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Considerations and reflections concerning implementation of biosimilar MABs in the clinic - focus on trastuzumab

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DISCLOSURE

- Conflict of interest: Nothing to disclose

The birth of biosimilars – European perspective

- Directive 2001/83/EC (as amended)
- Article 10: „Generics“ and legal basis for „biosimilars“
  - Article 10(2a): *„**Generic medicinal product**” shall mean a medicinal product which has **the same** qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, (…).”*
  - Article 10(4): *„Where a **biological medicinal product which is similar** to a reference biological product does not meet the conditions in the definition of generic medicinal products, owing to, in particular, **differences relating to raw materials or differences in manufacturing processes of the biological medicinal product** and the reference biological medicinal product, the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided.”*

Large molecule biosimilars (MABs)

- Have given rise to concerns related to their pharmaceutical quality, safety (especially immunogenicity) and efficacy (particularly in extrapolated indications)
- Confusion about the practice of interchangeability between originator and biosimilar (pharmacy without consulting the prescriber?)
- Concern about traceability (batch number, tradename etc.)

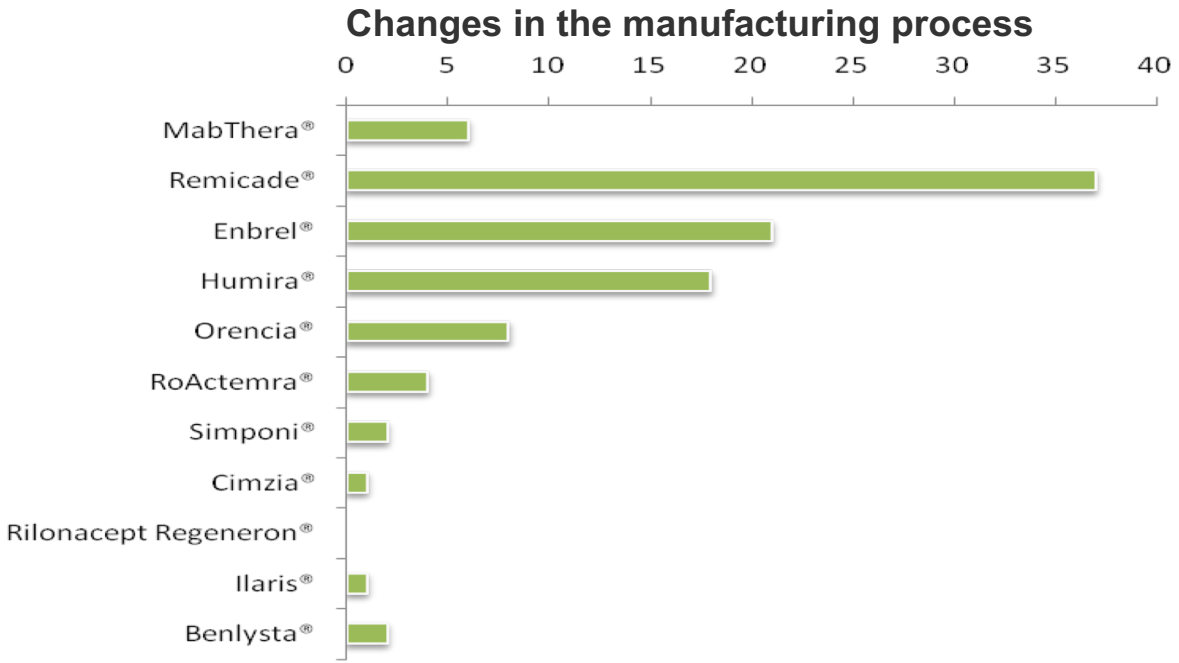
Biosimilar medicine in general; EMA

Requirements for authorisation of biosimilar medicines:

