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Improving healthcare decisions

VALUE ASSESSMENT OF BIOSIMILARS: CHALLENGES AND CONSIDERATIONS

Conflicts of interest

SS is one of the founders of the KU Leuven Fund on Market Analysis of Biologics and Biosimilars following Loss of Exclusivity (MABEL). He was involved in a stakeholder roundtable on biologics and biosimilars sponsored by Amgen, Pfizer and MSD; and he has participated in advisory board meetings for Amgen, Pfizer and Sandoz. SS has contributed to studies on biologics and biosimilars for Hospira, Celltrion, Mundipharma and Pfizer; and he had speaking engagements for Amgen, Celltrion and Sandoz.

EM is an employee of Janssen Cilag, but worked at KU Leuven at the time of the literature review

DD is an employee of the National Institute for Health and Care Excellence

DC is an employee of Amgen

Biosimilar value assessment: not as easy as it seems!

We identified the following challenges in the HTA of biosimilars:

- choice of appropriate technique of economic evaluation and of appropriate comparator
- approach to filling the clinical evidence gap when biosimilar indication has been granted on basis of extrapolation
- approach to biosimilar value assessment in biologic-naïve patients and in biologic-experienced patients
- lack of clarity as to how biosimilar value assessment accounts for the potential ‘nocebo’ effect
- management of uncertainty and role of managed entry agreements for biosimilars
- valorization of value-added services
- valorization of expanding access to treatment

Steven Simoens
KU Leuven
Insights from literature

Dalia Dawoud
NICE
Perspective from HTA agency

Evelien Moorkens
KU Leuven
Insights from literature

Delphine Courmier
Amgen
Perspective from industry

SECTION

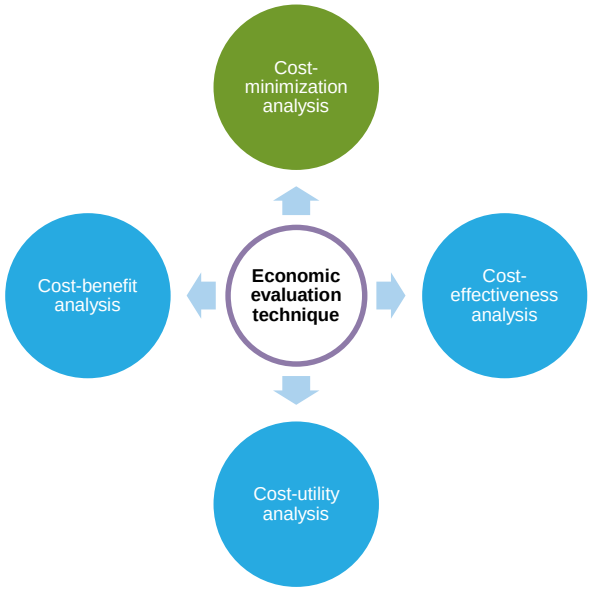
1

ISPOR Biosimilar SIG key project on biosimilar value assessment

Steven Simoens, Evelien Moorkens

Literature insights are illustrated with key references, but presentation does not list all relevant references

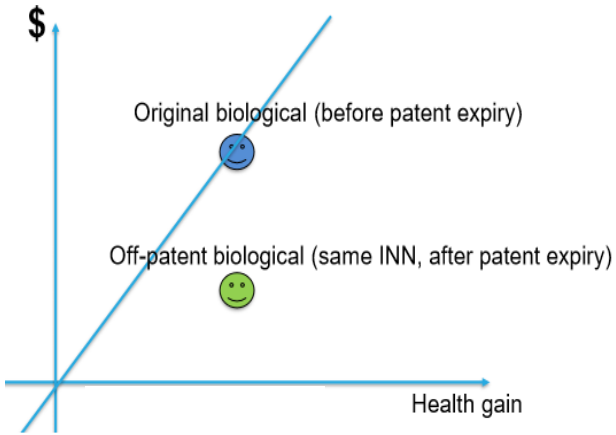
Choice of appropriate technique for economic evaluation and of comparator: *challenge*



- Which technique is recommended to conduct economic evaluation of a biosimilar?
- Which technique of economic evaluation applies to biosimilars under which circumstances? Does it depend on:
  - the meaning of ‘similarity’?
  - biosimilar reimbursement application in same indication/population as reference biologic?
  - absence of use or reimbursement of reference biologic for that indication/population?
  - standard of care (reference biologic or non-biological therapy)?
  - administration form of biosimilar and reference biologic?
  - availability of next-generation biologic?

