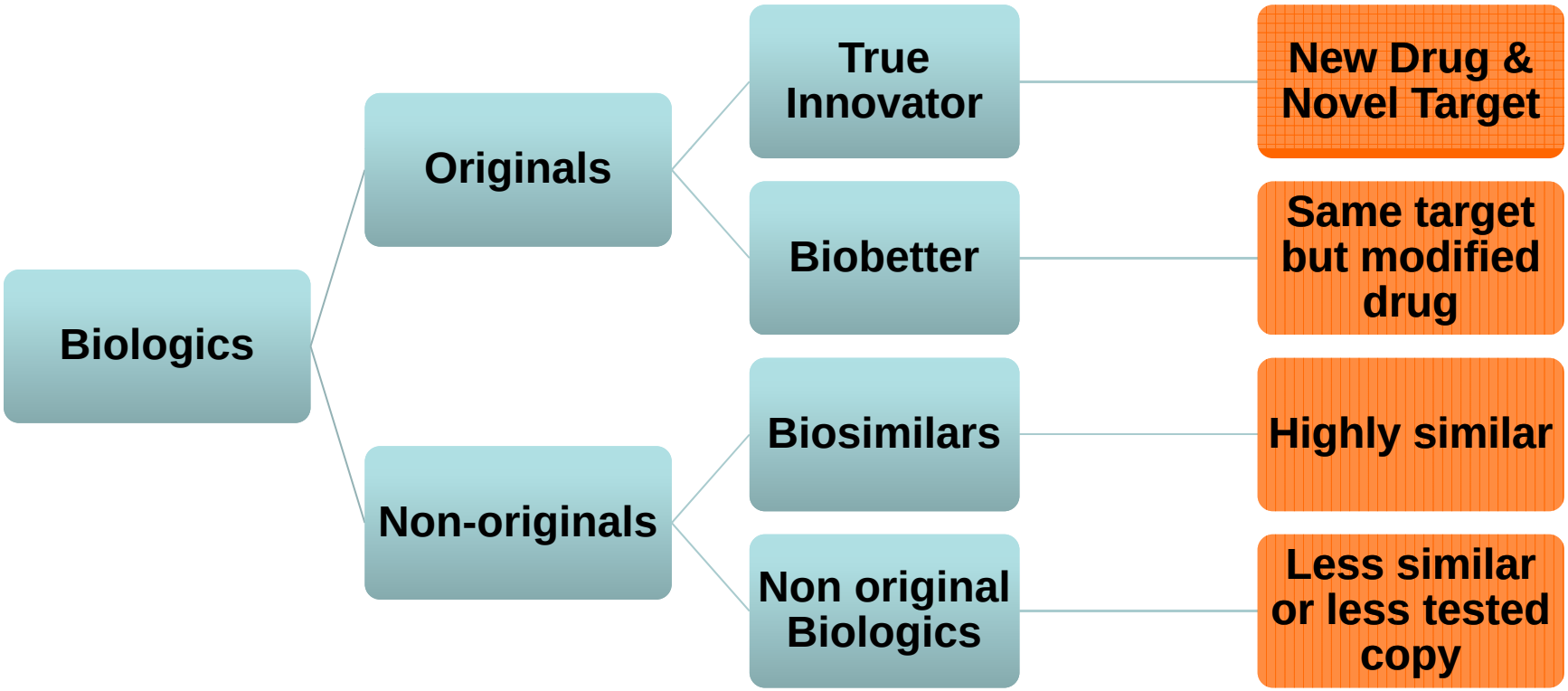
- Observational studies of non-innovator copy drugs

- Question Revisited

A new classification of Biologic drugs



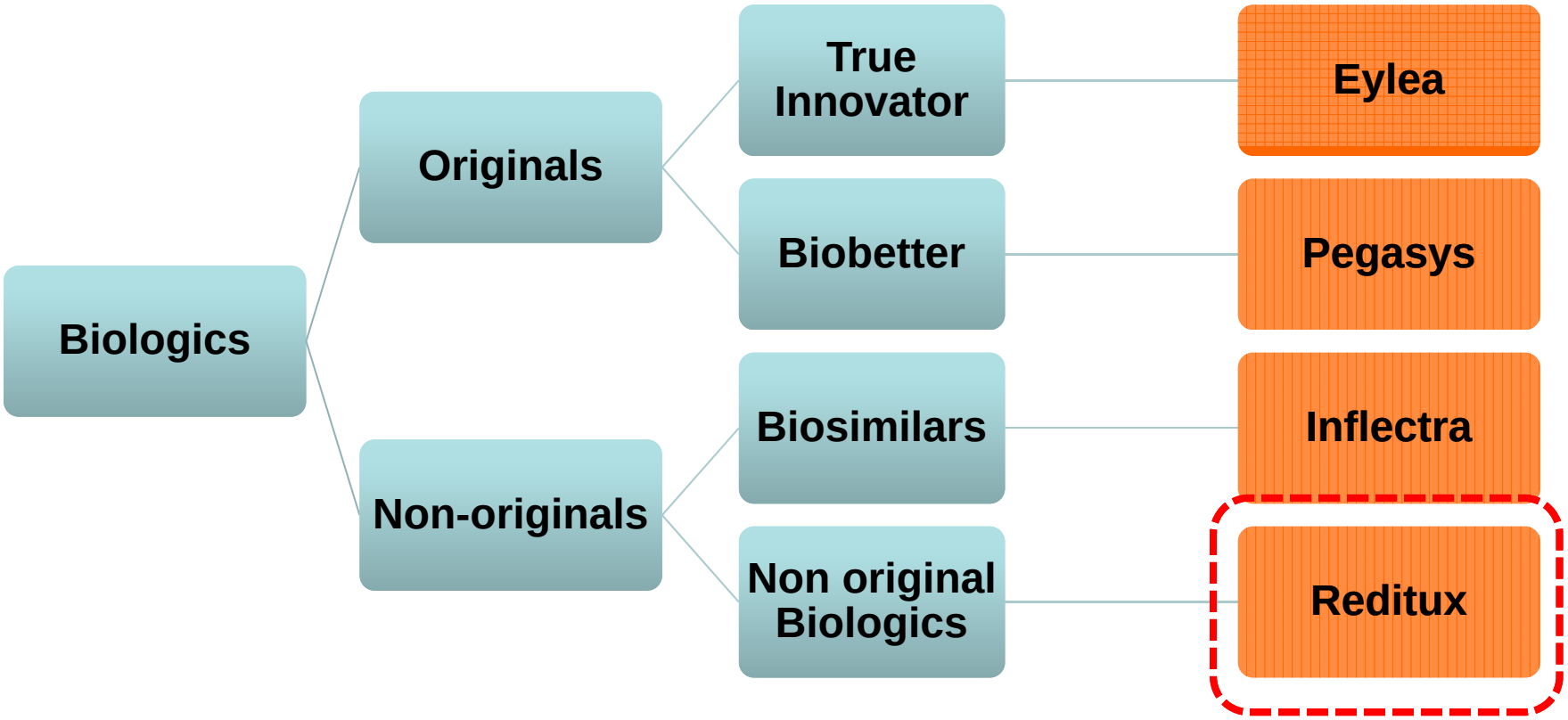
CLASSIFICATION OF BIOLOGICS - adapted from IMS Health report - http://www.imshealth.com/deployedfiles/imshealth/Global/Content/Healthcare/Life%20Sciences%20Solutions/Generics/IMSH_

A new classification of Biologic drugs

True Innovator: Scientific evolution. Phase 0, 1, 2, 3 and 4 trials required by EMA	New Drug & Novel Target
Biobetter: Better efficacy, safer, easier administration, longer shelf life..etc. Phase 0, 1, 2(?not always), 3 & 4 trials required by EMA	Same target but modified drug
Biosimilars: Clinically equivalent and comparable to originators. Phase 0, 1, 3 and 4 trials required by EMA	Highly similar
Non original Biologics: Copy drugs developed outside Europe and USA – registration often based on basic chemical similarity and very limited clinical trial data	Less similar or less tested copy

CLASSIFICATION OF BIOLOGICS - adapted from IMS Health report - http://www.imshealth.com/deployedfiles/imshealth/Global/Content/Healthcare/Life%20Sciences%20Solutions/Generics/IMSH_

A new classification of Biologic drugs: Examples



CLASSIFICATION OF BIOLOGICS - adapted from IMS Health report - http://www.imshealth.com/deployedfiles/imshealth/Global/Content/Healthcare/Life%20Sciences%20Solutions/Generics/IMSH_

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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.**

    – World Health Organization. Expert Committee on Biological Standardization. Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs). World Health Organization. [Online] October 23, 2009. http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf.

