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HEALTH ECONOMICS OF BIOLOGICS AND BIOSIMILARS: the essentials

Prof. dr. Steven Simoens

Conflict of interest

I am one of the founders of the KU Leuven Fund on Market Analysis of Biologics and Biosimilars following Loss of Exclusivity (MABEL).

I am involved in a stakeholder roundtable on biologics and biosimilars sponsored by Amgen, Pfizer, and MSD.

I have participated in advisory board meeting and studies on biologics and biosimilars for Pfizer.

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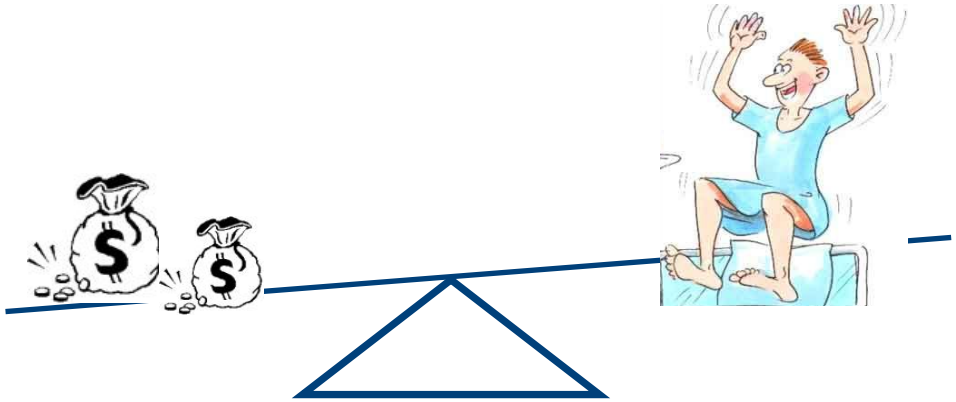
What is health economics?

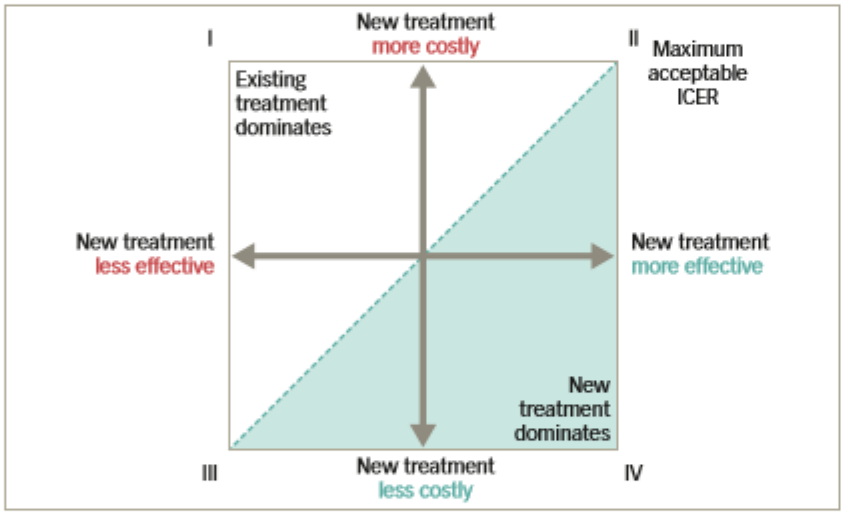
Goal of health care policy = to maximise health of population within limits of available resources, and within ethical framework built on equity and solidarity principles

In economic evaluation, we identify, measure, value and compare the costs and consequences of the alternatives being considered



Cost-effectiveness

Figure 2: Cost-effectiveness plane diagram to assess the ICER and whether the additional health gained from using a certain drug outweighs any additional cost to the healthcare system resulting from its use



ICER = incremental cost-effectiveness ratio.

Table 1: World Health Organization cost-effectiveness threshold for selected European countries

Country	WHO cost-effectiveness threshold (US$)[38]	
	GDP per capita in 2016	3 x GDP per capita in 2016
Belgium	44,881	134,643
Denmark	46,603	139,809
France	42,384	127,152
Germany	48,190	144,570
Italy	36,313	108,939
Norway	69,296	207,888
Portugal	28,515	85,545
Spain	36,451	109,353
Sweden	49,678	149,034
The Netherlands	50,846	152,538
UK	42,514	127,542

GDP is the total market value of all final goods and services produced in a country in a given year. GDP per capita is calculated by dividing GDP by midyear population. To make meaningful comparison between countries, GDP per capita PPP data were used, by adjusting for differences in prices in different countries. The WHO cost-effectiveness threshold of 3 x GDP per capita per life year/QALY gained was calculated from GDP per capita per life year/QALY gained using 2016 projected GDP per capita data from the International Monetary Fund.[38] GDP = gross domestic product; PPP = purchasing power parity; QALY = quality-adjusted life year; WHO = World Health Organization.

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Simoens S., van Harten W., Lopes G., Vulto A., Meier K., Wilking N. What happens when the cost of cancer care becomes unsustainable? European Oncology & Haematology 2017;13 (2),108-113.

Cost-effectiveness of biologics

Table 5. Distribution of weighted cost-utility ratios* by type of intervention

	No.	Median	Inter-quartile range	Cost-saving[a] (%)	Dominated[b] (%)
All ratios	**4608**	**$9,041**	**$2,439–$26,478**	**16.9**	**8.5**
Biopharmaceuticals	538	$15,412	$3,2845–$45,287	15.2	5.6
Care delivery	493	$11,617	$3,239–$37,385	17.6	6.3
Conv. pharmaceuticals	1863	$7,094	$1,813–$23,323	18.6	9.6
Diagnostic	422	$8,846	$2,705–$29,775	13.7	19.0
Health ed. or behavior	362	$5,279	$1,662–$17,988	21.0	3.0
Immunizations	366	$8,852	$2,697–$21,931	18.0	4.1
Medical device	366	$14,236	$4,778–$48,761	23.2	8.2
Medical procedure	429	$13,877	$4,307–$44,995	21.0	17.2
Screening	617	$8,785	$2,763–$20,893	11.0	9.9
Surgical	574	$8,790	$1,937–$25,492	15.3	10.8

*Presented as $US/QALY (in 2008 USD); [a]Interventions with improved health benefits and decreased costs; [b]Interventions with decreased health benefits and greater costs.