Choice of appropriate technique for economic evaluation and of comparator: *considerations*

a) Relative (long-term) efficacy and safety of biosimilar vs reference biologic



If appropriately designed and adequately powered equivalence or non-inferiority studies demonstrate similar effectiveness of biosimilar and reference biologic, a cost-minimisation analysis needs to be carried out

Joint forum of ISPOR Special Interest Group on Biosimilars and ISPOR Central Eastern European Consortium. ISPOR Copenhagen, November 2019.
Simoens. ClinicoEconomics and Outcomes Research 2011:3 29–36. Hughes. Clin Pharmacol Ther. 2010;87(3):257–261.

Choice of appropriate technique for economic evaluation and of comparator: *considerations*

What if such clinical studies are not available, studies do not consider long-term efficacy and safety, or studies employ surrogate outcome measures?

Two approaches can be followed:

- Conduct scenario analyses
- If later evidence refutes biosimilar similarity to reference biologic, then biosimilar value needs to be re-assessed and full economic evaluation is required

Ventola. P&T 2013,38:6,329-335. Stewart et al. Current Medical Research and Opinion 2010,26:9,2119-2126.

Choice of appropriate technique for economic evaluation and of comparator: *considerations*

b) Absence of use or reimbursement of reference biologic for that indication/population
   - If reference biologic with same INN is not reimbursed, is not reimbursed for indication of biosimilar, has not been appraised or is not standard of care, a full economic evaluation of biosimilar as compared to standard of care needs to be carried out

c) Administration form
   - If there is difference in administration form, this may lead to different costs and/or outcomes, and full economic evaluation is required

Mestre-Ferrandiz and Towse. London: Office of Health Economics, 2014. Simoens. Expert Review of Pharmacoeconomics and Outcomes Research (in press).

Choice of appropriate technique for economic evaluation and of comparator: *considerations*

This point of view seems to be supported by HTA agencies

SMC, Scotland	A full submission is not needed for indications of the reference product that have been accepted for reimbursement. A full submission is required for indications/populations for which the reference product is not recommended.
NICE, England	Biosimilars might be included in a Multiple Technology Appraisal.
AWMSG, Wales	The advice for the reference product will automatically apply for the biosimilar (same indications/populations). When the reference product is not reimbursed, it is advised to engage with AWMSG.
TLV, Sweden	A health economic evaluation is not required for a biosimilar. Reference is made to the data provided for the originator product. The price of the biosimilar cannot exceed the price of the originator product.
HAS, France	Biosimilars are included in ASMR class V: no added therapeutic value. A health economic assessment is not conducted for these products.
KCE, Belgium	Class 2 reimbursement is applied for biosimilars, where no added value is claimed. Applications for reimbursement in class 2 are not required to include an economic evaluation of the medicine.
Germany	Biosimilars are not included in HTA assessment.
ZIN, Netherlands	No specific guidelines for biosimilars. An economic evaluation is not required when no added therapeutic value is claimed (List 1A).
AOTMiT, Poland	Biosimilars are not included in an HTA assessment, except when the reference product is not reimbursed.
Hungary	Biosimilars can be reimbursed through a simplified procedure when the reference product is already reimbursed. This simplified procedure does not require an economic evaluation, only a comparison of price.

SMC: Scottish Medicines Consortium, NICE: National Institute for Health and Care Excellence, AWMSG: All Wales Medicines Strategy Group, TLV: Dental and Pharmaceutical Benefits Agency, HAS: High Health Authority, ASMR: Improvement in Actual Benefit, KCE: Belgian Health Care Knowledge Centre, ZIN: National Health Care Institute

Moorkens et al. Journal of Market Access & Health Policy 2020,8:1,1739509.