- For biosimilar medicines, the company needs to carry out studies to show that the medicine:
  - is similar to the reference medicine
  - does not have any meaningful differences from the reference medicine in terms of quality, safety or efficacy
  - EMA has very high demands regarding similarity/comparability ie. physiochemical and biological characterization, immunogenicity, PK/PD studies etc. → *"no easy solutions…no fast track approval…"*

http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/document_listing/document_listing_000318.jsp

Changes to originator biologicals



Schneider CK: Biosimilars in rheumatology: the wind of change. Ann Rheum Dis
(Data source: EPARs on EMA website)

Biosimilar/originator switch

- Europe: NOT an EMA matter, but local/national authorities…

- USA: FDA → Two possible ways of application

    1. Biosimilar product (similar to reference product in conventional way)
    2. Interchangeable biosimilar product (meeting of additional standards required)

Biosimilar MABs

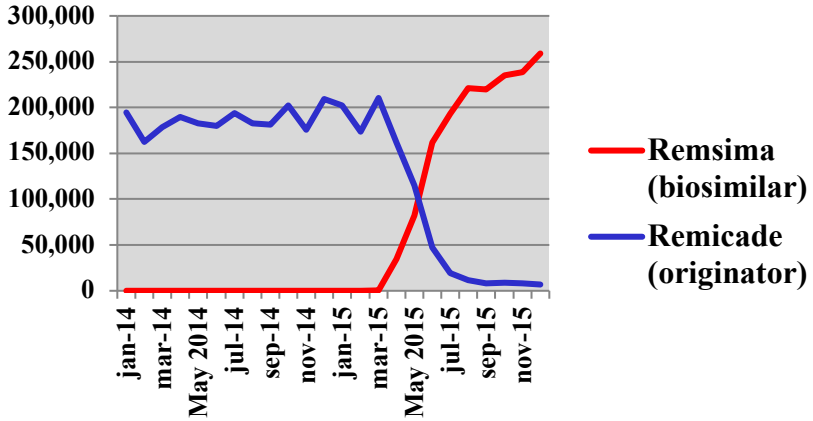
- Present: Infliximab (fx CT-P13, Remsima/Inflectra), etanercept (fx SB4, Benepali) and Rituximab but many more soon to come…. *trastuzumab, adalimumab…*
- Use of biosimilars can reduce medicine expenditures! *At the moment the only reason for application…*
- Bio-betters!?

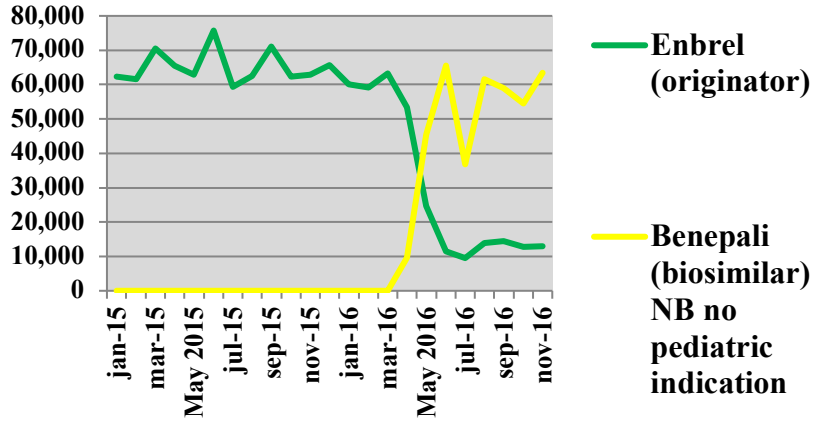
*MR recommendation regarding application of biosimilar infliximab and etanercept (switching)

1. Patients treated with biologics for the first time
2. Patients who failures one biologic treatment and MR guidelines recommend switch to another TNFi
3. Unless special individual patient related issues need to be taken into account, patients well treated with infliximab and etanercept can be switched to the cheapest originator/biosimilar