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Wilson A.W., Neumann P.J. The cost-effectiveness of biopharmaceuticals: a look at the evidence. MAbs. 2012;4(2):281-288.

Cost-effectiveness of biologics

rheumatoid arthritis

Review of 15 economic evaluations comparing a combined biologic and non-biologic DMARD with a non-biologic DMARD only

Study populations included patients who either had severe RA or who had previously failed treatment with TNFα inhibitors and were being considered for non-anti–TNF biologics

Cost-effectiveness ratios (in 2012 US$) (N=15):

- Mean of $47,500 per QALY
- Median of $38,900 per QALY
- Range of $5,000-$230,000 per QALY

(abatacept, adalimumab, etanercept, infliximab, rituximab, tocilizumab)

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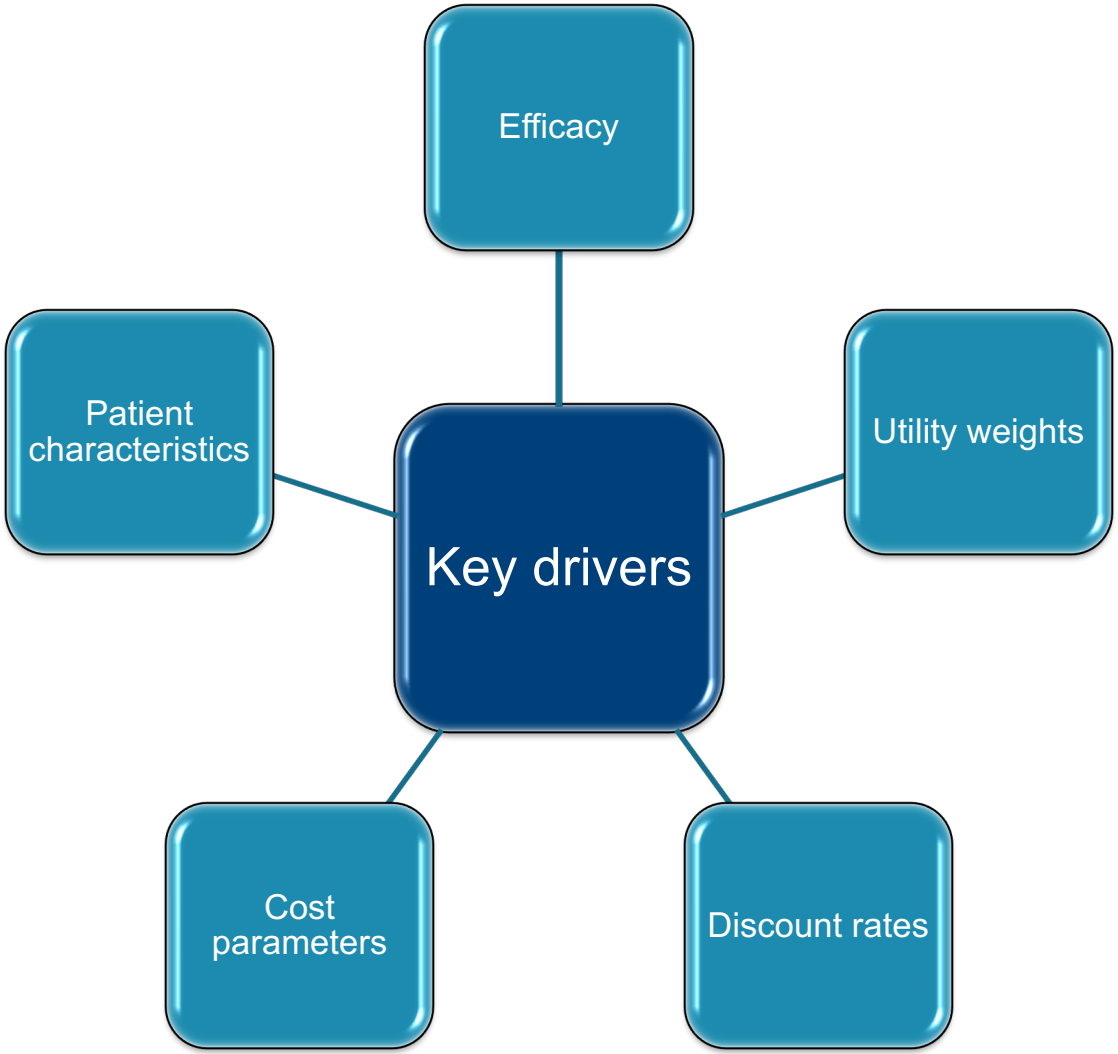
Zalesak M., Greenbaum J.S., Cohen J.T., Kokkotos F., Lustig A., Neumann P.J., Pritchard D., Stewart J., Dubois R.W. The value of specialty pharmaceuticals - a systematic review. Am J Manag Care 2014;20(6):461-472.

