10 years of biosimilars - who benefits?

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  - Janssen
  - Lilly
  - Merck Serono
  - Napp
  - National Cancer Society Malaysia
  - Pharmaceutical Association of Malaysia
  - Roche
  - Sandoz
  - Synsana EEIG
  - Teva

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Please let me know if there are errors or omissions...

...or you have a better way of explaining it
CME question: After 10 years of European Biosimilars – which statement do you think is correct?

A. There is clear evidence that patient access and outcomes are improved by biosimilars

B. Most of the rich nations of the world have sufficient resource for healthcare

C. Biosimilars are not yet an essential component of European Healthcare

D. Biosimilars are not interchangeable with reference drugs

E. There is no evidence in March 2017 that trastuzumab biosimilars in development can match reference drugs for efficacy in breast cancer

10 years of biosimilars - who benefits?

- The problem of sustainable healthcare
- The value of biosimilars
- Is there a risk to biosimilars?
- The future of biosimilars
10 years of biosimilars - who benefits?

- The problem of sustainable healthcare
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- The future of biosimilars

We live in the era of Non-Communicable Disease

Noncommunicable diseases (NCDs), including heart disease, stroke, cancer, diabetes and chronic lung disease, are collectively responsible for almost 70% of all deaths worldwide.

Our main treatments for these will be medicines!
We live in the era of Non-Communicable Disease – with cancer the main threat

This is the map of Non-Communicable Disease – the darker the colour – the higher the risk

Good news for cancer treatment: worldwide – more people survive cancer

- Reduction in cancer deaths –

UK: 19.4% in 20 years
Good news for cancer treatment: worldwide more people survive cancer

Estimated - new medicines have accounted for 50-60 percent of the increase in cancer survival rates since 1975.


Good news for cancer treatment: Innovation in cancer drugs

At this rate our decade could add more than 100 new cancer drugs by 2020

Almost two-thousand cancer medicines were in development in 2015

New targeted precision medicines are transforming cancer care

Chemotherapy era vs. targeted medicines era

Examples where survival has more than tripled

The possibility at the millennium, 2000

The aspirations for personalised medicine are realistic – not just “blue sky” thinking

- Reduction in cancer deaths –

Where were we?

I am sorry to report that you have breast cancer

Tell me doctor – what have I got?

Malignant Neoplasm of Female Breast
ICD-10-CM (Category C50)
Nipple and areola – right, left, unspecified
Central portion – right, left, unspecified
Upper-inner quadrant – right, left, unspecified
Lower-inner quadrant – right, left, unspecified
Upper-exterior quadrant – right, left, unspecified
Lower-exterior quadrant – right, left, unspecified
Axillary tail – right, left, unspecified
Overlapping and Unspecified

Anatomic diagnosis
Where are we now?

I am sorry to report that you have cancer type

Tell me doctor – what have I got?

Breast cancer is now thought of as at least ten separate diseases, each with a different cause, life expectancy and needing a different treatment [2]

Anatomic diagnosis with complex biomarkers

Where are we heading?

The Cancer Genome Atlas is a working Map of functional and actionable alterations across different tumour types [4]

Describes pathways deregulated

And drug class required to counter it

The Cancer Genome Atlas is a working Map of functional and actionable alterations across different tumour types

Describes pathways deregulated

And drug class required to counter it
Where are we heading?

**The cancer revolution: Personalised treatment that's 'six times better' than traditional methods at beating the disease**

- The revolutionary approach tailors treatment to each cancer patient
- Experts have hailed the 'personalised medicine' as a huge breakthrough
- Research will show how the technique increases chances of survival

By SOPHIE BORLAND, HEALTH EDITOR IN CHIEF FOR THE DAILY MAIL.

**PUBLISHED: 00:12, 4 June 2016 | UPDATED: 01:39, 4 June 2016**

A revolutionary approach to cancer which tailors treatment to each patient is six times as effective as traditional methods, a landmark study has found.

Experts have hailed the so-called 'personalised medicine' as the biggest breakthrough since chemotherapy.

The technique sees a patient's tumour genetically tested as soon as they are diagnosed. This allows doctors to determine whether the cancer is aggressive, whether chemotherapy is necessary and exactly which drugs are needed.