Choice of appropriate technique for economic evaluation and of comparator: *considerations*

d) Comparator and stable/new patients

		Comparator		
		Non-biologics (1)	Biologics with same INN (2)	Other biologics with different INN (3)
New patients (A)	decision problem	Choice of starting therapy		
	necessary clinical evidence	Relative effectiveness of biosimilar compared to non-biologics	Phase III trial result	Relative effectiveness of biosimilar compared to biologics with different INN
	necessary health economic analysis*	• CUA • BIA	• CMA • BIA	• CMA or CEA/CUA** • BIA
Stable patients on therapy (B)	decision problem	single switch of patients on non-biologicals to biosimilar	single switch of patients on original biologic to its biosimilar alternative	not realistic clinical scenario
	necessary clinical evidence	Relative effectiveness of switching to biosimilar compared to staying on non-biologics	• Phase III trial results (if available) • Risk assessment for immunogenicity based on literature review or existing clinical trial data • (Ongoing data collection)	
	necessary health economic analysis*	• CEA/CUA • Budget impact	• CMA (in expedited review) or CEA/CUA (in full review) • Budget impact	

*CMA: Cost-minimization Analysis; CEA: Cost-effectiveness Analysis; CUA: Cost-utility Analysis; BIA: Budget Impact Analysis; INN: International Non-proprietary Name

**Choice of economic evaluation depends on the assumption and/or evidence on equal health gain

Inotai et al. Journal of Bioequivalence and Bioavailability 2017,9:467-472.

Choice of appropriate technique for economic evaluation and of comparator: *considerations*

e) Consideration of criteria other than efficacy/safety
   - Apply multi-criteria decision analysis to account for multiple relevant decision making criteria (e.g. safety, budget impact, cost-effectiveness/unmet medical need, patient preferences and strategic considerations)

Zah et al. Value in Health 2015,A703.

Approach to filling clinical evidence gap when biosimilar indication was granted on basis of extrapolation: *challenge*

- Cost-effectiveness of a biosimilar can be demonstrated by an economic evaluation based on a clinical study. However, a biosimilar indication can be granted on the basis of extrapolation, implying that no clinical study investigating the safety and efficacy of the biosimilar in the extrapolated indication has been carried out

How can the value of the biosimilar in the extrapolated indication be assessed?

Approach to filling clinical evidence gap when biosimilar indication was granted on basis of extrapolation : *considerations*

- Payers accept principle of extrapolation, but some doubts remain
- You only need to address clinical evidence gap if there is a need to conduct a full economic evaluation of biosimilar
  - For instance, a non-inferiority study comparing biosimilar and reference biologic has been carried out in primary indication, but full economic evaluation needs to establish cost-effectiveness of biosimilar vs a non-biological therapy in extrapolated indication
- Approaches to fill clinical evidence gap:
  - Draw on data from reference biologic trials or conduct indirect comparison, and carry out sensitivity analyses on clinical efficacy given that such data are likely to be of lower quality

Pinheiro et al. Value in Health 2014,A326. Catt et al. Pharmacoeconomics 2019;37(12):1509-1523. Ventola. P&T 2013,38:6,329-335.

Biosimilar value assessment in biologic-naïve patients and biologic-experienced patients: *challenge*

- Does value assessment of a biosimilar depend on whether it is administered to patients who start biologic therapy or to patients who already receive biologic therapy?

Biosimilar value assessment in biologic-naïve patients and biologic-experienced patients: *considerations*

- Same value assessment unless previous treatment with biologic with different INN or switching process from reference biologic to biosimilar with the same INN influences costs and/or outcomes of therapy in patients:
  - Previous biologic treatment can alter impact of subsequent biologic therapy
  - Switching process may generate health care professional time costs and may be associated with nocebo effect

- In these cases, conduct separate economic evaluations for biologic-naïve patients and for biologic-experienced patients

Kim et al. Drugs 2020,80:99–113.

How does biosimilar value assessment account for the 'nocebo' effect? *challenge*

- The nocebo effect refers to a patient's negative expectation towards switching from reference biologic to its biosimilar. The occurrence of nocebo effect may translate into decreased adherence to therapy or even therapy discontinuation and, hence, has a negative impact on the cost-effectiveness of biologic therapy

Whether and how can the value assessment of a biosimilar account for the potential nocebo effect?

Simoens and Vulto. Expert Opinion on Biological Therapy 2021,21:1,9-17.

How does biosimilar value assessment account for the ‘nocebo’ effect? *considerations*

- To date, no economic evaluation of a biosimilar has considered the nocebo effect

- There is a need to conduct scenario analyses, i.e. scenario without nocebo effect and scenario with nocebo effect

Management of uncertainty and role of managed entry agreements for biosimilars: *challenge*

- Stakeholders such as policy makers, physicians and patients may face residual uncertainties associated with biosimilar use: for example, is it appropriate to switch patients from a reference biologic product to its biosimilar; from one biosimilar to another biosimilar; from a biosimilar back to the reference biologic product, or to switch patients on multiple occasions?