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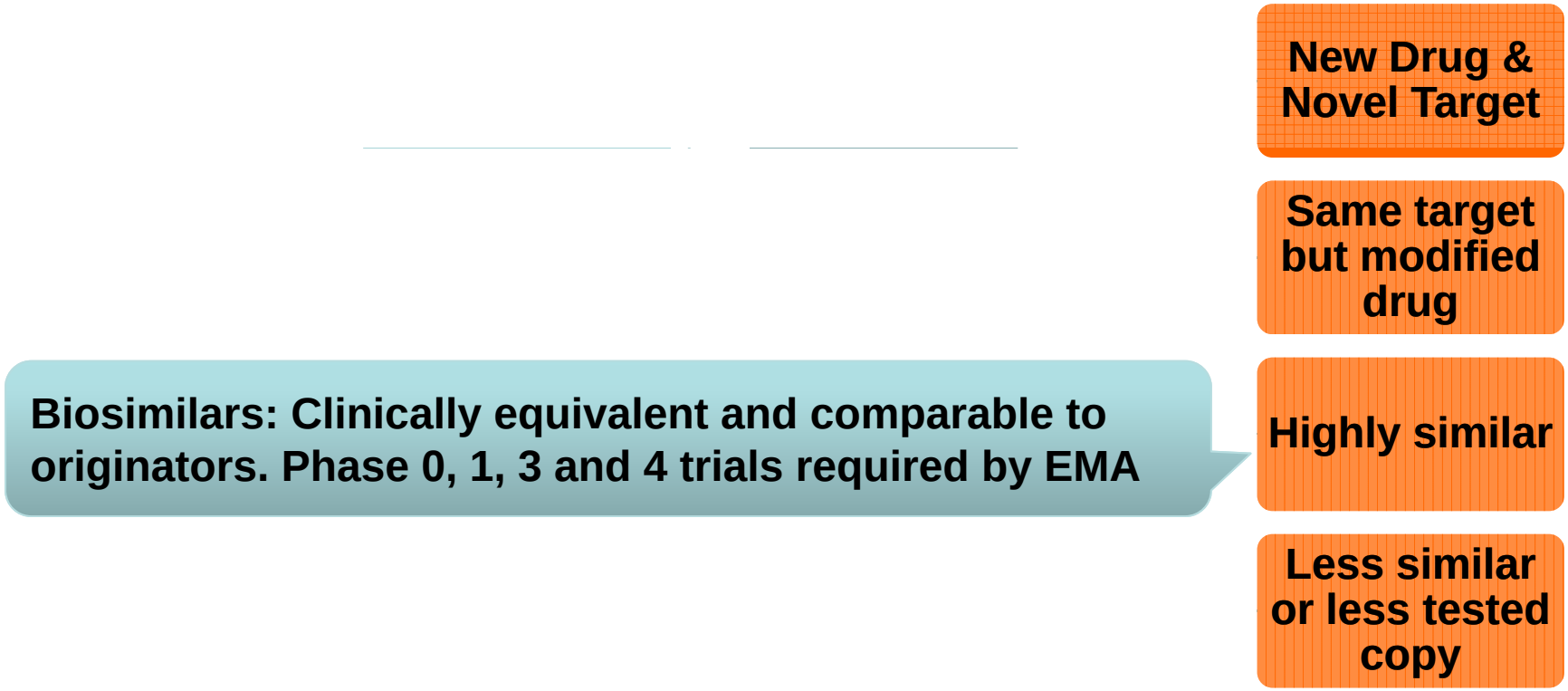

CLASSIFICATION OF BIOLOGICS - adapted from IMS Health report - http://www.imshealth.com/deployedfiles/imshealth/Global/Content/Healthcare/Life%20Sciences%20Solutions/Generics/IMSH_

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)

safety assessment of SBPs was as a critical component for licensing and post-marketing surveillance

2009 WHO revision

WHO consultation meeting: 2009 Canada

Malaysia is one of the countries to present its experience for national requirements

Approved by WHO Expert Committee on Biological Standardization, October 2009

Ref Knezevica I et al, Biosimilarse Global issues, national solutions. Biologicals 2011;39:252e255
ArpahAbas. Regulatory guidelines for biosimilars in Malaysia. Biologicals 2011;39:339e342

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

Ref Knezevica I et al, Biosimilarse Global issues, national solutions. Biologicals 2011;39:252e255

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- Question Revisited

Is it a biosimilar?

biosimilarnews.com http://www.biosimilarnews.com/intas-launches-rituximab-biosimilar-mabtas-in-india

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 subsidary 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.

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.

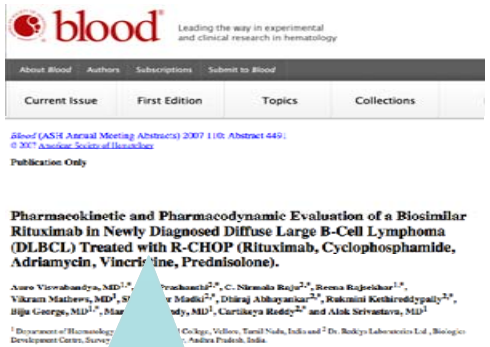
treating diseases characterized by excessive numbers of B cells, overactive B cells, or dysfunctional B cells. Such diseases include many forms of lymphoma, leukemia, and transplant rejection, autoimmune disorders such as Rheumatoid Arthritis, Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis. Mabtas may be used alone or in combination with other chemotherapy medicines to treat Non-Hodgkin's lymphoma (NHL) and chronic lymphocytic leukemia (CLL)." the company said in their news update.

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.

Intas launches rituximabbiosimilar, Mabtas in India. biosimilarnews.com. April 22, 2013 10:08 AM, http://www.biosimilarnews.com/intas-launches-rituximab-biosimilar-mabtas-in-india. Accessed Sept 9, 2014.

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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Blood (ASH Annual Meeting Abstracts) 2007 110: Abstract 4491

Publication Only

Pharmacokinetic and Pharmacodynamic Evaluation of a Biosimilar Rituximab in Newly Diagnosed Diffuse Large B-Cell Lymphoma (DLBCL) Treated with R-CHOP (Rituximab, Cyclophosphamide, Adriamycin, Vincristine, Prednisolone).

is NOT a biosimilar, as it has never been studied head to head vs. the reference product, Rituxan/MabThera (Roche)

Ref AuroViswabandya et al. Pharmacokinetic and Pharmacodynamic Evaluation of a BiosimilarRituximab in Newly Diagnosed Diffuse Large B-Cell Lymphoma (DLBCL) Treated with R-CHOP (Rituximab, Cyclophosphamide, Adriamycin, Vincristine, Prednisolone). Blood (ASH Annual Meeting Abstracts) 2007 110: Abstract 4491

Indian “Similar Biologics” Guidelines 2012

Screen Reader Acce

CENTRAL DRUGS STANDARD CONTROL ORGANIZATION

DIRECTOR GENERAL OF HEALTH SERVICES,
MINISTRY OF HEALTH AND FAMILY WELFARE,
GOVERNMENT OF INDIA

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You are here: HOME | Left Bar | BIOLOGICALS