Research involving 13,003 patients, to be unveiled at the world's largest cancer conference next week, will show the technique drastically increases chances of survival and reduces the risk of the disease spreading and returning.

**4 June 2016**

2016: Targeting two deregulated pathways with lapatinib and trastuzumab - Tumours can be gone in as short as 11 days! [5]

Describes pathways deregulated

And drug class required to counter it

Gene directed precision therapy is six times better at controlling cancer – ASCO meeting 2016 [6]

Describes pathways deregulated

And drug class required to counter it
Where are we heading?

“Basket trials” now mean we will treat cancers by genomic diagnosis, not anatomic site [4]

With 3 key steps deregulated – we need 3 concurrent cancer therapies

How should we treat it?
Where are we heading?

With 3 key steps deregulated – we need 3 concurrent cancer therapies

the average cost per month for a branded oncology drug in the U.S. is now approximately $10,000 [2]

$10,000 x 3 x 12 = $360,000 a year

Will my health insurance cover that?

We Have a Problem …

Access to innovation has one key rule

“The only treatment that works is a one that we can afford to give”

On our current spending patterns – healthcare is unsustainable

Especially for cancer

There is no new money to fund a wave of investment in innovative medicine

- Since 2008 there has been a massive gap between the value of what is earned and what is being spent

Debt of the industrialized countries

Economic output of the industrialized countries


Action - What we can do about it

- We need to create a budget to expand access

Innovation Fund

Innovation Fund

Savings that don't compromise care

Current Budget

Ref: [1]

Costs already limit access to healthcare – even in the richest nations of the world

- Many patients did not fill or skipped a prescription, did not visit doctor with medical problem, or did not get recommended care.

Many Europeans may be surprised to see rich nations where >10% of those on below average income fail in 1 or more tests of access to healthcare

Patients in only 6 countries had access to at least half of the 49 new oncology medicines launched 2010–2014

Availability of Oncology Medicines Launched 2010-2014


Patients in only 2 countries had access to reimbursement for at least half of the new oncology medicines launched 2014–2015

Reimbursement status of cancer medicines approved in 2014 and 2015

The innovative cancer drug market is still only for the richest – 2015 data

Leaving 25% for the other 193 nations of the world

Just 7 countries use 75% of the world’s innovative cancer drugs

The reality of cancer care now

"We must confront a stark reality: cancer care is not affordable for most patients, many payers, and nearly all governments. This is a real and immediate issue across the world"

Reference:


Biologic drugs transform more than just cancer

- Targeted biologic therapies offer more efficacy and less toxicity than past generations of small-molecule medicines—transforming many once hard-to-treat diseases.

10 years of biosimilars - who benefits?

- The problem of sustainable healthcare
- The value of biosimilars
- Is there a risk to biosimilars?
- The future of biosimilars
The EU notes the potential savings from Biosimilar medicines

- The cumulative potential savings to health systems in the five major European Union (EU) markets and the U.S., as a result of the use of biosimilars,
  - EUR 50 -100 billion in aggregate over the next five years


The EU reports on strategies for sustainable care place biosimilars as a central policy imperative

- Key recommendations include

## The Promise of biosimilar medicines

<table>
<thead>
<tr>
<th>Challenge</th>
<th>Cost Savings from Biosimilars</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective targeted therapy held back for later stage of disease</td>
<td></td>
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</tr>
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<td>More patients have access to treatment</td>
</tr>
<tr>
<td>Innovative therapies unaffordable</td>
<td></td>
<td>Biosimilars free up budget to buy innovative medicines</td>
</tr>
<tr>
<td>Budgets for certain therapy areas are inadequate</td>
<td></td>
<td>Additional budget can be directed to areas of unmet need</td>
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</table>

The impact of biosimilar filgrastim in London

- NHS London – daily volumes of G-CSF prescribed

  ![Graph showing biosimilar and original reference drugs](graph.png)

  - 5 times more patients treated within 2 years
  - While still saving almost 3 million euros each year
  - Biosimilars enabled treatment to be given to patients with lower risk or earlier stage disease

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The impact of biosimilar filgrastim in Sweden

- Savings from Biosimilar G-CSF switch in Southern Health Care region in Sweden (population 1.7 million)

  ![Map of Sweden](map.png)

  - Five-fold increase in daily G-CSF usage
  - But still net savings of €2 million
  - This represents a saving of 4%–5% of the total drug budget

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New Zealand experience: “More for less – the biosimilar filgrastim story”

- Biosimilar filgrastim introduced to New Zealand in 2012

Oncologist, Dr Richard Isaacs said... “The impact of this change for patients and hospitals has been dramatic,”

“Previously around one third of women receiving docetaxel-based chemotherapy suffered from neutropenic fever. We now see it in less than 7 percent.”