Is there a role for managed entry agreements (including collection of real-world data, pharmacovigilance data, switching data, outcome and adverse event data) to address residual uncertainties associated with biosimilar use?

Management of uncertainty and role of managed entry agreements for biosimilars: *considerations*

- At market launch, there may be residual uncertainties regarding long-term efficacy and safety of biosimilars and about impact of switching practices. With respect to latter, any impact on cost-effectiveness of therapy originates from practice of switching, but not from biosimilar itself
- Possible approaches:
  - Re-assess cost-effectiveness of biosimilar at multiple points during lifecycle when new evidence becomes available
  - Conduct scenario analyses
- Application of managed entry agreements to biosimilars has not been discussed or proposed in the literature

Ventola. P&T 2015,40:10,680-689. Stewart et al. Current Medical Research and Opinion 2010,26:9,2119-2126.

Valorization of value-added services: *challenge*

Value-added services

Disease programs designed to enhance patient adherence

Programs to improve hospital services & treatment delivery (e.g. infusion therapy)

Physician and patient education

Patient lifestyle management

- Some manufacturers provide a biologic in combination with value-added services in order to improve patient and health outcomes and to gain a competitive advantage

How does the provision of value-added services impact the cost-effectiveness of a biosimilar?

Valorization of value-added services: *considerations*

- The literature recognises existence of value-added services, but is silent on its valorization
- The impact of value-added services is distinct from the impact of the biosimilar itself, but provision of value-added services may influence costs and effectiveness of biosimilar therapy
- Possible approaches:
  - Conduct scenario analysis (with scenario establishing cost-effectiveness of biosimilar alone and scenario calculating cost-effectiveness of biosimilar in combination with value-added services)
  - Apply multi-criteria decision analysis to score biosimilar and comparator in terms of multiple criteria, including value-added services

Simoens and Cheung. Journal of Market Access & Health Policy 2020,8:1,1705120.

Valorization of expanding access to treatment: *challenge*

- In jurisdictions where access to reference biologic is restricted or not provided at all, biosimilars may offer extra health gain at an incremental cost as compared to the current (non-biologic) reimbursed treatment

How can the value of expanding access to treatment be accounted for in economic evaluation of a biosimilar?

Valorization of expanding access to treatment: *considerations*

- Multiple studies calculate how many additional patients with same disease can be treated with the biosimilar or how many additional patients with different disease can be treated with another therapy as a result of biosimilar cost savings
- No studies have valorized expanded access to treatment as a result of biosimilars
- This could be done by conducting an economic evaluation of treating these additional patients as compared to relevant alternative and calculating the total number of QALYs gained in this patient population by funding this treatment with the savings generated by the biosimilar

McBride et al. Journal of Medical Economics 2020,23:8,856-863. McBride et al. Value in Health 2017,A443. McBride et al. Blood 2017,130(Suppl 1):3380.

SECTION

2

VALUE ASSESSMENT OF BIOSIMILARS: CHALLENGES AND CONSIDERATIONS

HTA perspective

Dalia Dawoud, PhD

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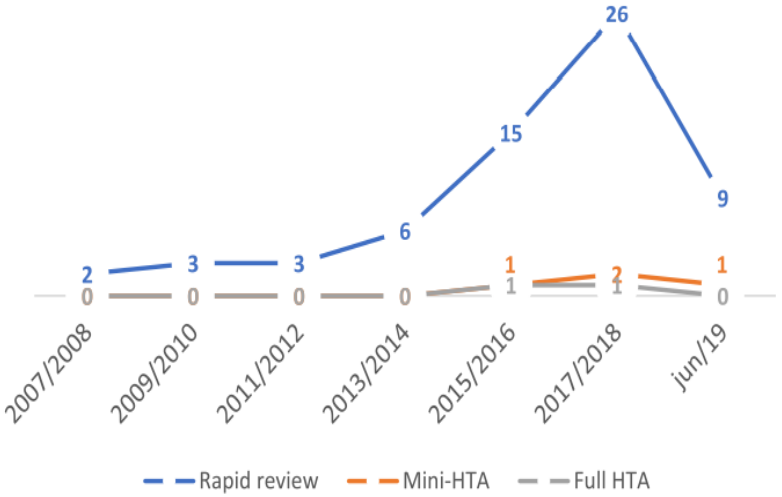
Co-Chair, Member Engagement, ISPOR Biosimilars Special Interest Group