Factors affecting cost-effectiveness of biologics

ulcerative colitis



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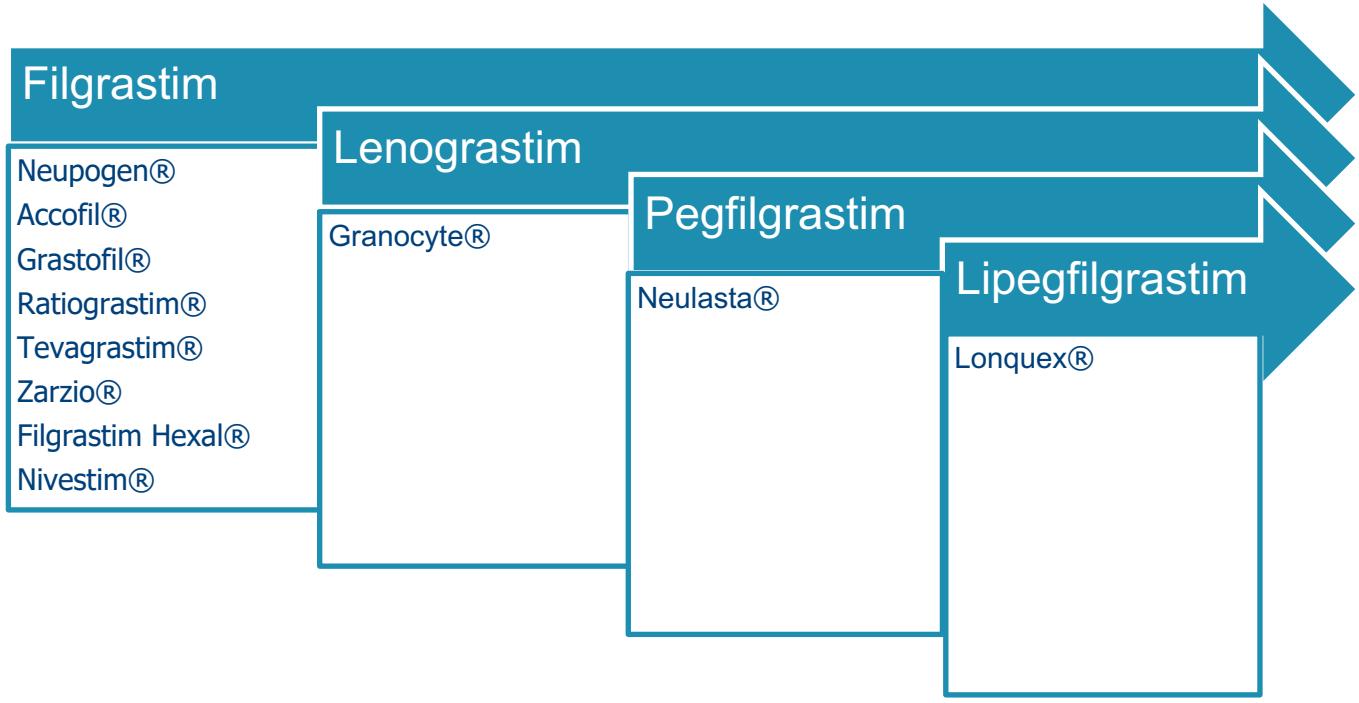
Stawowczyk E., Kawalec P. A Systematic Review of the Cost-Effectiveness of Biologics for Ulcerative Colitis. Pharmacoeconomics. 2018;36(4):419-434.

Biologics, biosimilars, and next-generation biologics



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Cost-effectiveness of biologics

small differences matter

Lipegfilgrastim is non-inferior to pegfilgrastim in reducing duration of SN in patients with stage II−IV breast cancer. Lipegfilgrastim also has statistically significant lower time to ANC recovery in cycles 1–3, lower incidence of SN in cycle 2 and lower depth of ANC nadir in cycles 2 and 3 vs. pegfilgrastim.

At equivalent price of €1,169, lipegfilgrastim treatment had costs of €9,845 vs. €10,208 for pegfilgrastim; and QALYs of 13.977 vs. 13.925.

Difference in costs stems from avoided infection, SN and FN cases with lipegfilgrastim vs. pegfilgrastim. Difference in QALYs stems from difference in number of patients in chemotherapy/G-CSF Markov state followed by infection and FN between lipegfilgrastim and pegfilgrastim.

Probability of lipegfilgrastim to be cost-effective compared to pegfilgrastim was 79% at willingness-to-pay threshold of €30,000 per QALY gained.

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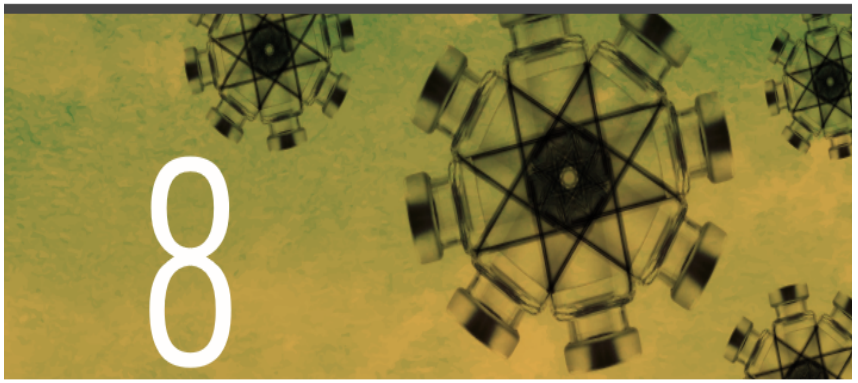
Akpo E.I.H., Jansen I.R., Maes E., Simoens S. Cost-Utility Analysis of Lipegfilgrastim Compared to Pegfilgrastim for the Prophylaxis of Chemotherapy-Induced Neutropenia in Patients with Stage II-IV Breast Cancer. Front. Pharmacol. 2017;8:614.



BIOSIMILARS

DETERMINING THEIR VALUE

Just as the development and marketing of biosimilars has not been on the same timeline around the world, the estimation of their value also cannot be considered in the same way across countries.

The use of biosimilars is expected to generate between €11.8 billion and €33.4 billion in savings between 2007 and 2020.

Regulatory requirements for biosimilars in the European Union, United States, Latin America, and Asia-Pacific regions are similar and yet slightly different.[19,20] The European Medicines Agency took the lead on developing an approval process for biosimilars, introducing an abbreviated registration process in 2005 to 2006. According to the *Generic and Biosimilars Initiative Journal*, the use of biosimilars is expected to result in overall savings from €11.8 billion and €33.4 billion between 2007 and 2020, with the largest savings expected for France, Germany, and the United Kingdom.[21]

Biosimilars have the potential not only to provide cost savings to the healthcare system but also to give patients a wider set of treatment options. However, costs of switching, potential differences between the original and the biosimilar, pricing considerations around the appropriate discounts for both original and biosimilar products, and the potential for utilization by more patients given lower biosimilar prices (although not as low in absolute terms as small molecule generics) must also be taken into account. As a result, careful evaluation, management, and cost-effectiveness considerations in this category are expanding areas of focus.

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ISPOR 2018 TOP 10 HEOR TRENDS. https://www.ispor.org/top10trends.pdf?v2

Budget impact of biosimilars

Examines impact on health expenditure from adopting a new technology such as biosimilars

Assesses the affordability of biosimilars

Budget impact analyses focus on substitution and expansion of originator biologics and biosimilars

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Simoens S., Jacobs I., Popovian R., Isakov L., Shane L.G. Assessing the Value of Biosimilars: A Review of the Role of Budget Impact Analysis. Pharmacoeconomics 2017;35(10):1047-1062.