**MR = The National Council of Medicine*

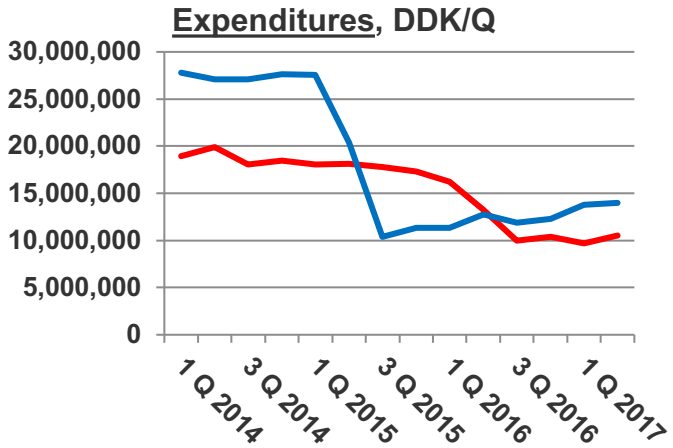
Originator/biosimilar INFX and ETAN volume consumption (DDD/month) in DK

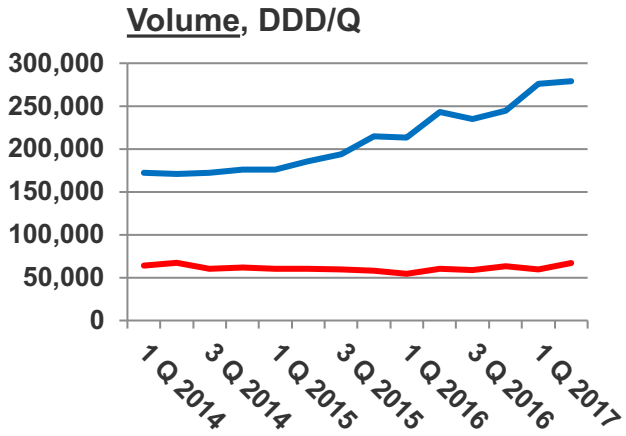




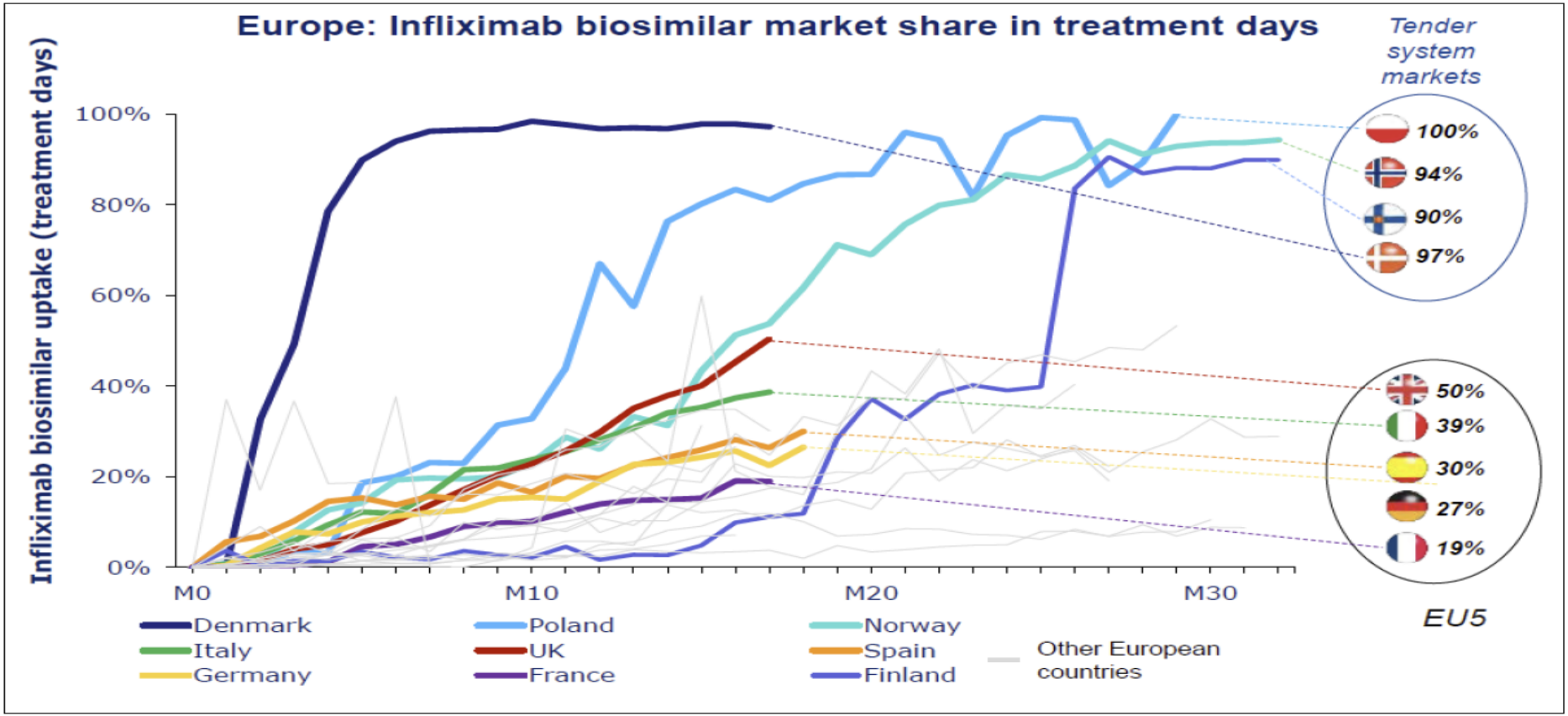
With a little help….