Disclaimer: The views expressed are my own and not those of NICE

HTA of biosimilars: Current status

- Up to July 2019, **EMA** had approved **55 biosimilars of 16 biologics**, mostly between 2017 and 2019[1]
- **Ascef et al (2020)** identified **70 HTA reports for biosimilars of 16 biologic products** (65.71% in 2015–2018) produced by **13 HTA organisations** from **10 countries**
- Most of the HTA reports were produced **between 2017 and 2018**



Production of HTA reports of biosimilars from 2007 to June 2019

1. Ascef BO, Lopes ACF, de Soárez PC. Health technology assessment of biosimilars worldwide: a scoping review. Health Res Policy Syst. 2020 Aug 26;18(1):95. doi: 10.1186/s12961-020-00611-y. PMID: 32843051; PMCID: PMC7448328.

HTA of biosimilars: Current status

- Of the 70 HTA reports included[1]:
  - 2 (2.86%) **full HTA**
  - 4 (5.71%) **mini-HTA**
  - **64 (91.43%) rapid reviews**
- **16 active substances** from 4 main anatomical groups (range **1 to 17 reports per active substance**)
- Most frequently assessed biosimilars:
  - **Infliximab**: 17 HTA reports (24.29%),
  - **Pegfilgrastim** (10%)
  - **Insulin glargine** and **trastuzumab** (both 8.57%)

1. Ascef BO, Lopes ACF, de Soárez PC. Health technology assessment of biosimilars worldwide: a scoping review. Health Res Policy Syst. 2020 Aug 26;18(1):95. doi: 10.1186/s12961-020-00611-y. PMID: 32843051; PMCID: PMC7448328.

HTA of biosimilars: Current status

- **Special considerations** for biosimilars:
  - immunogenecity
  - the risk of switching
  - interchangeability
  - extrapolation to one or more conditions

- **No report rejected the adoption or reimbursement** of the biosimilar assessed

1. Ascef BO, Lopes ACF, de Soárez PC. Health technology assessment of biosimilars worldwide: a scoping review. Health Res Policy Syst. 2020 Aug 26;18(1):95. doi: 10.1186/s12961-020-00611-y. PMID: 32843051; PMCID: PMC7448328.

HTA of biosimilars: Process and methods

- **NICE**
  - Position Statement (2015)
  - 2020 Methods update consultation:

    "There is parallel work being done to consider how NICE should approach **scenarios in which the reference product was not submitted to or not recommended by NICE in a particular indication** that a biosimilar becomes available. **The position statement will be reviewed as part of this parallel work**."

NICE position statement (2015)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

NICE's biosimilars position statement

a. Published Appraisals

2. NICE has decided that normally all relevant published guidance that includes the originator molecule will apply to the biosimilar medicinal product at the time it is made available for use in the NHS. A funding direction will apply to a new biosimilar if the active drug substance has already been recommended by NICE.

5. NICE will consider appraising the evidence for any new relevant biosimilar product(s) when a published Technology Appraisal is considered for review; the introduction of a biosimilar would not automatically trigger an earlier consideration for review or an automatic decision to update the guidance.

NICE position statement

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

NICE's biosimilars position statement

b. Future appraisal topics (before invitation to participate or scoping)