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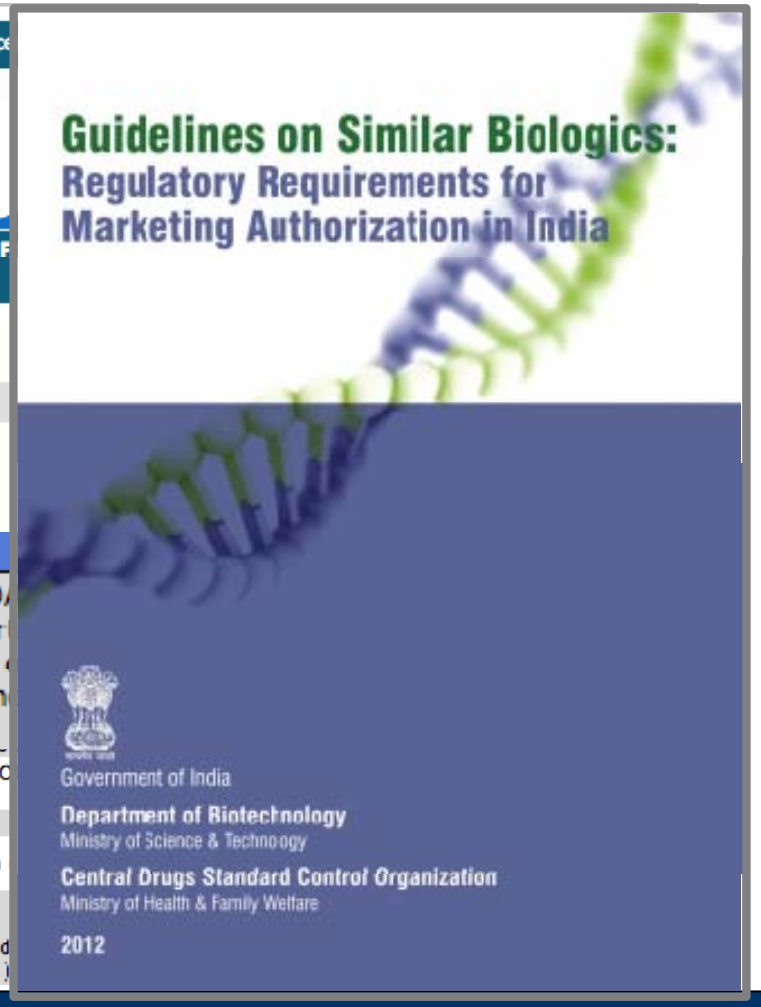
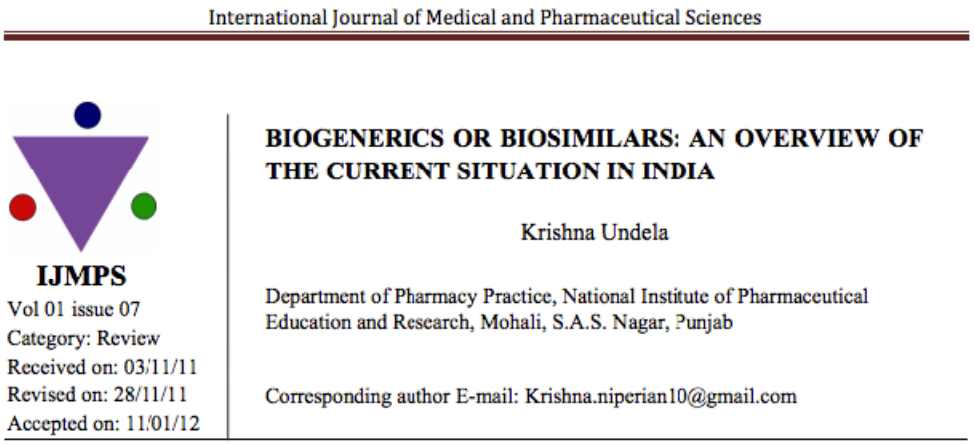
SR NO	Name
1	As decided in the meeting held on 03/07/2012 at CDSCO HQ, FD/ Delhi, under the chairmanship of Dr. M.K.Bhan, Secretary, Depar Biotechnology Ministry of Science and Technology, the Guideline Biologics: Regulatory requirements for Market Authorization in In implemented from 15th Sept, 2012 (20 Jul 2012)
2	Application Format for Obtaining the Export NO Trial for Testing (20 Jul 2012)
3	Vaccines Registered (24 Jul 2012)
4	Notice for Submission of Biological Application
5	Clarification & Amendments in guidance for ind Changes in Biologicals Products (20 Jul 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



International Journal of Medical and Pharmaceutical Sciences

IJMPS
Vol 01 issue 07
Category: Review
Received on: 03/11/11
Revised on: 28/11/11
Accepted on: 11/01/12

BIOGENERICS OR BIOSIMILARS: AN OVERVIEW OF THE CURRENT SITUATION IN INDIA

Krishna Undela

Department of Pharmacy Practice, National Institute of Pharmaceutical Education and Research, Mohali, S.A.S. Nagar, Punjab

Corresponding author E-mail: Krishna.niperian10@gmail.com

- Phase III trials with a minimum of 100 patients are mandatory for establishing bioequivalence in India

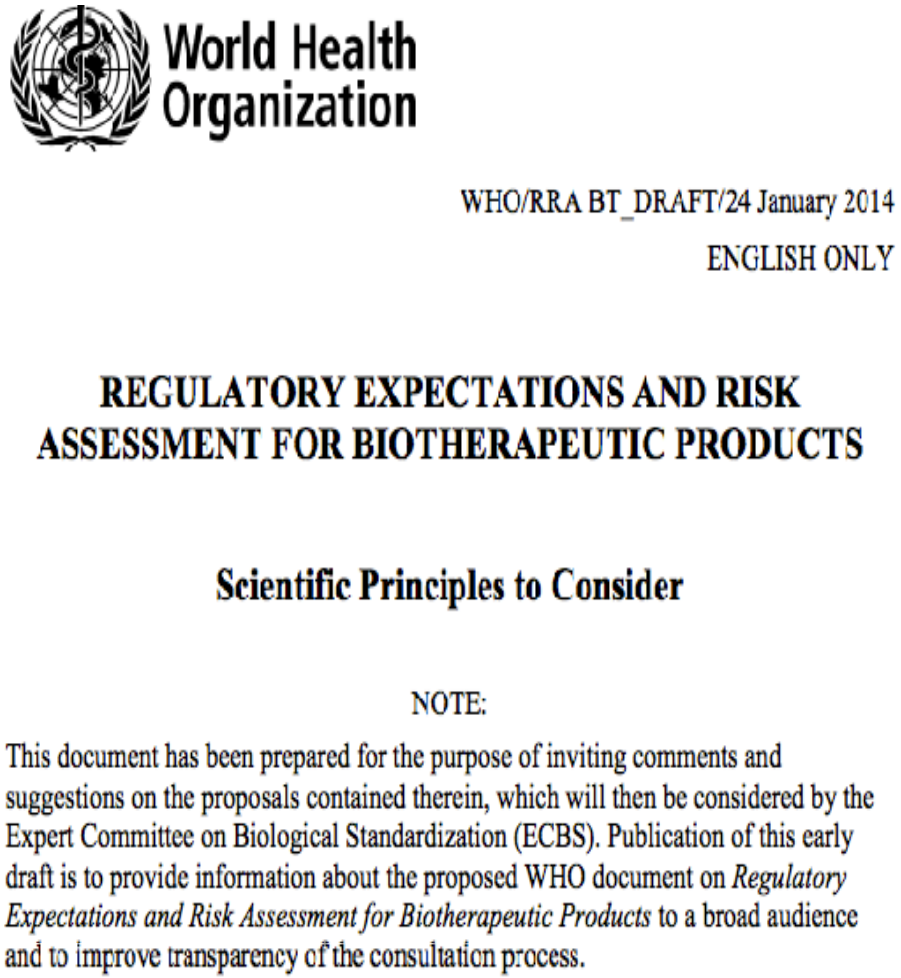
Undela K. Biogenerics or biosimilars: an overview of the current situation in India. International Journal of Medical and Pharmaceutical Sciences 2012,Vol 01 issue 07. file:///Users/paulcornes/Downloads/2011%20Biogenerics%20or%20Biosimilars.pdf. Accessed Sept 9, 2014

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



World Health Organization

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'**

Ref WHO. Regulatory expectations and risk assessment for biotherapeutic products Scientific Principles to Consider. WHO/RRA BT_DRAFT/24 January 2014. URL: http://www.who.int/biologicals/WHO_Risk_Assessment_for_Biotherapeutics_1st_PC_24_Jan_2014.pdf. Accessed Nov 8, 2014

Biologic copy drugs: Terminology matters

World Health Organization

WHO/RRA BT DRA… 2014

NOTE:

- **Names used for biosimilars include:**
  - **‘follow-on biologic’,**
  - **‘subsequent entry biologic’,**
  - **‘similar biotherapeutic**
  - **‘**

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

confusion over terminology is not just a potential concern for patient safety and efficacy

and have not been evaluated using the comparability approach which is essential if the guidelines are followed.

leads to misconceptions which arise from misleading published reports on apparent problems with ‘biosimilars’

Ref WHO. Regulatory expectations and risk assessment for biotherapeutic products Scientific Principles to Consider. WHO/RRA BT_DRAFT/24 January 2014. URL: http://www.who.int/biologicals/WHO_Risk_Assessment_for_Biotherapeutics_1st_PC_24_Jan_2014.pdf. Accessed Nov 8, 2014

Biologic copy drugs: Terminology matters

- **Keithi-Reddy SR, Kandasamy S, Singh AK. Pure red cell aplasia due to follow-on epoetin. Kidney Int. 2008;74:1617-22**
  - **Describes EpoetinWepox™ (Wockhardt Limited, India) as a biosimilar**

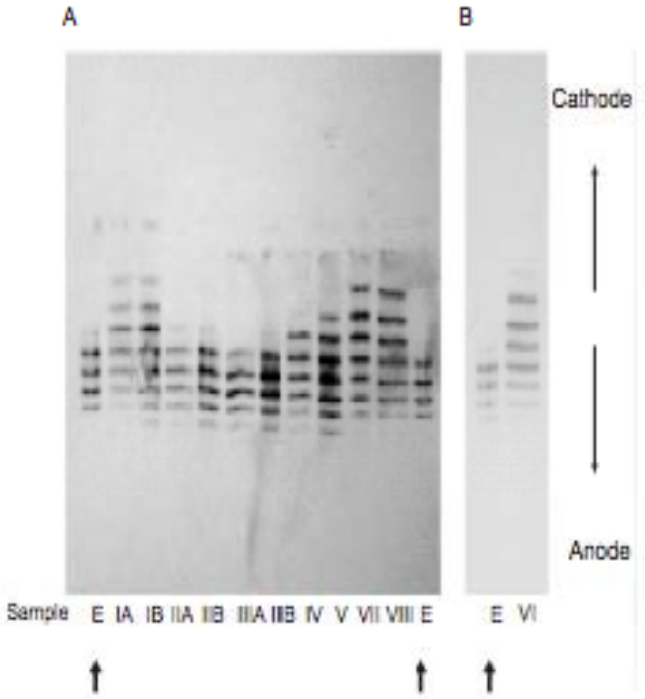
no evidence it was approved using the comparability approach required in EMA or WHO biosimilarity guidelines.