“The price reduction and expanded patient access that resulted from this competition underscores the importance of biosimilars...” PHARMAC


Biosimilars Bring Treatments into Reimbursement That Might Otherwise Be Unaffordable

- Trends in use of white cell growth factors – G-CSF before and after biosimilar introduction in the EU


Biosimilars Bring Treatments into Reimbursement That Might Otherwise Be Unaffordable

- Trends in use of white cell growth factors – G-CSF before and after biosimilar introduction in the EU


Biosimilars reverse negative funding decisions

- 2008 – NICE Technology Appraisal Guidance No. 142
  - Epoetin alfa, epoetin beta and darbepoetin alfa are clinically effective for cancer treatment-induced anaemia
  - But not cost-effective

- 2014 – NICE Technology Appraisal Guidance No. 323
  - Erythropoiesis-stimulating agents (epoetin and darbepoetin) for treating anaemia in people with cancer having chemotherapy are clinically effective
  - And are now cost-effective at real contract prices

Biosimilar savings fund access to innovative therapy

- Roche has outlined its plan to adapt to biosimilars - using the savings to allow payers to reinvest in their next generation of innovation

The savings we make from switching to generics and biosimilars can be used to fund the next generation of innovative therapy

The chart from Roche’s presentation at the J.P. Morgan Healthcare Conference demonstrates how biosimilars are expected to affect sales in coming years [1]

The Promise of biosimilar medicines

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- “All countries can do something, many of them a great deal, to improve the efficiency of their health systems, thereby releasing resources that could be used to cover more people, more services and/or more of the costs”

Ten leading causes of inefficiency

1. Medicines: underuse of generics and higher than necessary prices for medicines

The WHO top priority is to control drug spending

The commonest treatment we use in medicine is drug treatment

10 years of biosimilars - who benefits?

- The problem of sustainable healthcare
- The value of biosimilars
- Is there a risk to biosimilars?
- The future of biosimilars


Is there a risk despite the financial benefits of Biosimilars?

By definition – biosimilars carry no clinically meaningful differences for patients.

The only reason to use a biosimilar is economic: to make healthcare sustainable and increase patient access to effective treatment.


In a decade of use – with more than 400 Million patient days exposure – there has never been an indication that an EMA approved biosimilar shows a different risk or benefit profile to the reference drug.

European Approved Biosimilars have never failed to match the reference drug in an extrapolated indication.

Biosimilars are interchangeable.

Confidence is high: “Position Statements” by Medical Societies against Biosimilars have been reversed.

Interchange of biologics is frequent: Often between originator drugs!

- Switching patterns of erythropoiesis-stimulating agents (ESAs) over one year
  - The size of each node indicates the number of users;
  - the size of each arrow indicates the proportion of users (minimum 4%) who switched between one product and another;
  - switching was counted only once per patient, and only the first switch after the index date was considered.

Most switching occurs between reference epoetin-alfa and epoetin-beta reference drugs

In practice – Physicians have regarded the 4 different reference drugs in the epoetin class as “Interchangeable”

49,491 patients on ESAs in 4 regions of Italy

4006 switchers (17.0%)

Is switching to a biosimilar more of a risk than switching to another originator drug?

Is switching to a biosimilar more of a risk than switching to another originator drug?