- Intervention

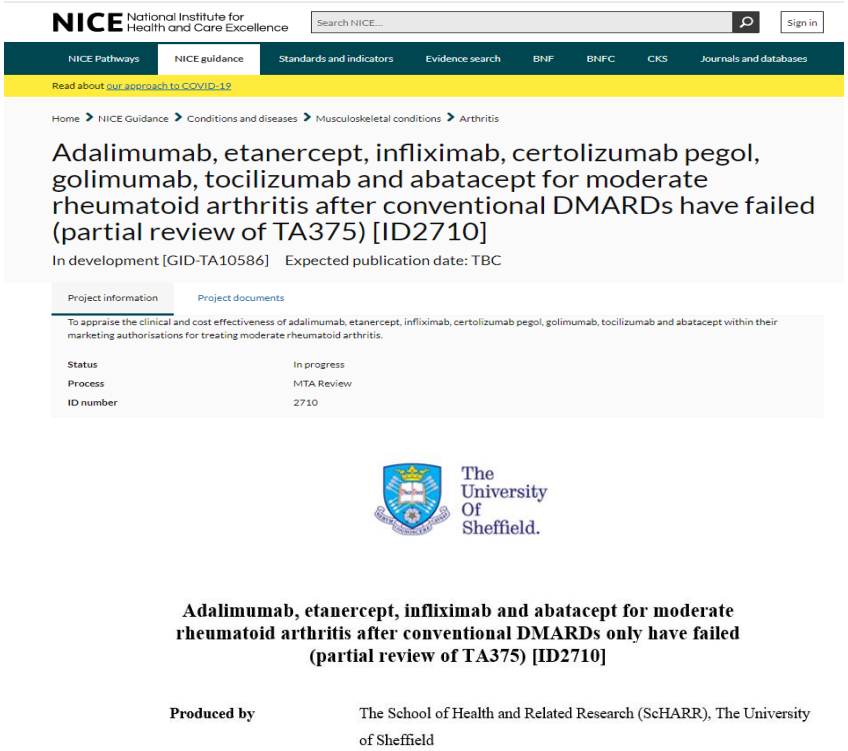
- Comparator

10. Biosimilar medicines will be considered to differ from the originator product only in terms of price.

HTA of biosimilars: Example

- partial review (ongoing)
  - **biosimilar versions of adalimumab and etanercept became available**,
  - changes in the prices for some of the other technologies.

- includes **4 different biological medicines** as either the originator medicine (the medicine first authorised for use) or a biosimilar product (**MTA**)



HTA of biosimilars: Example

Clinical and cost effectiveness assessment

- The partial review has taken a **pragmatic approach**, which was consulted on in a review proposal,
- The **assessment group** used the **original NMA** and made only **minor updates to the original model**
- The assessment group's **base-case analyses used the cheapest formulation of each intervention** and prices included homecare support (when available)

HTA of biosimilars: Example

- **Other considerations**
  - **New options** for those with moderate RA
  - **Increased patient choice**

HTA of biosimilars: Challenges and considerations

- **Operational**:
  - Reference biologics with **multiple indications**
  - **Recommendation**: by brand name or molecule?
- **Methodological**:
  - Different **formulations**/route of administration
  - Which price to use?
  - Including homecare costs

  - Assuming equivalence compared to reference biologic (**no added therapeutic value**?)

Concluding Remarks

- Progress has been made towards **streamlining the appraisal process** of biosimilars

- **More to be done** to refine the **approach to valuing biosimilars** in order to reflect all elements of value and characterise any outstanding uncertainties

Thank you!

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SECTION

3

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Trend to streamlining of biosimilar HTA assessment when originator is already recommended

Standard HTA process

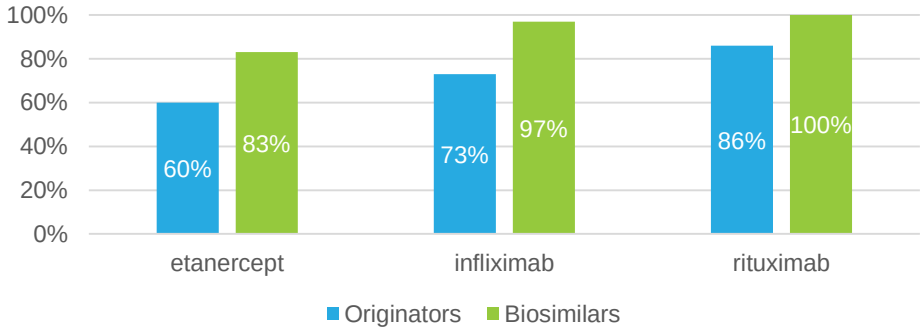
Biosimilar HTA pathway

No national biosimilar HTA

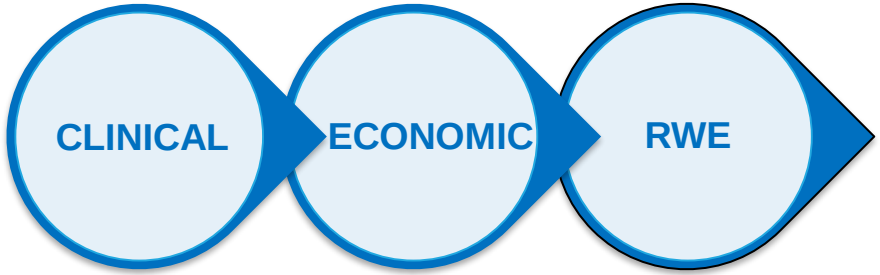
Maintaining robust regulatory standards is critical in light of increasingly streamlined HTA biosimilar processes