- **Praditpornsilpa K, et al. Biosimilar recombinant human erythropoietin induces the production of neutralizing antibodies. Kidney Int. 2011;80:88-92.**
  - **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**

Ref: Thorpe R, Wadhwa M. Terminology for biosimilars–a confusing minefield. Generics and Biosimilars Initiative Journal (GaBI Journal). 2012;1(3-4):132-4. DOI: 10.5639/gabij.2012.0103-4.023

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

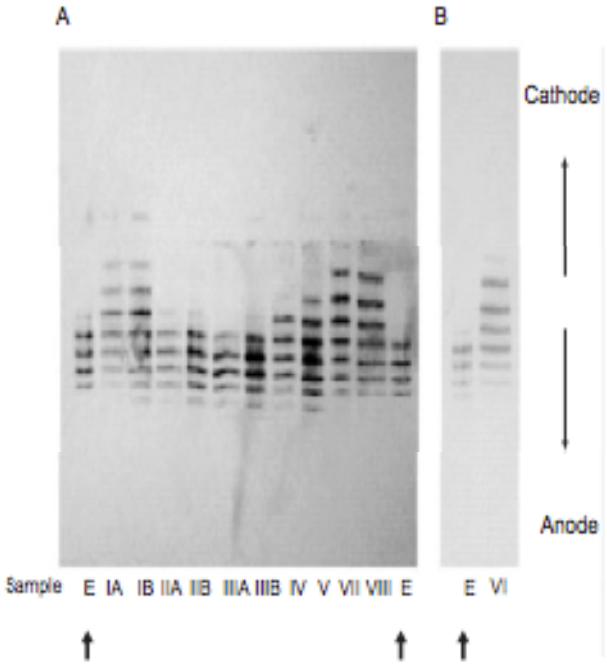
None were developed by a recognised EMA or WHO Biosimilar pathway

Isoelectric focusing/Western Isoform distribution of 12 epoetins. Epoetinalfa (E) is the control.

Biologic copy drugs: Terminology matters

- **Became figue 1 in - Schellekens H. (2005) Follow-on biologics: challenges of the “next generation”. Nephrol Dial Transplant 20:Suppl 4, iv31–iv36.**

Epoetin alfa products			
Sample	Expiration dale	Concentration (IU/mL)	Country
IA	April 2004	2000	Korea
IB	April 2004	4000	Korea
IIA	August 2003	2000	Korea
IIB	Nov 2003	10000	Korea
IIIA	January 2004	2000	Korea
IIIB	January 2004	10000	Korea
IV	April 2004	2000	Argentina
V	July 2003	10000	Argentina
VI	March 2004	4000	India
VII	July 2004	10000	China
VIII	August 2003	6000	China

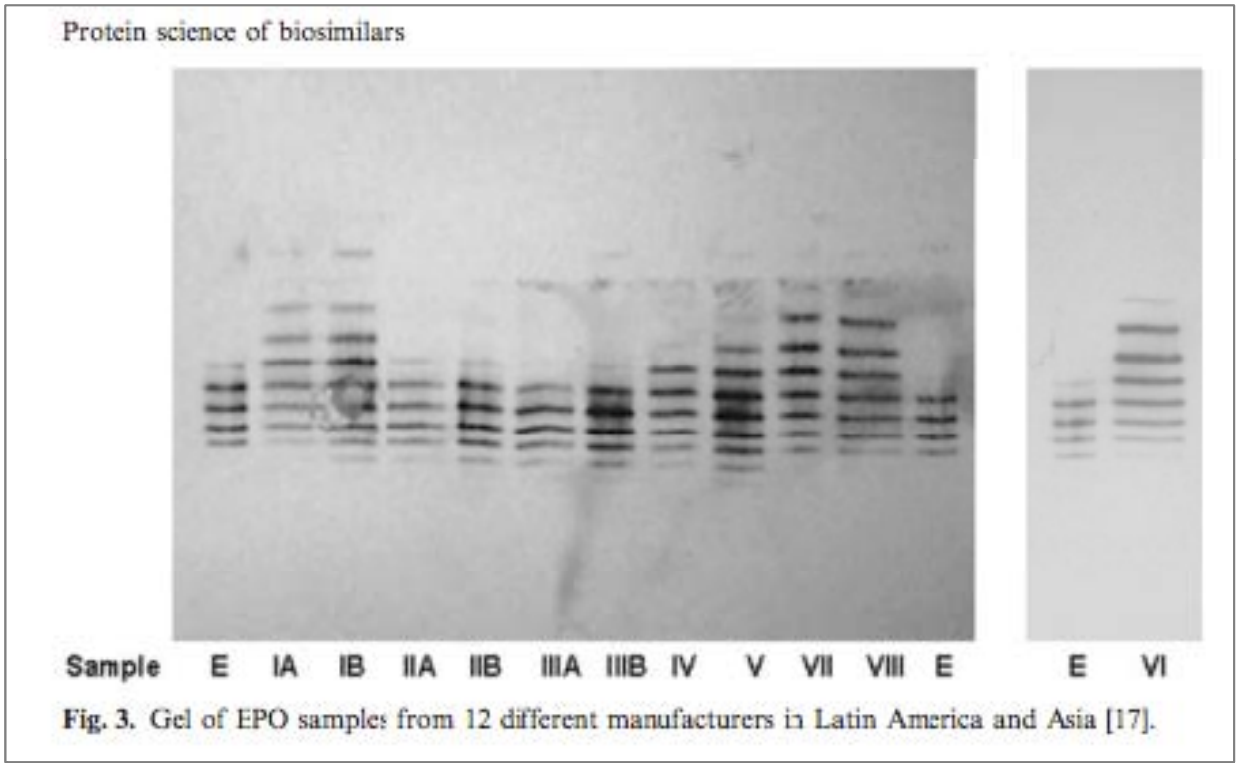


Isoelectric focusing/Western Isoform distribution of each sample is shown. Epoetin alfa (E) is the control.
Schellekens H, Combe C. Poster presented at: XLI ERA-EDTA Congress, Lisbon, Portugal, 15–18 May 2004

Ref

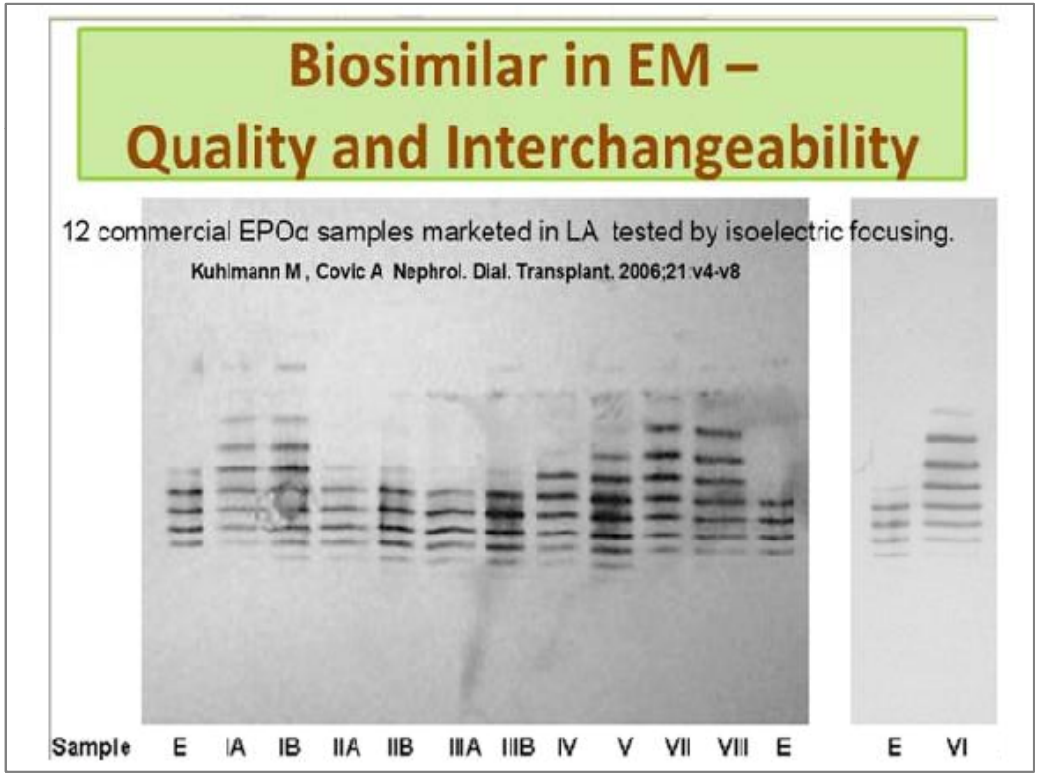
Biologic copy drugs: Terminology matters

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



Biologic copy drugs: Terminology matters

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



Ref

Biologic copy drugs: Terminology matters

- **Then became figure 4 in an article by Aris R on Pharmaphorum**
  - **Aris R. Biosimilars 2012 – what does the current landscape look like?. Pharmaphorum 08th March 2012. URL: www.pharmaphorum.com/articles/biosimilars-2012-%E2%80%93-what-does-the-current-landscape-look-like. Accessed Nov 9, 2014**

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).