Dissimilar drugs, with clear structural differences, not studied formally for switching safety [2]

Highly similar structure, same INN with no clinically meaningful differences. Extensively studied switching [1,2]

Yet “position statements” from our medical societies caution against only biosimilar switching [3,4,5]

Replacing one biologic with another is not necessarily an issue

Patients have been switched between human insulin products for more than 20 years. These in turn have been subject to multiple manufacturing changes

Source Drugs @FDA,
Can switching to a biosimilar be harmful? **Theory**

- For switching to be a problem – there would have to be a “carry over” effect from one drug to another
  - The only mechanism that we can imagine causing this would be immunogenicity leading to anti-drug antibody formation

- For switching to be a problem, the two drugs would need to have a different immune profile
  - For this reason, regulators set strict guidance on immunogenicity before a biologic can be approved [2]


Can switching to a biosimilar be harmful? **Theory – Anti-drug immunity**

- No observed differences in clinically relevant immunogenicity between the approved biosimilar and originator products following authorization by EMA.
- Enhanced immunogenicity has not yet been seen
- So in theory – this risk should be small

Can switching to a biosimilar be harmful? Practice

- In practice, with 10 years of experience of biosimilars in Europe, no problems have been identified.
  - Over that time, patient exposure to biosimilars has been measured in millions.

Reversing negative “Position Statements” – UK British Society of Gastroenterology

- Between 1 March 2015 and 29 February 2016, 138 (87%) of the 159 eligible adult trusts / health boards and 19 (76%) of the 25 IBD specialist paediatric sites in the UK participated in this audit or the Personalised Anti-TNF Therapy in Crohn’s disease study.
  - 2722 adult and 278 paediatric patients entered to the audit.

Key recommendations:

- Clinicians should use infliximab biosimilars as the first line anti-TNFα for appropriate patients with active IBD.
Reversing negative “Position Statements” – European Crohn’s and Colitis Organization (ECCO)

- December 2016 - Updated position statement on biosimilars
- “Switching from the originator to a biosimilar in patients with IBD is acceptable following appropriate discussion between physicians, nurses, pharmacists, and patients, and according to national recommendation”
- “When a biosimilar product is registered in the European Union, it is considered to be as efficacious as the reference product when used in accordance with the information provided in the Summary of Product Characteristics”


The greatest challenge in switching has been Infliximab in Rheumatoid Disease

- Infliximab is the most important 2nd generation drug to learn from
  - Rheumatoid disease is an immune disease of anti-antibody formation
  - Infliximab is the drug with the highest rate of ADAb in the class: 20-40% of patients exposed with Rheumatoid

1: Infliximab Biosimilars – Safety & Efficacy: Systematic review
September 2015

- By September 15, 2015 there were 15 English-language reports that confirmed equivalence in the safety, efficacy, or pharmacokinetic profiles of biosimilar and reference TNF-α inhibitors -
  - 8 randomized controlled trials (RCTs), 4 abstracts describing trial extensions, 2 retrospective case series and 1 cross-sectional study

The risk of bias was generally low for all trials
Treatment-emergent adverse events and serious adverse events were comparable
Biosimilars showed similar efficacy with American College of Rheumatology Remission Criteria (ACR20) responses


2: Infliximab Biosimilars – Safety & Efficacy: Systematic review
August 2016

- A systematic review of 19 efficacy & switching studies with anti-TNF biosimilars shows
  - Ten trials assessed immunogenicity

Results
- no clinically significant differences in efficacy
- No clinically significant loss of effect from switching [1]


- Moots et al: AJR 2016: Systematic review of switching studies of infliximab (INF), etanercept (ETN), adalimumab (ADA), or rituximab (RTX) switched between originator biologics and biosimilars.

- Switching data was available for 12 studies in rheumatic diseases with 2104 patients
  - Switch Number of studies
  - INF/CT-P13 4
  - INF/SB2 1
  - INF/unidentified biosimilar 2
  - ETN/SB4 2
  - ETN/GP2015 1
  - ADA/SB5 1
  - RTX/CT-P10 1

  The INF/CT-P13 studies showed efficacy and safety of INF and CT-P13 to be similar in switch and maintenance groups, and similar pre- and post-switch.

  Immunogenicity was assessed in 3 studies and did not change post-switch.