- Faster assessment time for biosimilars (**288 days**) vs their originators (**853 days**) as of 2018

Ratio of positive HTA recommendations of biosimilars and originators
(NICE, SMC, HAS, IQWIG, TLV, CADTH, PBAC)



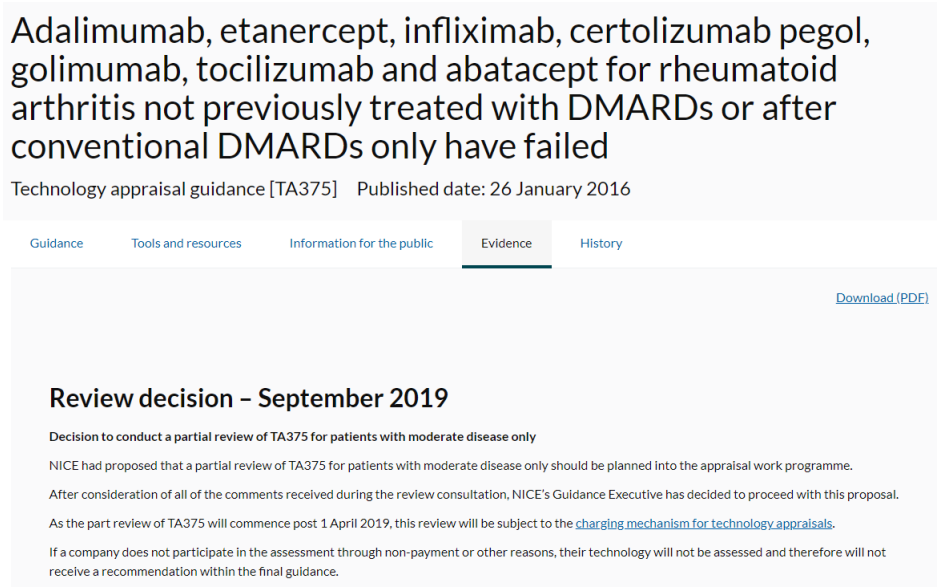
- In practice, HTA dossier content was focused on Totality of Evidence and Economic Value



- Based on totality of evidence:
  - ✓Analytical similarity data
  - ✓PK/PD
  - ✓Comparative clinical data (Ph1 & Ph3)
- Limited to Cost-Minimization Analysis (CMA) & Budget Impact Model (BIM)
- Post-marketing studies rarely requested (none since 2018)

HTA assessment of biosimilars when originator was not recommended

- In the initial TA375 MTA in 2016, adalimumab was not recognized as cost-effective to treat moderate RA by NICE
- The **streamlined re-assessment** initiated in 2019 reversed the recommendation for adalimumab. Thanks to biosimilars, adalimumab is now cost-effective according to the NICE threshold
- Biosimilars enabled coverage and reimbursement by NHS England and this brings a new treatment option to moderate RA patients in the UK



Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed

Technology appraisal guidance [TA375] Published date: 26 January 2016

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

Download (PDF)

Review decision – September 2019

Decision to conduct a partial review of TA375 for patients with moderate disease only

NICE had proposed that a partial review of TA375 for patients with moderate disease only should be planned into the appraisal work programme.

After consideration of all of the comments received during the review consultation, NICE's Guidance Executive has decided to proceed with this proposal.

As the part review of TA375 will commence post 1 April 2019, this review will be subject to the charging mechanism for technology appraisals.

If a company does not participate in the assessment through non-payment or other reasons, their technology will not be assessed and therefore will not receive a recommendation within the final guidance.