Biosimilars generate savings

Budgetary impact of introducing CT-P10 in EU-28 for patients with rheumatoid arthritis and cancer diagnoses

Three scenarios:

1. One-year uptake of CT-P10 at 30% and cost at 70% of cost of RTX
2. One-year uptake of CT-P10 at 50% and cost at 70% of cost of RTX
3. Three-year uptake of CT-P10 at 30%, 40%, and 50% in first, second, third years

1. *Savings of €90 million*
2. *Savings of €150 million*
3. *Savings of €570 million*

CAVEAT: includes drug costs only

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Gulácsi L., Brodszky V., Baji P., Rencz F., Péntek M. The Rituximab Biosimilar CT-P10 in Rheumatology and Cancer: A Budget Impact Analysis in 28 European Countries. Adv Ther. 2017;34(5):1128-1144.

And may expand access to treatment

Table III. Cost savings and expanded treatment access achieved under 100% conversion from originator filgrastim to biosimilar filgrastim (per a panel of 10,000 patients with cancer).

Variable	100% Conversion to Biosimilar Filgrastim
Day 4	
Cost savings from conversion, €	3,924,000
Expanded treatment access, No.	
Rituximab (NHL)	347 (additional treatments, ie, 2% of annual incident patients)
Trastuzumab (BC)	132 (additional treatments, ie, 1% of annual incident patients)
Day 6.1	
Cost savings from conversion, €	5,984,100
Expanded treatment access, No.	
Rituximab (NHL)	529 (additional treatments, ie, 4% of annual incident patients)
Trastuzumab (BC)	201 (additional treatments, ie, 2% of annual incident patients)
Day 6.5	
Cost savings from conversion, €	6,376,500
Expanded treatment access, No.	
Rituximab (NHL)	563 (additional treatments, i.e., 4% of annual incident patients)
Trastuzumab (BC)	214 (additional treatments, ie, 2% of annual incident patients)
Day 7	
Cost savings from conversion, €	6,867,000
Expanded treatment access, No.	
Rituximab (NHL)	607 (additional treatments, ie, 4% of annual incident patients)
Trastuzumab (BC)	231 (additional treatments, ie, 3% of annual incident patients)
Day 11	
Cost savings from conversion, €	10,791,000
Expanded treatment access, No.	
Rituximab (NHL)	953 (additional treatments, ie, 6% of annual incident patients
Trastuzumab (BC)	362 (additional treatments, ie, 4% of annual incident patients)
Day 14	
Cost savings from conversion, €	13,734,000
Expanded treatment access, No.	
Rituximab (NHL)	1213 (additional treatments, ie, 8% of annual incident patients)
Trastuzumab (BC)	461 (additional treatments, ie, 5% of annual incident patients)

BC = breast cancer; NHL = non-Hodgkin's lymphoma.

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Sun D., et al. Potential cost savings from chemotherapy-induced febrile neutropenia with biosimilar filgrastim and expanded access to targeted antineoplastic treatment across the European Union G5 countries: a simulation study. Clin Ther. 2015;37(4):842-57.

But impact of biosimilars may go further…

Impact on prices and utilisation of originator biologic, biosimilars, biologic alternatives, and future market entries

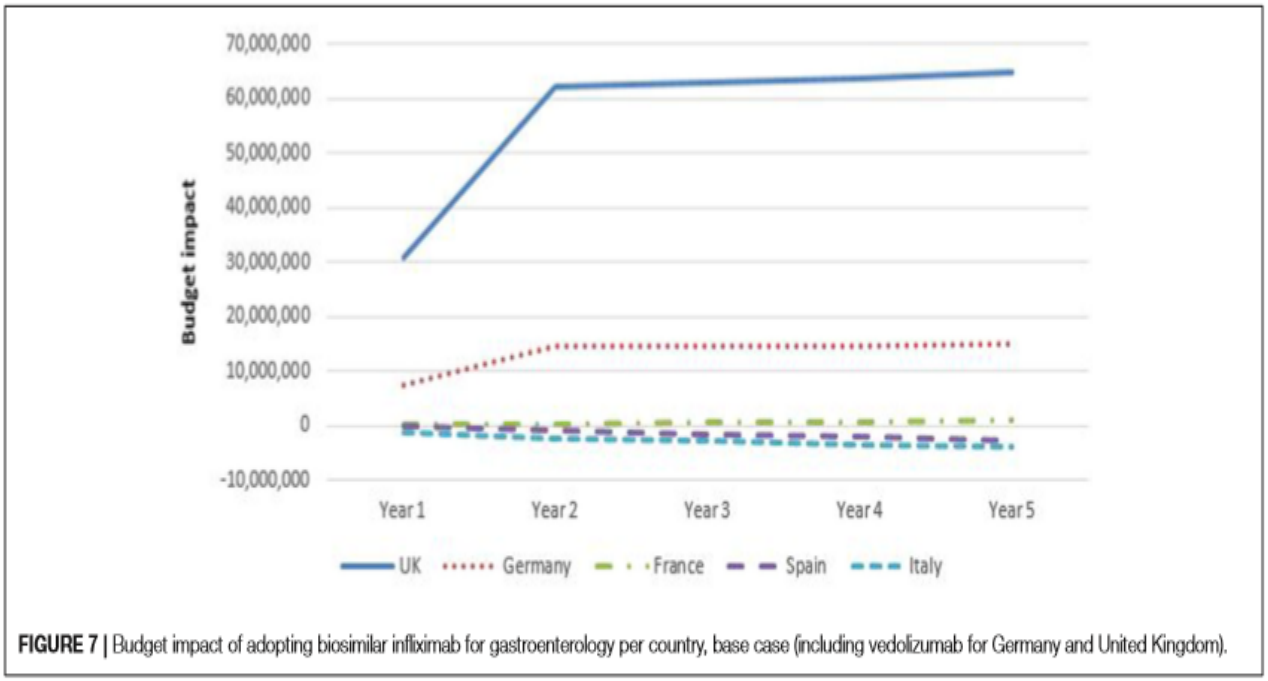

FIGURE 7 | Budget impact of adopting biosimilar infliximab for gastroenterology per country, base case (including vedolizumab for Germany and United Kingdom).