4: February 2017

- Further metanalysis anti-TNF-a Biosimilars vs Reference drugs:
  - infliximab,
  - adalimumab
  - etanercept

  Nine studies reporting outcomes in 3291 patients with rheumatoid arthritis (RA) and ankylosing spondylitis (AS) were identified
  - (5 infliximab, 2 adalimumab, and 2 etanercept)

  Conclusion: “biosimilars of anti-TNF-a agents had an overall comparable efficacy and safety profile compared to their reference agents in RA and AS”

Interchangeability –
EU National regulators Speak Up

- Finland
- Germany
- Netherlands
- Norway

The changing trend of publications about biosimilars: 2004-2015

- Thorsten Daubenfeld, and colleagues analysed the trends in approach to biosimilars in papers published 2004 through 2015

This should not surprise us - following decades of use of the same regulatory processes to manage manufacturing changes in Biologics
10 years of biosimilars - who benefits?

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Expectations of Future Biosimilars: Therapeutic Oncology Drugs

- Biologic drugs are now essential medicines for the world that we must provide to the world at affordable prices
- Crucially The latest WHO essential drugs list for cancer now includes 3 biologics

Expectations of Future Biosimilars: Therapeutic Oncology Drugs

11 Proposed Biosimilars of trastuzumab are in development

& 23 Proposed Biosimilars of rituximab

Trastuzumab

Rituximab

A biosimilar medicine, Truxima (rituximab), received a positive opinion from the CHMP for the treatment of non-Hodgkin's lymphoma, chronic lymphocytic leukaemia, rheumatoid arthritis, granulomatosis with polyangiitis and microscopic polyangiitis.

Expectations of Future Biosimilars: Therapeutic Oncology Drugs: Trastuzumab

11 Proposed Biosimilars of trastuzumab are in development

3 RCTs of proposed biosimilars of trastuzumab have reported clinical outcomes to date December 9, 2016

A 4th study has reported headline results only

Expectations of Future Biosimilars: Therapeutic Oncology Drugs: Trastuzumab

- Amgen ABP-980
  - Phase III trial in Early Breast Cancer expected to be completed in December 2016
  - ClinicalTrials.gov Identifier: NCT01901146

725 patients randomised – early breast cancer Her2++

The primary endpoint had a prespecified equivalence margin of +/- 13 percent and the observed upper end of the confidence interval was 13.4 percent.

ABP-980 is not inferior but could be superior to trastuzumab reference

3 RCTs of proposed biosimilars of trastuzumab in Metastatic Disease have reported clinical outcomes to date Dec 9, 2016

2 RCTs have met their targets for Clinical Equivalence of the Primary Endpoint

1 RCT met a Non-Inferiority Target
Expectations of Future Biosimilars: Therapeutic Oncology

Drugs: Trastuzumab

- Biocad BCD-022
- Non-originator biological approved in Russia in January 2016 [2]
- Trial: NCT01764022
- Launched in at least Russia, Vietnam, Sri-Lanka

126 patients randomised – metastatic breast cancer Her2++: non-inferiority trial design

ORR (primary endpoint) in both groups had no statistically significant differences: 53.57% vs 53.70%

lower limit of 95% CI for ORR difference between the groups (-19.83%)


Expectations of Future Biosimilars: Therapeutic Oncology

Drugs: Trastuzumab

- Mylan Myl-1401O
- “HERITAge” study - Phase III trial in metastatic breast cancer expected to be completed in December 2018 [2]. Positive data reported June 2016 at ASCO [3,4]
- The same drug was launched as CanMab™ in India as an Intended Copy Biologic in 2013

500 pts randomized, 458 were evaluable for efficacy in an “equivalence” trial design with prespecified margin ORR 0.81 - 1.24.

Week 24 ORR was 69.6% for Myl-14010 compared to 64% for Herceptin

The ratio of ORR was 1.09; both 90% CI (0.974-1.211) and 95% CI (0.954-1.237) were within the pre-defined equivalence margin.