References
"HTAs of bevacizumab biosimilars: could a demonstration of cost-effectiveness change the recommendation for reimbursement versus the originator?" | Hinoosha, Courmier D F | PHP240 ISPOR Barcelona November 2018
https://www.nice.org.uk/guidance/ta375

Integrating biosimilars in the therapeutic strategy

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

https://esmoopen.bmj.com/content/2/3/e000245

Automatic substitution, which might be practice for generics, should therefore be avoided in the field of biosimilars. Interchangeability and switching should only be permitted if:

(1) the physician is well informed about the products;
(2) the patient is fully briefed by the physician and
(3) a nurse is closely monitoring the changes and tracking any adverse events

NICE
National Institute for Health and Care Excellence

Rheumatoid arthritis in adults: management

NICE guideline
Draft for consultation, January 2018

ECCO European Crohn's and Colitis Organisation

https://academic.oup.com/ecco-jcc/article/11/1/26/2632162

ECCO Position Statement on the use of Biosimilars for Inflammatory Bowel Disease – An Update

ASCO®
AMERICAN SOCIETY OF CLINICAL ONCOLOGY

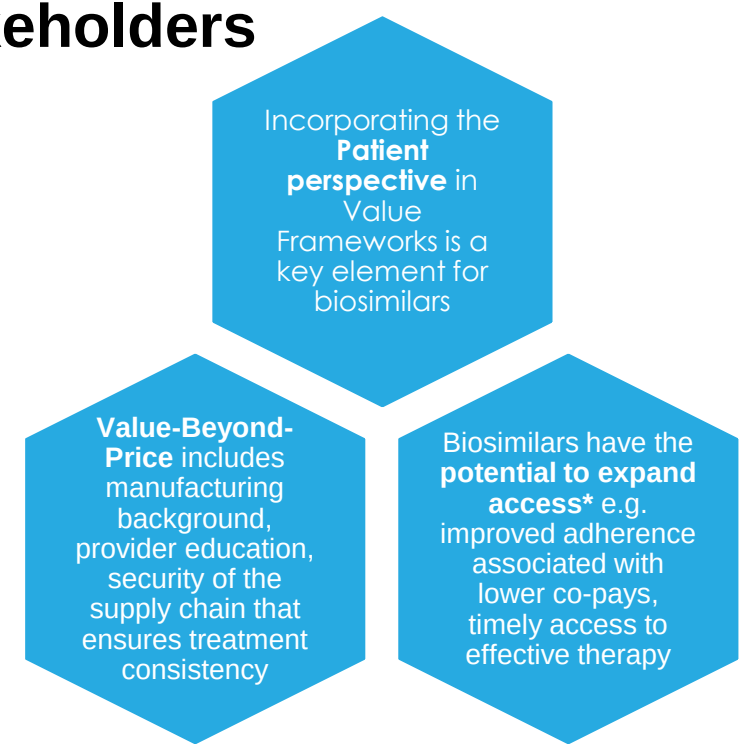
http://ascopubs.org/doi/full/10.1200/JCO.2017.77.4893

eular
fighting rheumatic & musculoskeletal diseases together

https://www.eular.org/myUploadData/files/Biosimilars_2015.pdf

TNF inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab and biosimilars), abatacept, tocilizumab and under certain circumstances, rituximab, are essentially considered to have similar efficacy and safety. EULAR listed the five presently approved agents and decided also to mention biosimilars under the provision that they become approved in the USA and/or Europe.

Recognizing the full value of biosimilars for all stakeholders



References
* IQVIA (2018). The Impact of Biosimilar Competition in Europe. https://www.medicinesforeurope.com/wp-content/uploads/2017/05/IMS-Biosimilar-2017_V[illegible].pdf
Smeeding J, Malone DC, Ramchandani M, Stolshek B, Green L, Schneider P. Biosimilars: considerations for payers. P T. 2019;44(2):54-63

Biosimilars and Hospital-Based HTA

CLINICAL

- Quality of biosimilar supportive evidence across all patient populations receiving originator in hospital (naïve/switch)
- Confidence to prescribe and acceptance of HCPs and Patients

ECONOMIC

- Savings through procurement vs originator
- Balanced by cost of adopting new drug on formulary (e.g. hospital IT system update)

HUMANISTIC

- Quality of Care Criteria can impact hospital revenue
- Patient outcomes and satisfaction can be impacted by PSPs that not all biosimilars may offer

OPERATIONAL

- Manufacturer reliability (risk of shortage)
- Inventory cost if numerous products stocked
- Increased risk of medication error

References
https://www.centerforbiosimilars.com/news/australias-pbac-recommends-2-adalimumab-biosimilars-for-pharmacylevel-substitution
http://www.adhophta.eu/ | https://htai.org/interest-groups/hospital-based-hta