Considering, for example:

- Vedolizumab

- Biosimilar etanercept

- Biosimilar rituximab

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Kanters T.A., Stevanovic J., Huys I., Vulto A.G., Simoens S. Adoption of Biosimilar Infliximab for Rheumatoid Arthritis, Ankylosing Spondylitis, and Inflammatory Bowel Diseases in the EU5: A Budget Impact Analysis Using a Delphi Panel. Front Pharmacol. 2017;8:322.

But impact of biosimilars may go further…

Impact on (incremental) innovation in originator biologics

Table: Average costs per one IV and one SC administration of trastuzumab and rituximab

	trastuzumab (n=82)			rituximab (n=44)		
	IV	**SC**	**Difference**	**IV**	**SC**	**Difference**
Preparation and administration costs						
Total staff costs	€ 29	€ 20	€ 9	€ 33	€ 24	€ 9
Staff costs administration	€ 20	€ 17	€ 3	€ 26	€ 18	€ 8
Staff costs preparation	€ 9	€ 3	€ 6	€ 7	€ 6	€ 1
Material costs	€ 15	€ 2	€ 12	€ 15	€ 3	€ 12
Premedication	€ 0	€ 0	€ 0	€ 1	€ 0	€ 0
Overhead	€ 75	€ 27	€ 47	€ 130	€ 61	€ 69
Societal costs	€ 51	€ 26	€ 24	€ 85	€ 57	€ 28
Total costs	**€ 169**	**€ 76**	**€ 93**	**€ 264**	**€ 146**	**€ 119**
Drug costs	€ 1,654	€ 1,651	€ 2	€ 1,871	€ 1,822	€ 49
Total costs per route of administration (including drug costs)	**€ 1,823**	**€ 1,728**	**€ 95**	**€ 2,136**	**€ 1,968**	**€ 168**

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Franken M., Kanters T., Groot C.U. Insights into healthcare and societal costs of subcutaneous injection and intravenous infusion of trastuzumab and rituximab in The Netherlands. https://www.imta.nl/assets/uploads/2017/12/Abstract-IMTA_2017_1205.pdf.

But impact of biosimilars may go further…

Lower price and similar effectiveness of biosimilars improve cost-effectiveness, implying that reimbursement can be granted or can be extended to other patient groups

TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis

Technology appraisal guidance [TA383] Published date: 01 February 2016

Guidance | Tools and resources | Information for the public | History

Overview

1 Recommendations

2 Clinical need and practice

3 The technologies

4 Committee discussion

5 Implementation

6 Review of guidance

7 Appraisal Committee members, guideline representatives and NICE project team

Guidance

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1 Recommendations

Next

1.1 Adalimumab, certolizumab pegol, etanercept, golimumab and infliximab are recommended, within their marketing authorisations, as options for treating severe active ankylosing spondylitis in adults whose disease has responded inadequately to, or who cannot tolerate, non-steroidal anti-inflammatory drugs. Infliximab is recommended only if treatment is started with the least expensive infliximab product. People currently receiving infliximab should be able to continue treatment with the same infliximab product until they and their NHS clinician consider it appropriate to stop.

https://www.nice.org.uk/guidance/ta383/chapter/1-Recommendations.

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But impact of biosimilars may go further…

Improved cost-effectiveness of biosimilars may change line of treatment

The experience of Neupogen (filgrastim) in the UK is instructive. Filgrastim is G-CSF used in the treatment of infection and neutropenic fevers in patients undergoing chemotherapy. Following the launch of the first biosimilar version of the medicine in November 2008, a number of Strategic Health Authorities (SHAs) in England opted to reassess their existing guidance relating to the use of G-CSF medicines.

The guidelines were updated to reflect the improved cost-effectiveness of biosimilar filgrastim versus alternative treatments; as a result, G-CSF was moved to first-line cancer treatment.

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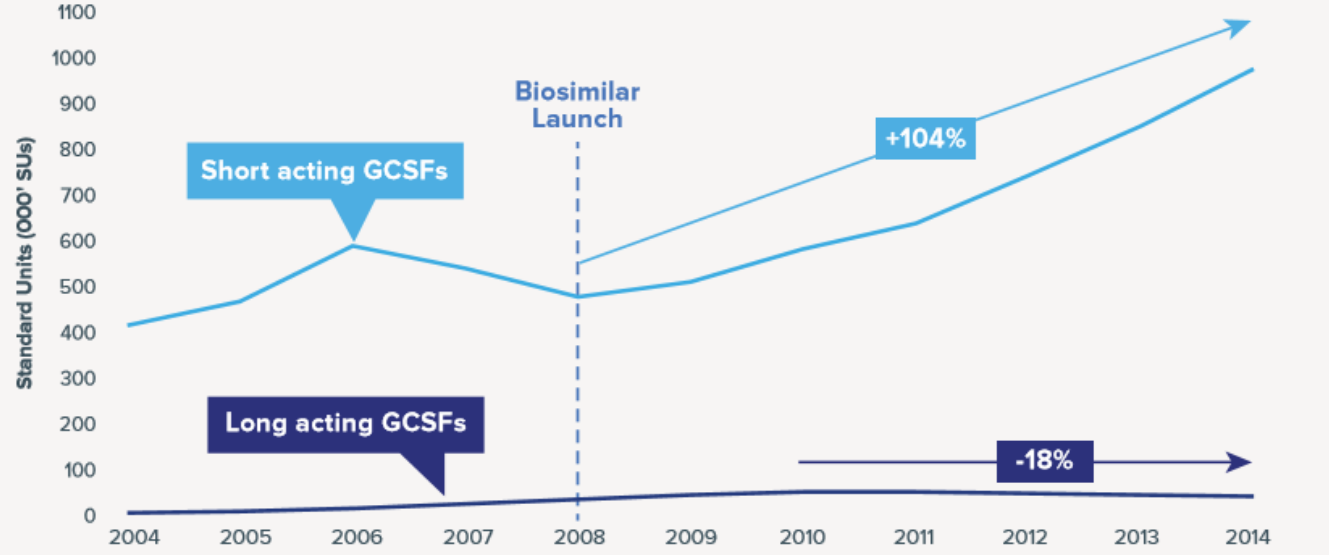
IMS Institute for Healthcare Informatics. Delivering on the Potential of Biosimilar Medicines. March 2016
https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/delivering-on-the-potential-of-biosimilar-medicines.pdf

But impact of biosimilars may go further…

Improved cost-effectiveness of biosimilars has budget impact



Source: IMS Health, MIDAS; IMS Consulting Group, Nov 2015

Notes:
Changes in development are depicted as overall changes in % between 2008 – 2014 (short acting) and 2010-2014 (long acting). UK market only.