Development of expenditures (DDK) and volume (DDD) 1. Q 2014 – 2. Q 2017, INFX and ETAN, *Danish hospitals in total*





Estimated annual savings in Denmark:
INFX ~ 180 mil. DDK
ETAN ~ 90 mil. DDK



Per Troein at 4th DIA Biosimilar Conference, Brussels November 2016

Questions

- Present practice → shift from originator to biosimilar; *but how about switching from one biosimilar to another; how many times*? *How often*?

- Biosimilar cancer medicine: Cancer medicine are often dosed after a certain schedule; *Should we shift from originator to biosimilar in this situation?*

Issues/hurdles related to the use of biosimilar trastuzumab

- Biosimilar trastuzumab only available ad IV formulation (but not as SC); > 80 % of the volume of trastuzumab in Denmark is on SC formulation

- Fewer patients in clinical trials; *but probably doesn't matter ie. "that's the nature of approval of biosimilar drugs"…* But physicians still need to be informed/convinced!

Fase III trials of present two EMA approved trastuzumab biosimilars → Ontruzant and Herzuma (*more to come*)

Trial objective: Establish equivalence with originator trastuzumab (Herceptin) - *NB Chemotherapy not explicit mentioned*

DRUG (Company)	SETTING	PRIMARY OBJEKTIVE	TRIAL	N	OUTCOME
Ontruzant (SB3) biosimilar trastuzumab (Samsung Bioepis)	Early breast cancer, neoadjuvant treatment	breast pathologic complete response (bpCR)	Phase III equivalence study[1]	800	Equivalence demonstrated between SB3 and originator trastuzumab for primary objective ie. breast pathologic complete response (bpCR). Safety and immunogenicity comparable.
Herzuma (CT-P6) biosimilar trastuzumab (Celltrion)	Early breast cancer, neoadjuvant treatment	pathologic complete response (pCR)	Phase III equivalence study[2]	549	Equivalence demonstrated between CT-P6 and originator trastuzumab for primary objective ie. pathologic complete response (pCR). Adverse events were similar.