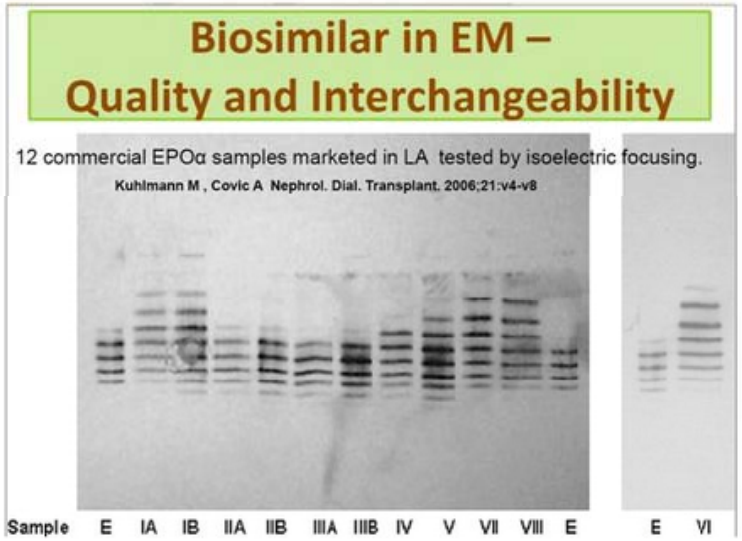


Figure 4: Gel electrophoresis of 12 'biosimilar' products. Results should be similar but this image shows the wide variance in similarity.[i]

Used with permission from Anna Harrington-Morozova

And whilst opportunities appear attractive challenges do remain. Quality is a big issue, which could create inferiority in patient care. In addition, post marketing support can often be insufficient in emerging markets and pharmacovigilance systems can be less developed.

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.**

Ref: Biological Qualifier An INN Proposal. WHO July 2014. http://www.who.int/medicines/services/inn/bq_innproposal201407.pdf?ua=1. Accessed Nov 21, 2014

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 mod**
2. **biologics with diff difference) should**
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!**

Ref: Biological Qualifier An INN Proposal. WHO July 2014. http://www.who.int/medicines/services/inn/bq_innproposal201407.pdf?ua=1. Accessed Nov 21, 2014

Global Dis-Harmonization of Biosimilar Naming and Labeling.

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

Ref: Global Dis-Harmonization of Biosimilar Naming and Labeling. http://www.biosimilarslawblog.com/2012/01/18/global-dis-harmonization-of-biosimilar-naming-and-labeling/. Accessed Nov 21, 2014

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.**

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

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 Pharmaco-vigilance reports & trials shows no unexpected toxicity from biosimilars

Some biosimilars have >300,000 patient years exposure

Ref: Global Dis-Harmonization of Biosimilar Naming and Labeling. http://www.biosimilarslawblog.com/2012/01/18/global-dis-harmonization-of-biosimilar-naming-and-labeling/. Accessed Nov 21, 2014

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

Ref: Barfield A. Pharmacovgilance in the US and EU. Jan 20, 2009. http://www.slideshare.net/Angelinabarfield/Drug-Safety-Regulations-in-the-US-and-EU. Accessed Nov 21, 2014

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).

Ref: Barfield A. Pharmacovgilance in the US and EU. Jan 20, 2009. http://www.slideshare.net/Angelinabarfield/Drug-Safety-Regulations-in-the-US-and-EU. Accessed Nov 21, 2014

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

Knox R. Merck Pulls Arthritis Drug Vioxx from Market. NPR September 30, 200412:00 AM ET. URL: http://www.npr.org/templates/story/story.php?storyId=4054991. Accessed Nov 21, 2014

Pharmacovigilance: Malaysia

National Pharmaceutical Control Bureau

National Pharmaceutical Control Bureau

HEALTHCARE PROFESSIONALS

- Information
- Safety Alert
- Reporting
  - Adverse Drug Reaction
  - Product Complaint
  - Cutaneous ADR Classification
- Useful Links

Reporting Adverse Drug Reaction

Report on suspected Adverse Drug Reactions (ADR) here.

Product Complaint

Use this to report on other medicinal problems.

Ref: Malaysian NPCB ADR reporting website. URL: http://portal.bpfk.gov.my/index.cfm?&menuid=26. Accessed Nov 21, 2014.

Globalization of Biosimilars

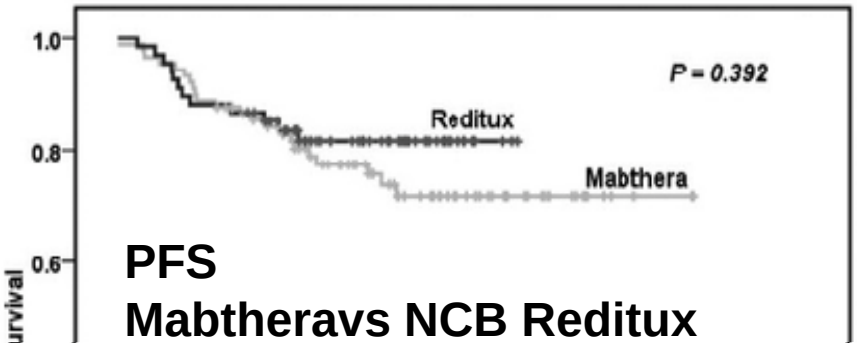
- Question

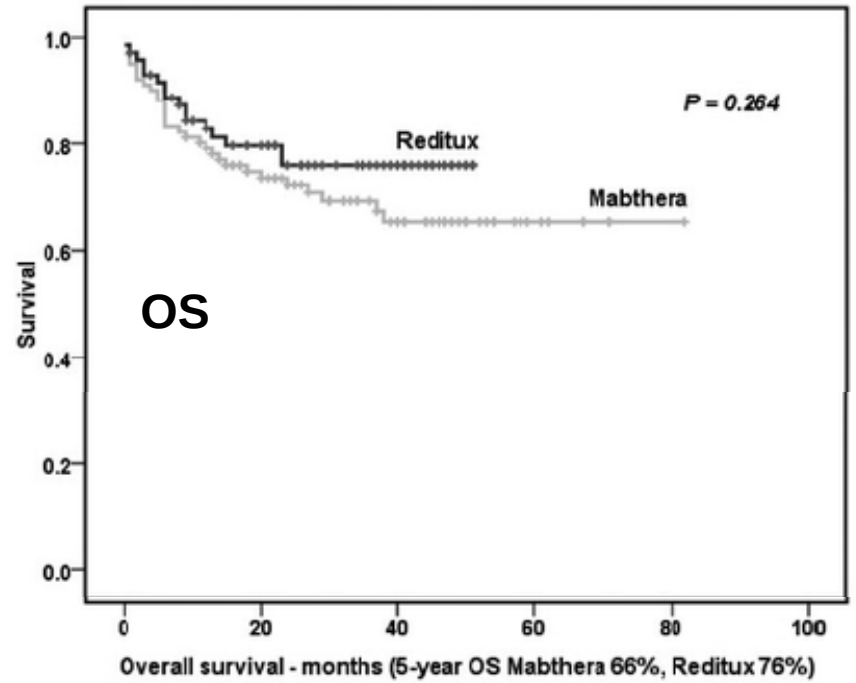
- Global cost problems
- Terminology for biologic copy drugs
- Rules for biosimilars
- Evidence for safety
  - Regulatory
  - Post marketing surveilance
- Observational studies of non-innovator copy drugs

- 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





Ref: Roy PS et al. Comparison of the efficacy and safety of Rituximab (Mabthera™) and its biosimilar (Reditux™) in diffuse large B-cell lymphoma patients treated with chemo-immunotherapy: A retrospective analysis. Indian J Med PaediatrOncol. 2013 Oct;34(4):292-8

What is NOT a biosimilar - Example

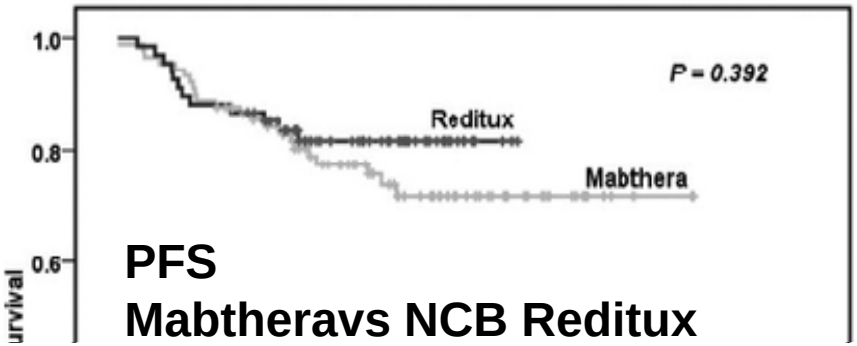
- "Not Biosimilars" are called "non-comparable biologics"