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IMS Institute for Healthcare Informatics. Delivering on the Potential of Biosimilar Medicines. March 2016
Lopes G., Vulto A., Wilking N., van Harten W., Meier K., Simoens S. Potential solutions for sustaining costs of cancer drugs. Eur Oncology & Haematology 2017;13 (2):102-7.

But impact of biosimilars may go further…

Budget impact is influenced by:

Expanded access to treatment	Supply chain benefits	Wrap-around services	Financial incentives
• More patients treated with biologics • Patients treated sooner with biologics	• Reduced administrative burden • Manufacturing consistency • Inventory maintenance • Supply reliability	• Specialist pharmacy services • Patient access support mechanisms • Assistance with reimbursement administration	• Gainsharing • Uptake

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Simoens S., Jacobs I., Popovian R., Isakov L., Shane L.G. Assessing the Value of Biosimilars: A Review of the Role of Budget Impact Analysis. Pharmacoeconomics 2017;35(10):1047-1062.

But impact of biosimilars may go further…

wrap-around services and tendering

Some tendering authorities do not only focus on price, but also consider value-added services

Infliximab tenders take account of:

- Therapeutic Drug Monitoring assay and other assays
- Calculator demonstrating savings from biosimilars
- Information and educational material

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But impact of biosimilars may go further…

gainsharing

Arrangements which share savings generated from off-patent biologic and biosimilar competition between stakeholders (e.g. health care payers, hospitals, physicians and patients)

Non-cash gainsharing at hospital level	Gainsharing at hospital level	Gainsharing at level of physician (association)
Fixed drug program/hospital budgets Generated savings (e.g., via lower drug acquisition cost) enable more patients to be treated within existing budget and therefore help improve patient care	Hospitals entitled to keep generated savings (difference between DRG and expenditures) Hospitals incentivized to purchase T2A products** at low prices: difference between the reimbursement and price paid are split (hospitals, payers) Region of Campania: €2.7m savings in H2 2015 from biosimilar use lead to €1.3m being re-allocated to health units. On average, each unit received €165k reward to further invest in patient care	Agreement between physicians' association (KV Westfalen-Lippe) and statutory health insurance (Barmer GEK) to improve quality of care of patients with IBD*: – **Part of this agreement:** Absolute savings generated from prescribing infliximab biosimilar will be split equally between treating physician and health insurance Managed switching program (University Hospital Southampton): Payers benefit from reduced drug bills and providers can re-invest savings in improving patient care

Simon Kucher & Partners. Payers' price & market access policies supporting a sustainable biosimilar medicines market. Bonn; 2016.

But impact of biosimilars may go further…

uptake

Some countries implement financial incentives to promote biosimilar uptake

4.4.4.1. Biosimilars

Biosimilaire geneesmiddelen nemen meer en meer een belangrijke plaats in in het therapeutisch aanbod. Niettemin moet worden vastgesteld dat de uptake van deze geneesmiddelen in ons land in vergelijking met andere landen beperkt blijft hoewel op basis van de analyses van het Europees Geneesmiddelen Agentschap (EMA) ondubbelzinnig de gelijkwaardigheid wordt aangetoond met de originele biologische geneesmiddelen. Deze geneesmiddelen worden ook meer en meer in de publieke officina afgeleverd.

De Minister van sociale zaken en volksgezondheid heeft de wens uitgedrukt dat de NCAZ meewerkt aan het concretiseren van maatregelen die leiden tot een minimaal quotum biosimilaire specialiteiten in de totaliteit van de voorgeschreven en afgeleverde biologische geneesmiddelen in de publieke officina's. Hierbij zal een tijdelijke toeslag bij het accrediteringsforfait worden toegekend als incentive om deze doelstelling te helpen realiseren. Het voorschrijven van anti TNF geneesmiddelen zal als pilootproject worden gelanceerd.

Financial incentive for physicians to prescribe minimum percentage of anti-TNF biosimilars in retail market

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National Agreement Physicians-Health Insurance Funds 2018-2019.
http://www.riziv.fgov.be/nl/professionals/individuelezorgverleners/artsen/verzorging/Paginas/nationaal-akkoord-artsen-ziekenfondsen.aspx#.Wq4zM4WcFPY

Take home messages

Cost-effectiveness evolves over drug life cycle

- *Need to consider originator biologic, biosimilars, biologic alternatives, and future market entries*

Budget impact of biosimilars is not limited to price reductions

- *Need to consider expanded access to treatment, use of all drugs within a class, incremental innovation, reimbursement extension, change in treatment line, supply chain benefits, wrap-around services, financial incentives*