√

√

1. Pivot X et al. J Clin Oncol Januar 26., 2018
2. Stebbing J et al. Lancet Oncol 2017;18:917-283

Clinical trials of originator trastuzumab (Herceptin) → *selected as example, NOT exhaustive*

Trial objective: Investigate benefit (or not) with the use of originator trastuzumab (Herceptin) in different settings - *NB Chemotherapy not explicit mentioned*

DRUG (Company)	SETTING	PRIMARY OBJECTIVE / ENDPOINT	TRIAL	N	OUTCOME
Herceptin (Roche)	Early breast cancer, adjuvant treatment	Disease-free survival	11 year follow up (HERA)[1]	5102	1 year treatment with adjuvant trastuzumab significantly improves long term disease-free survival, compared with observation. 2 years of TRZ had no additional benefit.
Herceptin (Roche)	Early breast cancer, adjuvant treatment	Disease-free survival rate at 5 years	Evaluation of efficacy and safety of new nonanthracycline regimen with trastuzumab[2]	3222	Addition of 1 year adjuvant trastuzumab significantly improves disease-free survival and overall survival among women with HER2+ breast cancer.
Herceptin (Roche)	Metastatic breast cancer	Time to disease progression and incidence of adverse events	Chemotherapy with or without TRZ for HER2+ metastatic breast cancer[3]	469	Trastuzumab increases the clinical benefit of first-line chemotherapy in HER2+ metastatic breast cancer.
Herceptin and Perjeta (pertuzumab) (Roche)	Locally advanced breast cancer, Neoadjuvant treatment	Pathological complete response (pCR)	Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in early HER2+ breast cancer[4]	417	Patients given pertuzumab and trastuzumab plus docetaxel had a significantly improved pathological complete response rate compared with trastuzumab plus docetaxel, without substantial difference in tolerability.

1. Cameron D et al. Lancet 2017; 389:1195-205
2. Slamon D et al. N Engl J Med 2011;365:1273-83
3. Slamon D et al. N Engl J Med, Vol. 344, No. 11, March 15, 2001
4. Gianni L et al. Lancet Oncol 2012; 13: 25-32

Important factors to successfully implementation of the use of biosimilar trastuzumab (*and in general*)

- Strong organization of key stakeholders ie. in Denmark, recommendations from The National Council of Medicine (MR) → local implementation true meetings/agreement between Drug Committees and key oncologists, monitoring of drug use, discussing the concept of biosimilar approval etc.
- Economic incentive for hospital/ward
- Involvement of/information to patient organisation (political influence)

Switch from subcutaneous originator to biosimilar intravenous biosimilar – considerations?

- Guideline from The National Council of Medicine (MR; *former RADS*) recommends that TRZ IV and SC formulation are equally effective (neoadjuvant setting) – *supported by phase III study[1] by originator*

- In the process of making guidelines, MR is supported by *AMGROS with economic calculations, fx difference in total costs (drug price, nurse-time, patient chair-time etc.) when comparing the use of IV vs. SC formulations – this will be taken into account when deciding which formulation should be used

*Amgros is an institution under Danish Regions responsible for purchasing drugs (*as cheap as possible*) through tenders. Where relevant based on guidelines from The National Council of Medicine. Also contributing by "prizing the added value" of new drugs assisting the Council.

1. Jackisch C et al. (HannaH) European Journal of Cancer 62 (2016) 62-75

Switch from subcutaneous originator to biosimilar intravenous biosimilar – considerations? *Cont.*

- Practical facilities at hospital: SC administered over 2 – 5 min., IV given over 90 min. (first dose) or 30 min. (following doses – *studies[1,2] published by originator company indicates that 89 % of patients and 77 % of healthcare prof. preferred SC (vs. IV) and possible saving of pt. "chair time" (approx. 55 min.) and active health care (approx. 15 min.) when using SC (vs. IV)*

1. Pivot X et al. (PrefHer) Lancet oncol 2013; 14 (10):962-70
2. 3. De Cock E et al. Cancer Med 2016;5(3):389-97

Switch from subcutaneous originator to biosimilar intravenous biosimilar – considerations? *Cont.*