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

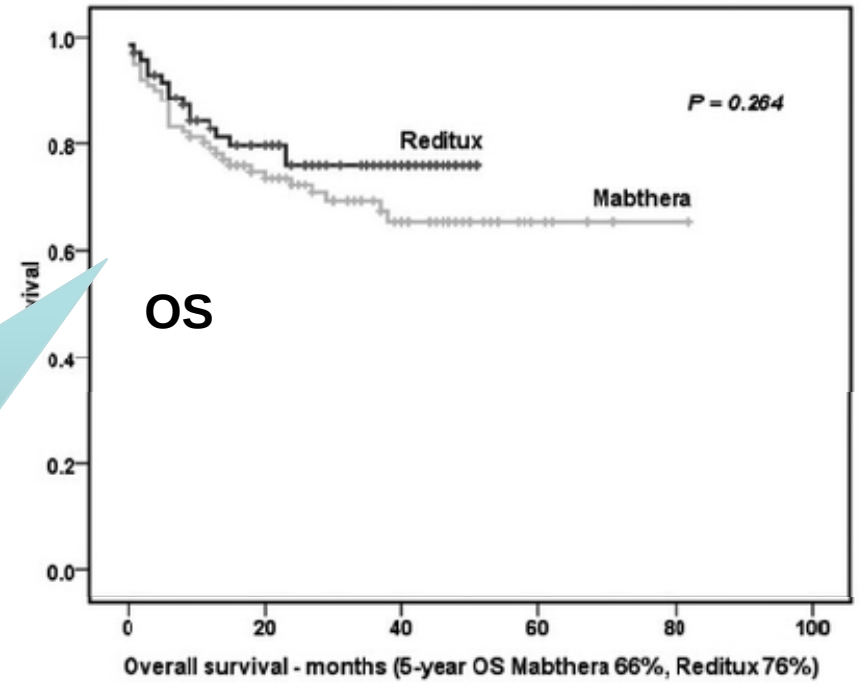
http://www.zenopa.com/news/801441483/dr-reddys-plans-eu-launch-for-biosimilar-cancer-treatment. Accessed Nov 21, 2014

study is so limi

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.



PFS
Mabtheravs NCB Reditux



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Ref: Roy PS et al. Comparison of the efficacy and safety of Rituximab (Mabthera™) and its biosimilar (Reditux™) in diffuse large B-cell lymphoma patients treated with chemo-immunotherapy: A retrospective analysis. Indian J Med PaediatrOncol. 2013 Oct;34(4):292-8

Would Substitution or Switching be safe?

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

Ref: Roy PS et al. Comparison of the efficacy and safety of Rituximab (Mabthera™) and its biosimilar (Reditux™) in diffuse large B-cell lymphoma patients treated with chemo-immunotherapy: A retrospective analysis. Indian J Med PaediatrOncol. 2013 Oct;34(4):292-8

Globalization of Biosimilars

- Question

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

- Question Revisited

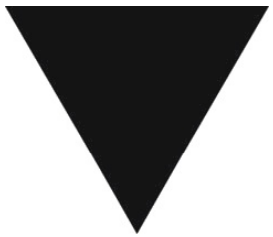
Question

- **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 "biosimilarrituximab" at a fraction of the Malaysian price.**
- **She asks if she can use this for her remaining treatment cycles?**

- **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. **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.

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Overview · Tuesday, January 1, 2008

A Mysterious Allergy Afflicts The South

by Jason Smith

When Bert O'Neil began giving Erbitux to colon-cancer patients in clinical trials, he had no reason to be wary. After all, the drug had already been tested and was FDA-approved for use in colon cancer.

Photo by Jason Smith; ©2008 Endeavors.

But at Carolina's Lineberger Comprehensive Cancer Center, the first three patients who received the drug had potentially life-threatening allergic reactions. They collapsed to the floor, O'Neil says. "They had lost their blood pressure; they had become hypotensive." He didn't realize it at the time, but these patients' reactions were O'Neil's first clue to a baffling regional pattern of hypersensitivity to Erbitux.

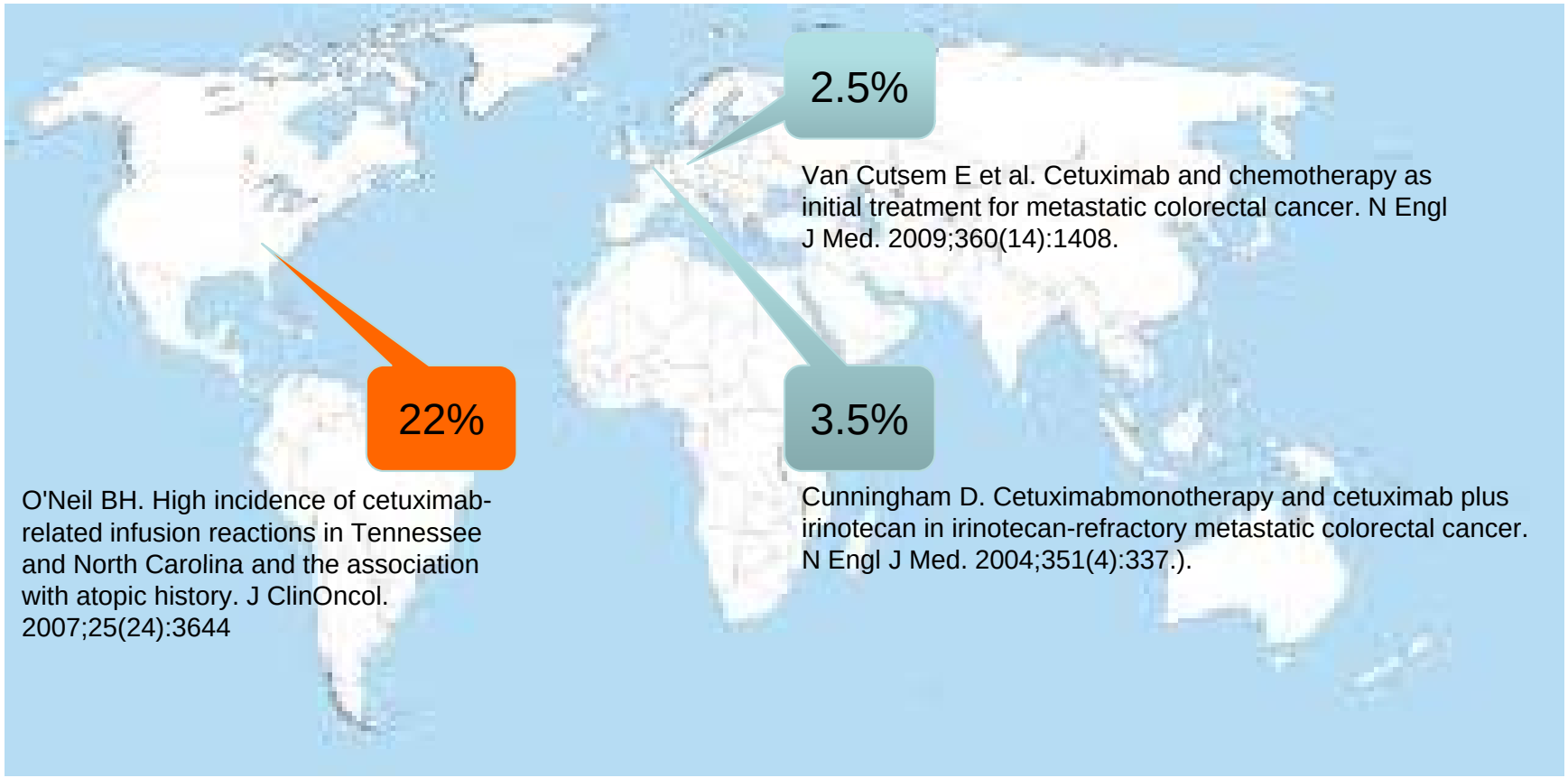
- **All the first 3 patients treated by Dr O'Neil with cetuximab at Carolina's Lineberger Comprehensive Cancer Center collapsed with anaphylaxis.**
- **Nashville, Tennessee, was finding the same problem**
- **The makers traced the doses:**
  - **they had come from different batches.**