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Contact

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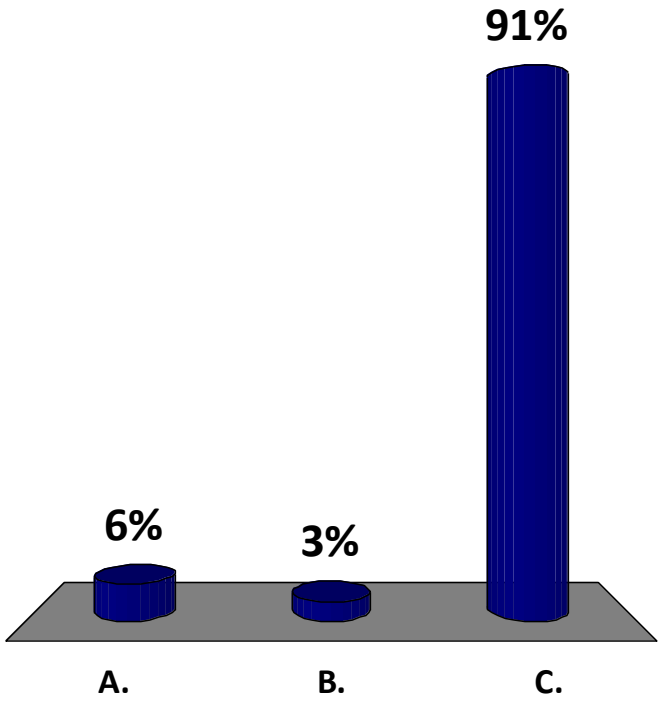
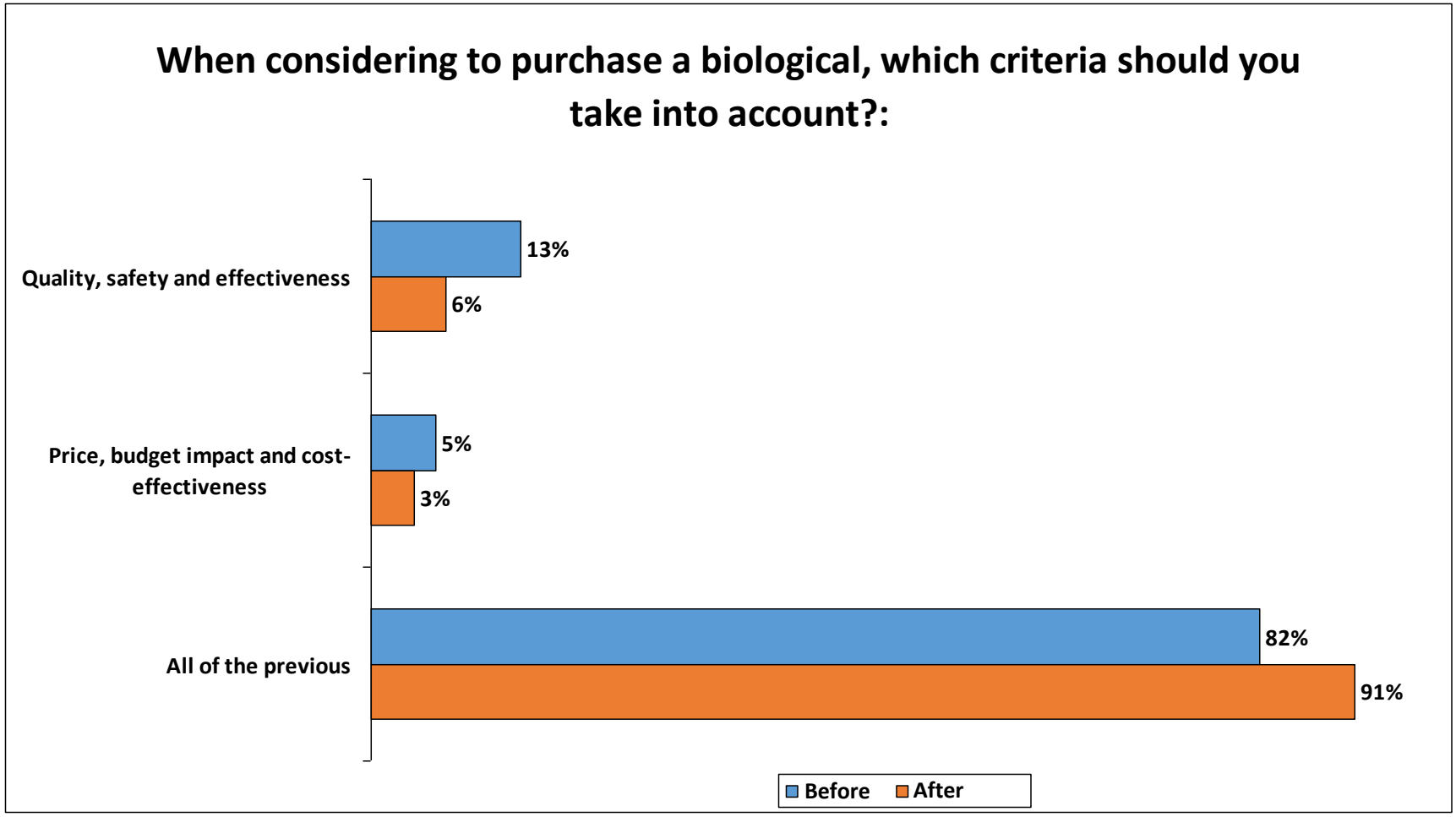
When considering to purchase a biological, which criteria should you take into account?:

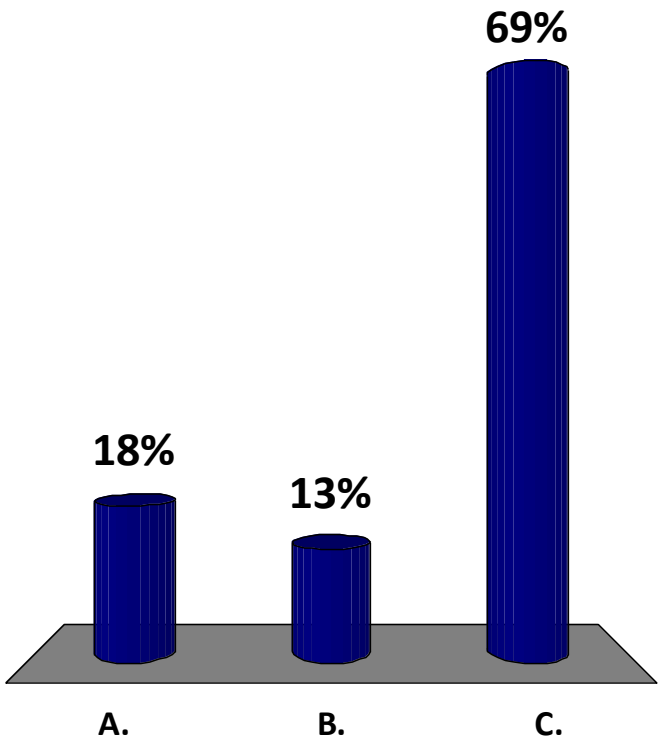
A. Quality, safety and effectiveness
B. Price, budget impact and cost-effectiveness
✓ C. All of the previous