Expectations of Future Biosimilars: Therapeutic Oncology Drugs: Trastuzumab

- Celltrion CTP6
  - Approved in Korea 2014 as Herzuma
  - 2014: started an EU trial of adjuvant breast cancer: 532 patients. Due 2019
  - ClinicalTrials.gov Identifier: NCT02162667

Phase 3 clinical trial data for 475 women with metastatic breast cancer in 18 countries: equivalence margin <15%, alpha 0.05

ORR by cycle 8: 56.6% vs 61.9% [CI -14.3/+3.6]
SAE: 33 v 28 p=0.65

3 RCTs of proposed biosimilars of trastuzumab have reported Clinical Outcomes

- All 3 are trials in advanced or metastatic HER2++ Breast Cancer
  - 1043 patients randomised in total
  - The most recent reports with any numeric clinical data were used for each trial that could be accessed Dec 9, 2016

<table>
<thead>
<tr>
<th>Drug</th>
<th>CR or PR absent</th>
<th>CR or PR present</th>
<th>SAE absent</th>
<th>SAE present</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCD-022</td>
<td>26</td>
<td>30</td>
<td>59</td>
<td>6</td>
</tr>
<tr>
<td>Herceptin</td>
<td>25</td>
<td>29</td>
<td>55</td>
<td>6</td>
</tr>
<tr>
<td>Myl 1410</td>
<td>70</td>
<td>160</td>
<td>136</td>
<td>94</td>
</tr>
<tr>
<td>Herceptin</td>
<td>82</td>
<td>146</td>
<td>139</td>
<td>89</td>
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<tr>
<td>CT-P6</td>
<td>88</td>
<td>143</td>
<td>211</td>
<td>33</td>
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<tr>
<td>Herceptin</td>
<td>105</td>
<td>139</td>
<td>203</td>
<td>28</td>
</tr>
</tbody>
</table>

All 3 trials reported Clinical Response rates at 24-25 weeks
Pooled – this gives >1000 patients’ data

3 RCTs of proposed biosimilars of trastuzumab have reported Clinical Outcomes

- 1043 patients analysed for Primary Outcome,
  - ORR at 24-25 weeks

```
<table>
<thead>
<tr>
<th>Sample size</th>
<th>Number positive</th>
<th>Confidence level</th>
<th>CI method</th>
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<tbody>
<tr>
<td>526</td>
<td>314</td>
<td>0.95</td>
<td>Wilson</td>
</tr>
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</table>
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- Herceptin ORR 60% (95%CI 55-64%)
- Biosimilar ORR 64% (95%CI 60-68%)

Pooled – this gives >1000 patients’ data

[2] 95% Confidence Intervals calculated to 2 decimal places with Epitools, Jan 5, 2017

3 RCTs of proposed biosimilars of trastuzumab have reported Clinical Outcomes

- 1049 patients analysed for SAE

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- Herceptin 25% (95%CI 20-27%)
- Biosimilar 25% (95%CI 21-28%)

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[2] 95% Confidence Intervals calculated to 2 decimal places with Epitools, Jan 5, 2017
10 years of biosimilars - who benefits?

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Rational Medicine Use

- “Medicine use is rational (appropriate, proper, correct) when
  • patients receive the appropriate medicines,
  • in doses that meet their own individual requirements,
  • for an adequate period of time, and
  • at the lowest cost both to them and the community.

- Irrational (inappropriate, improper, incorrect) use of medicines
  • is when one or more of these conditions are not met.”

We are given clear moral leadership guidance by the WHO
Conclusion: After 10 years of European Biosimilars

A. There is clear evidence that patient access and outcomes are improved by biosimilars

YES - New Zealand, UK, Sweden – wherever Biosimilars have been adopted into practice

B. Most of the rich nations of the world have sufficient resource for healthcare

NO - only 7 nations use 75% of the world’s targeted therapy

C. Biosimilars are not yet an essential component of European Healthcare

NO - EU 2016 Sustainable Care Report - PRIORITY !

D. Biosimilars are not interchangeable with reference drugs

NO - National Regulators Paper confirm Biosimilars are “interchangeable” Kurki, 2017

E. There is no evidence in March 2017 that trastuzumab biosimilars in development can match reference drugs for efficacy in breast

NO - You have just seen it !

A Final Problem? Physicians knowledge: Biosimilars Forum Survey 2016 – Results

- Do you believe biosimilars will be safe and appropriate for use in naïve and existing patients?

<table>
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<th>Hematology-Oncology</th>
<th>57.0 %</th>
<th>43 %</th>
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<tr>
<td>Medical Oncology</td>
<td>50.5 %</td>
<td>49.50 %</td>
</tr>
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Physicians seem to be split 50:50

What is the opinion of Europe’s Specialist Pharmacists?

CME question: After 10 years of European Biosimilars – which statement do you think is correct?

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