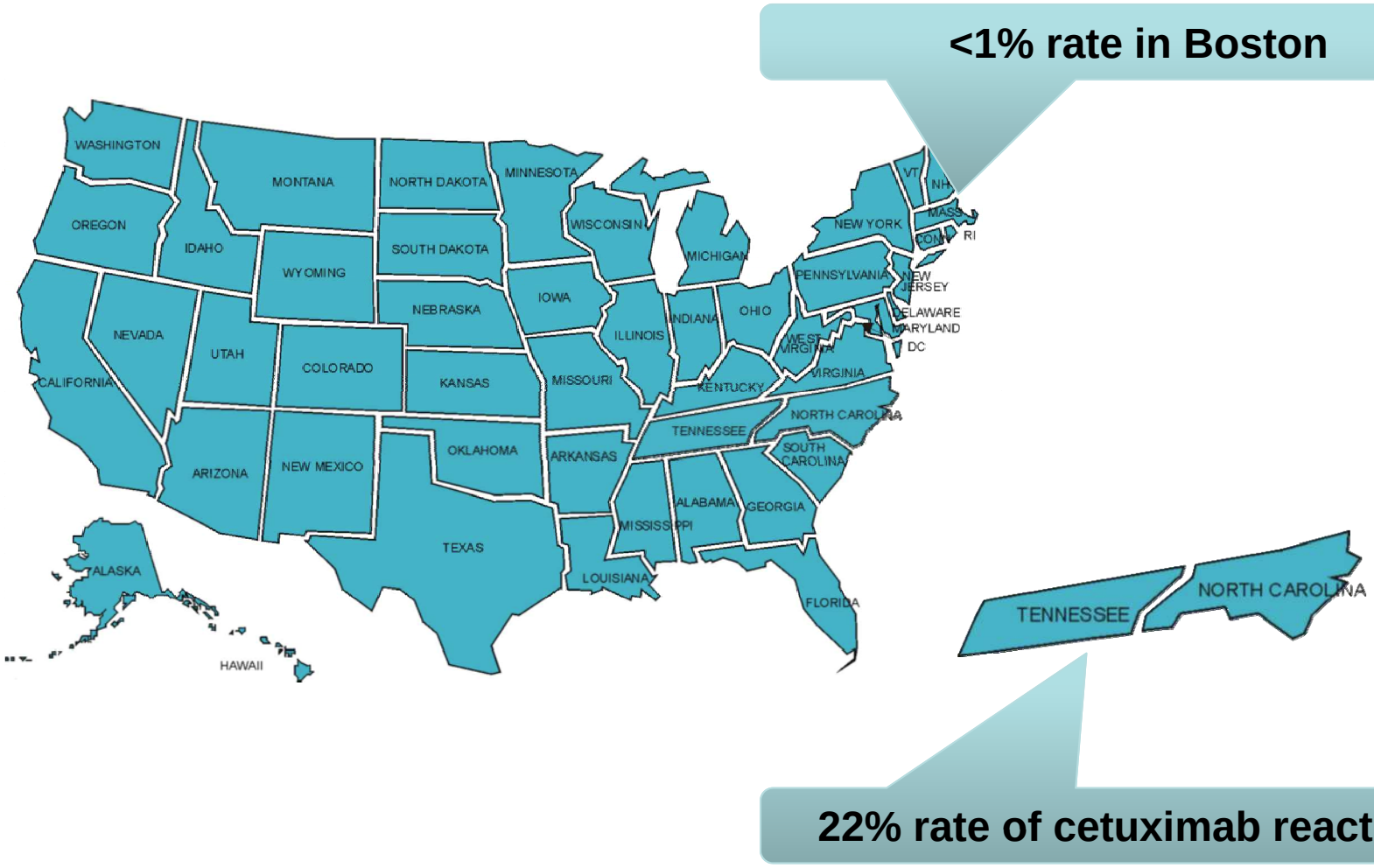
when O'Neil spoke to oncologists from other areas of the country, they didn't know what he was talking about.

A prominent colorectal oncologist in New York "thought we were lying or crazy," O'Neil recalls.

Jason Smith. A Mysterious Allergy Afflicts The South. Endeavours Jan 1st, 2008. http://endeavors.unc.edu/win2008/regional_allergy.php. accessed 3 Nov 2013

Cetuximab reactions





Commins SP, Platts-Mills TA. Allergenicity of carbohydrates and their role in anaphylactic events. Curr Allergy Asthma Rep. 2010 Jan;10(1):29-33. doi: 10.1007/s11882-009-0079-1.
O'Neil BH, Allen R, Spigel DR, et al. High incidence of cetuximab-related infusion reactions in Tennessee and North Carolina and the association with atopic history. J Clin Oncol.2007;25:3644–3648.

VOLUME 25 · NUMBER 24 · AUGUST 20 2007

JOURNAL OF CLINICAL ONCOLOGY

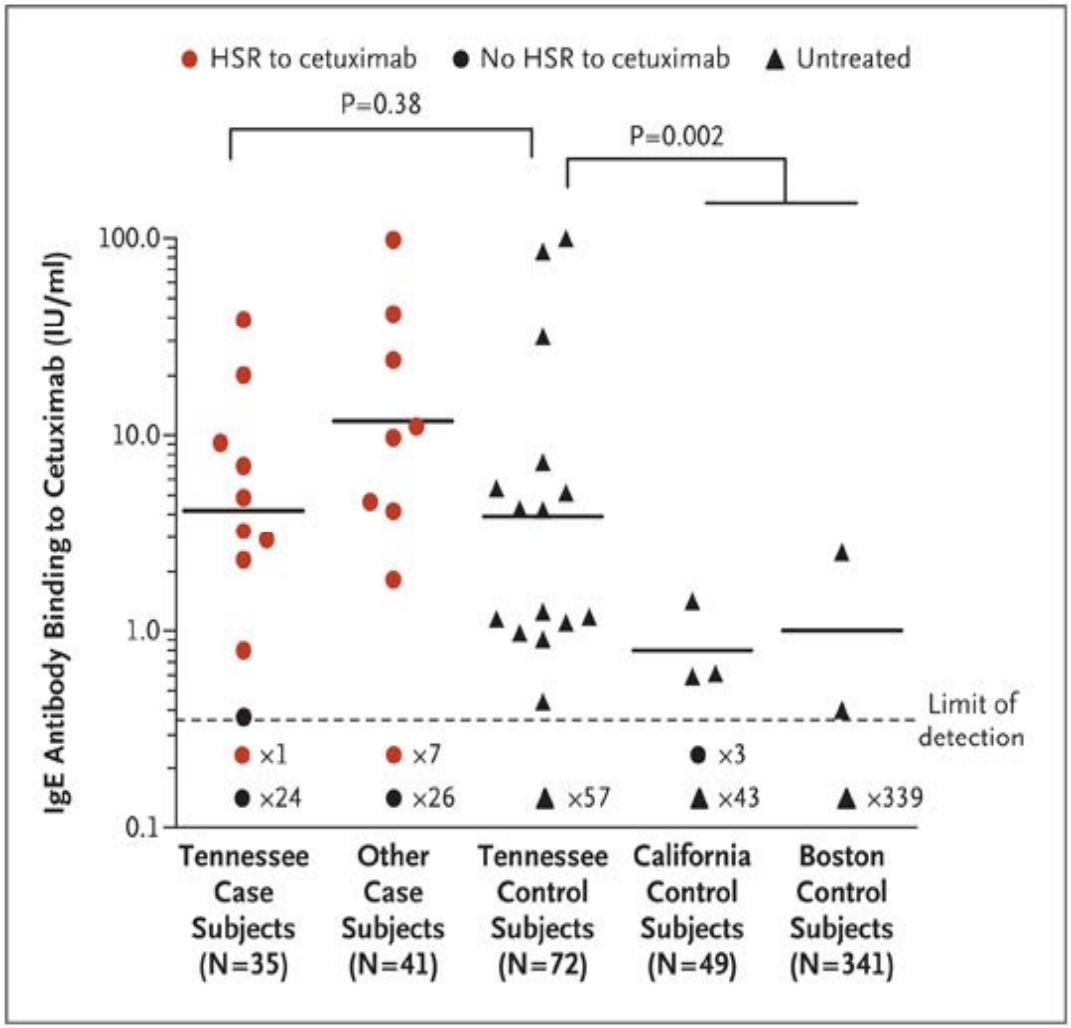
ORIGINAL REPORT

High Incidence of Cetuximab-Related Infusion Reactions in Tennessee and North Carolina and the Association With Atopic History

Bert H. O'Neil, Robert Allen, David R. Spigel, Thomas E. Stinchcombe, Dominic T. Moore, Jordan D. Berlin, and Richard M. Goldberg

R. Owera, High incidence of hypersensitivity reactions to cetuximab infusions in mid-Missouri: Association with prior history of atopy. Abstract, 2008 ASCO Annual Meeting Proceedings, Vol 26, No 15S, 2008:20747