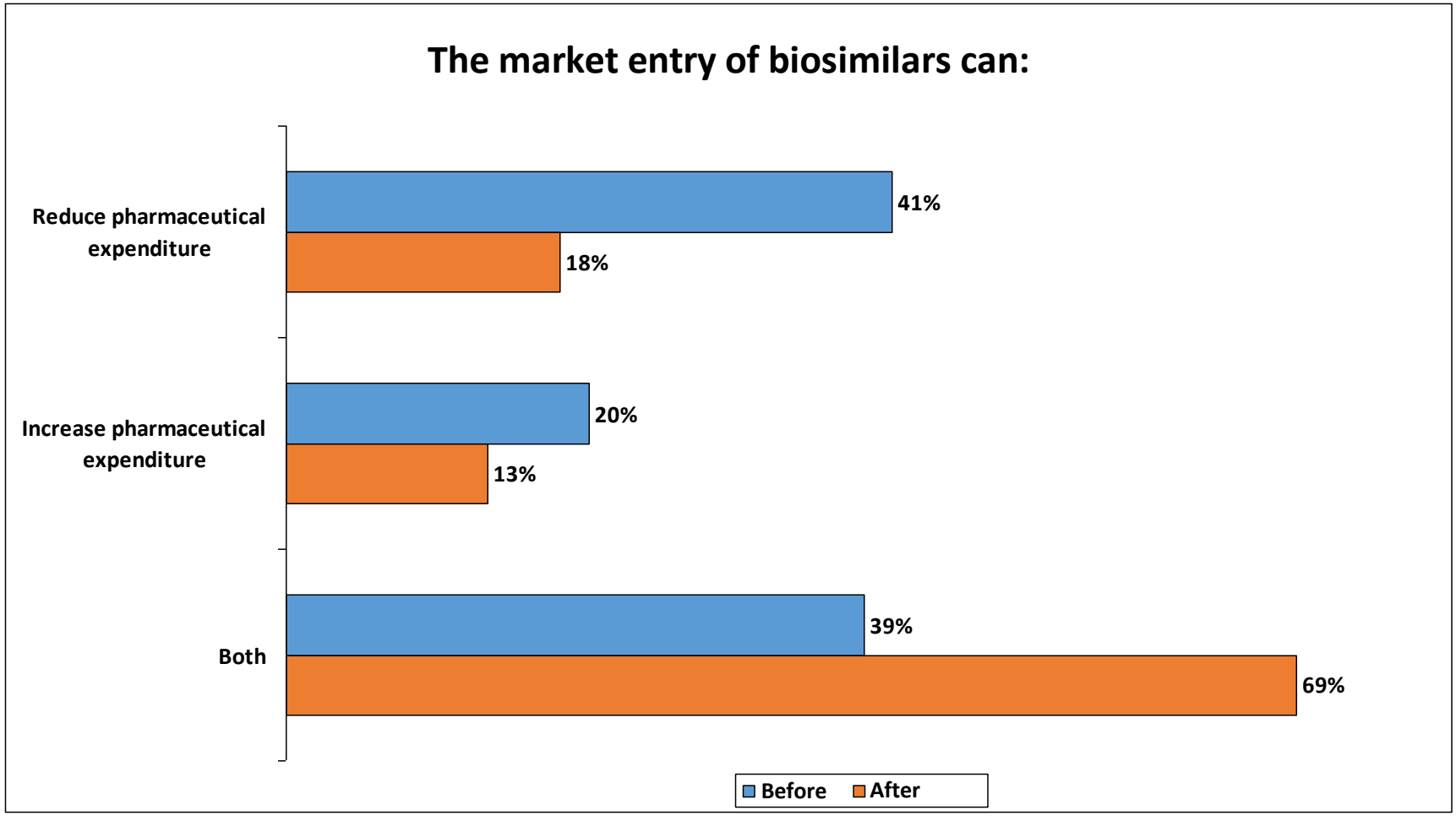



When considering to purchase a biological, which criteria should you take into account?:
Quality, safety and effectiveness
13%
6%
Price, budget impact and cost-effectiveness
5%
3%
All of the previous
82%
91%
Before
After

The market entry of biosimilars can:

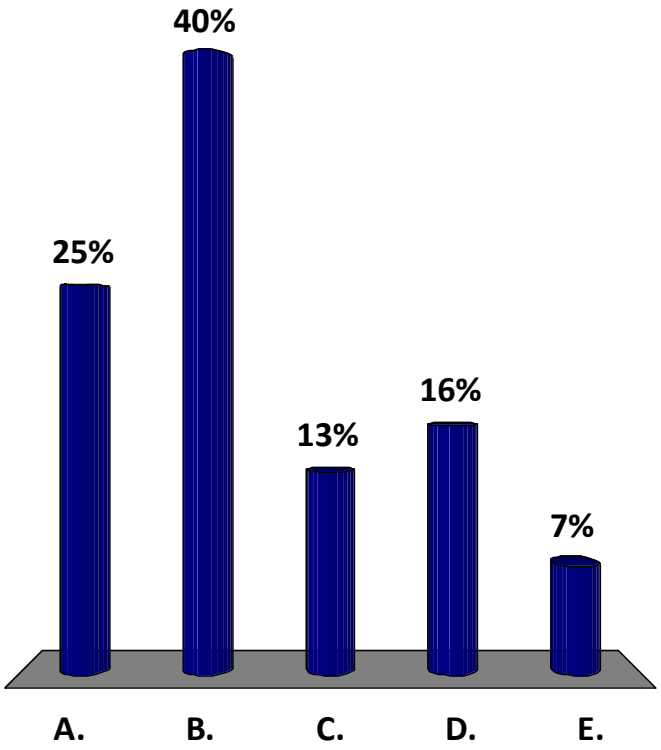
A. Reduce pharmaceutical expenditure
B. Increase pharmaceutical expenditure
✓ C. Both




The market entry of biosimilars can:
Reduce pharmaceutical expenditure
41%
18%
Increase pharmaceutical expenditure
20%
13%
Both
39%
69%
Before
After

Do you agree that the aim of policy should not be to stimulate biosimilar uptake, but to incite competition between reference product and biosimilars?

- ✓ A. Strongly agree
- ✓ B. Agree
- C. Neither agree nor disagree
- D. Disagree
- E. Strongly disagree



Do you agree that the aim of policy should not be to stimulate biosimilar uptake, but to incite competition between reference product and biosimilars?