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



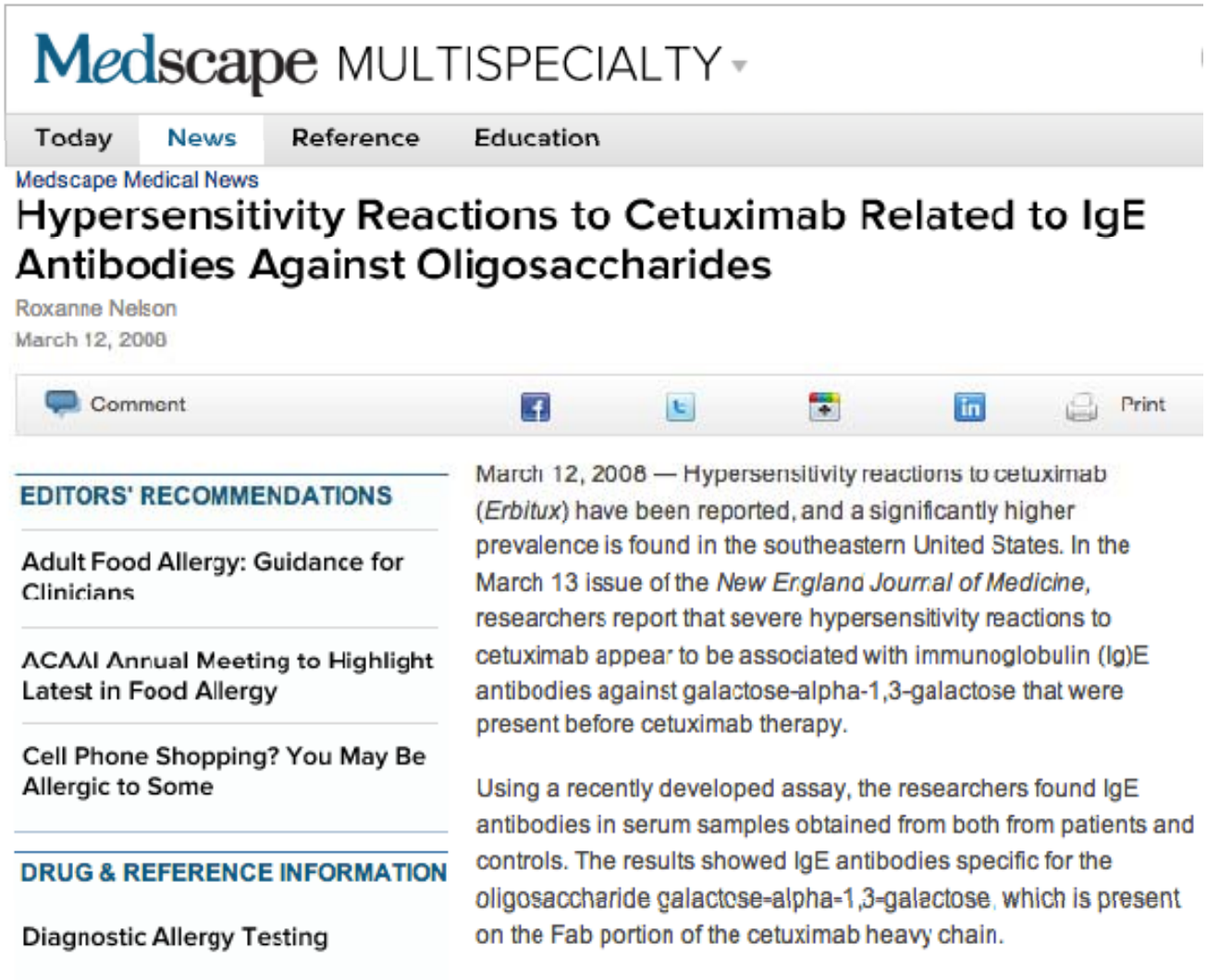
Results are shownaccordingtowhetherthe treatingphysicianreported a hypersensitivityreaction (HSR) tocetuximabor no HSR reaction.

Results are alsoshownforpretreatmentserumsamplesfromco ntrolsubjects and fromsubjects whohadnotreceivedcetuximab.

The horizontallines indicate geometricMeanvaluesfor the positive results.

Valueswithmultiplicationsigns indicate the numberof negative valuesforeachsymbol.

Chung CH et al. IgE Antibodies Binding to Cetuximab in Serum from 76 Case Subjects and 462 Controls. N Engl J Med 2008;358:1109-1117



Medscape MULTISPECIALTY

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Medscape Medical News

Hypersensitivity Reactions to Cetuximab Related to IgE Antibodies Against Oligosaccharides

Roxanne Nelson
March 12, 2008

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EDITORS' RECOMMENDATIONS

Adult Food Allergy: Guidance for Clinicians

ACAAI Annual Meeting to Highlight Latest in Food Allergy

Cell Phone Shopping? You May Be Allergic to Some

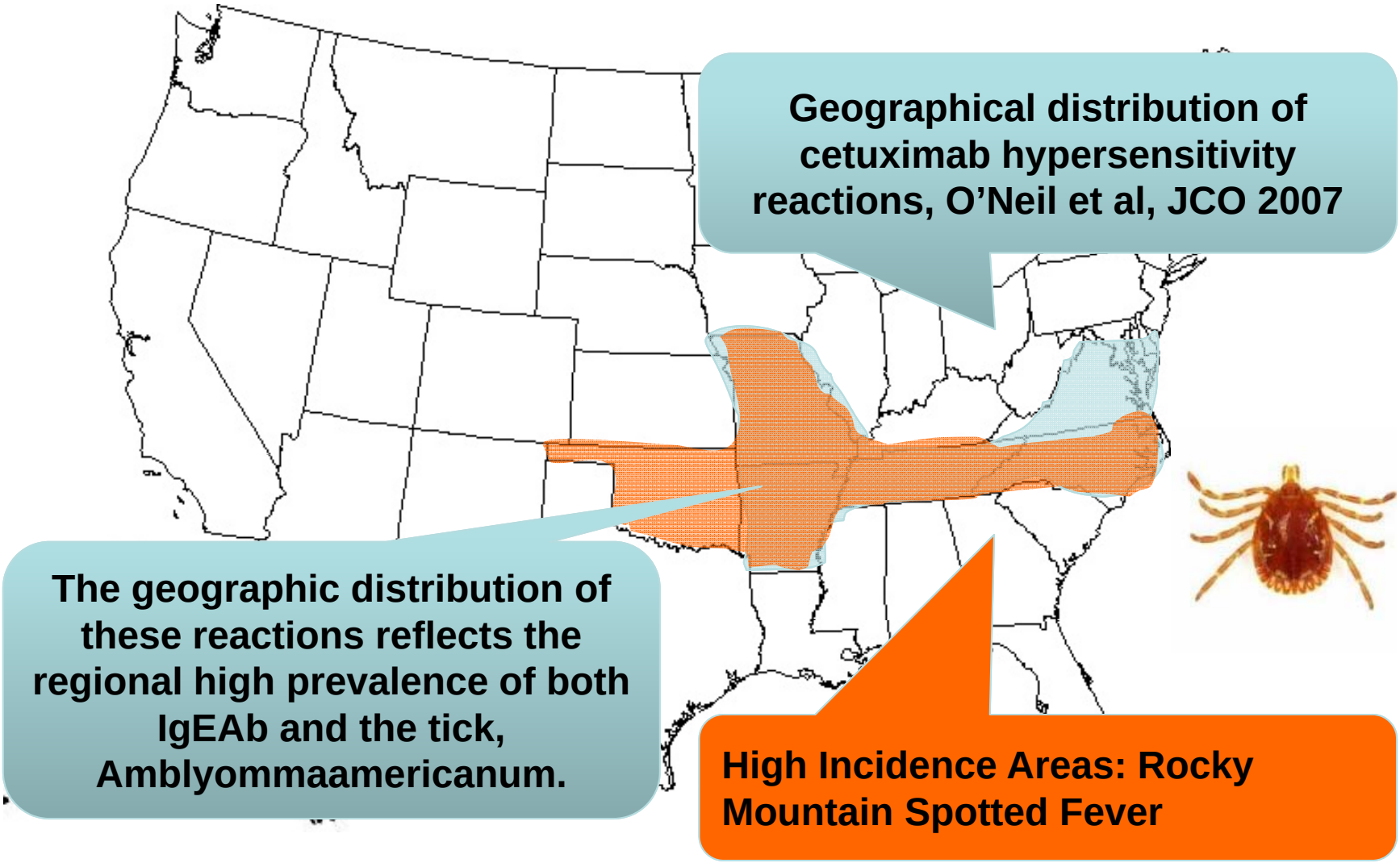
DRUG & REFERENCE INFORMATION

Diagnostic Allergy Testing

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 (Ig)E antibodies against galactose-alpha-1,3-galactose that were present before cetuximab therapy.

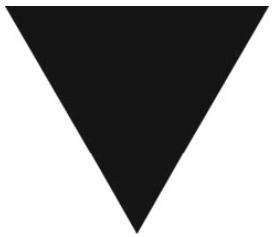
Using a recently developed assay, the researchers found IgE antibodies in serum samples obtained from both from patients and controls. The results showed IgE antibodies specific for the oligosaccharide galactose-alpha-1,3-galactose, which is present on the Fab portion of the cetuximab heavy chain.

Roxanne Nelson. Medscape Medical News - Hypersensitivity Reactions to Cetuximab Related to IgE Antibodies Against Oligosaccharides. March 12, 2008. http://www.medscape.com/viewarticle/571314



Geographic distribution of RMSF incidence in 2010: http://www.cdc.gov/rmsf/stats/ , accessed Oct 30th, 2013


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

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