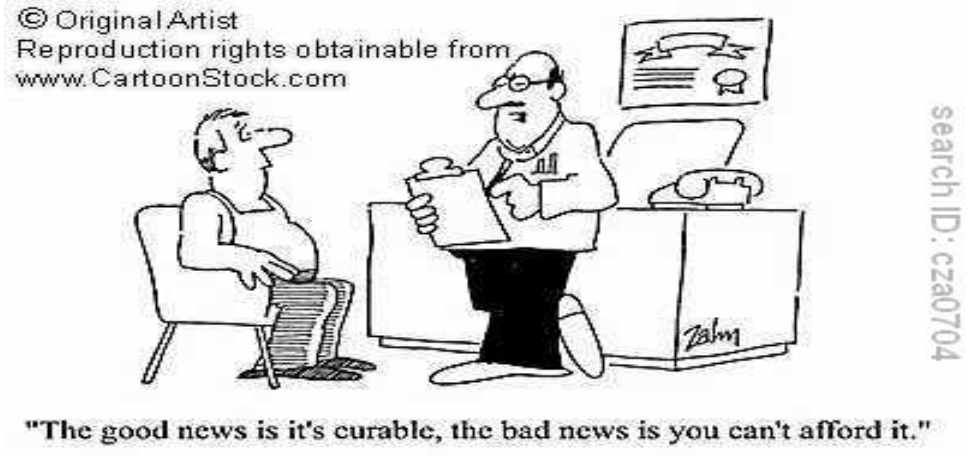
- Problems finding IV access? Probably true for some patients → SC administration
- Switching from originator SC (and IV) to biosimilar IV is “not allowed” when given in combination with pertuzumab due to patency for the combination (*same company*) – *according to estimates based on guidance from MR, approx. 20 – 25 % of treatments with TRZ are given in combination with pertuzumab (neoadjuvant and 1. line metastatic disease)*

Switching between trastuzumab products – considerations/concerns in general

- Switching a patient from trastuzumab originator SC/IV to IV biosimilar in the middle of a treatment period? *Patients in neo-adjuvant or adjuvant treatment? Patients with metastatic disease?*

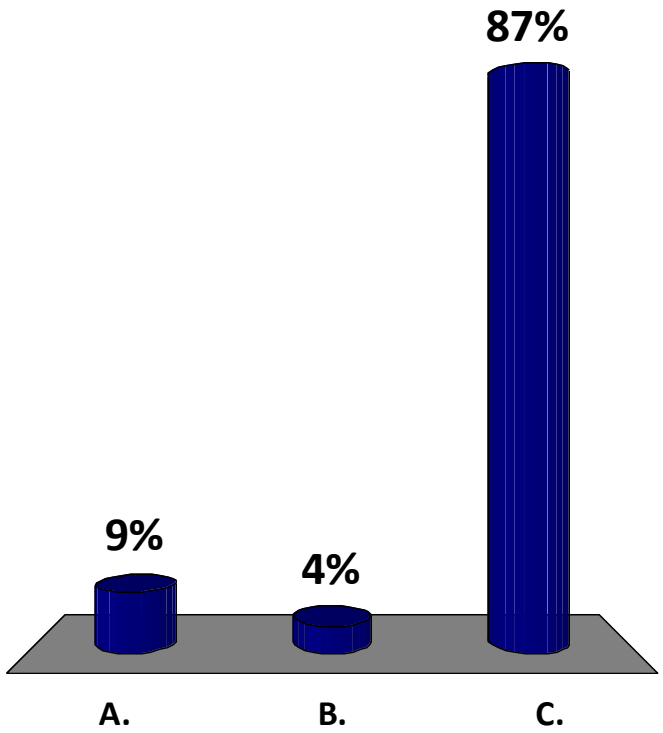
- Switching between to (or more) different biosimilar trastuzumab products in any given treatment period? *How many times?*

Thank you for your attention!

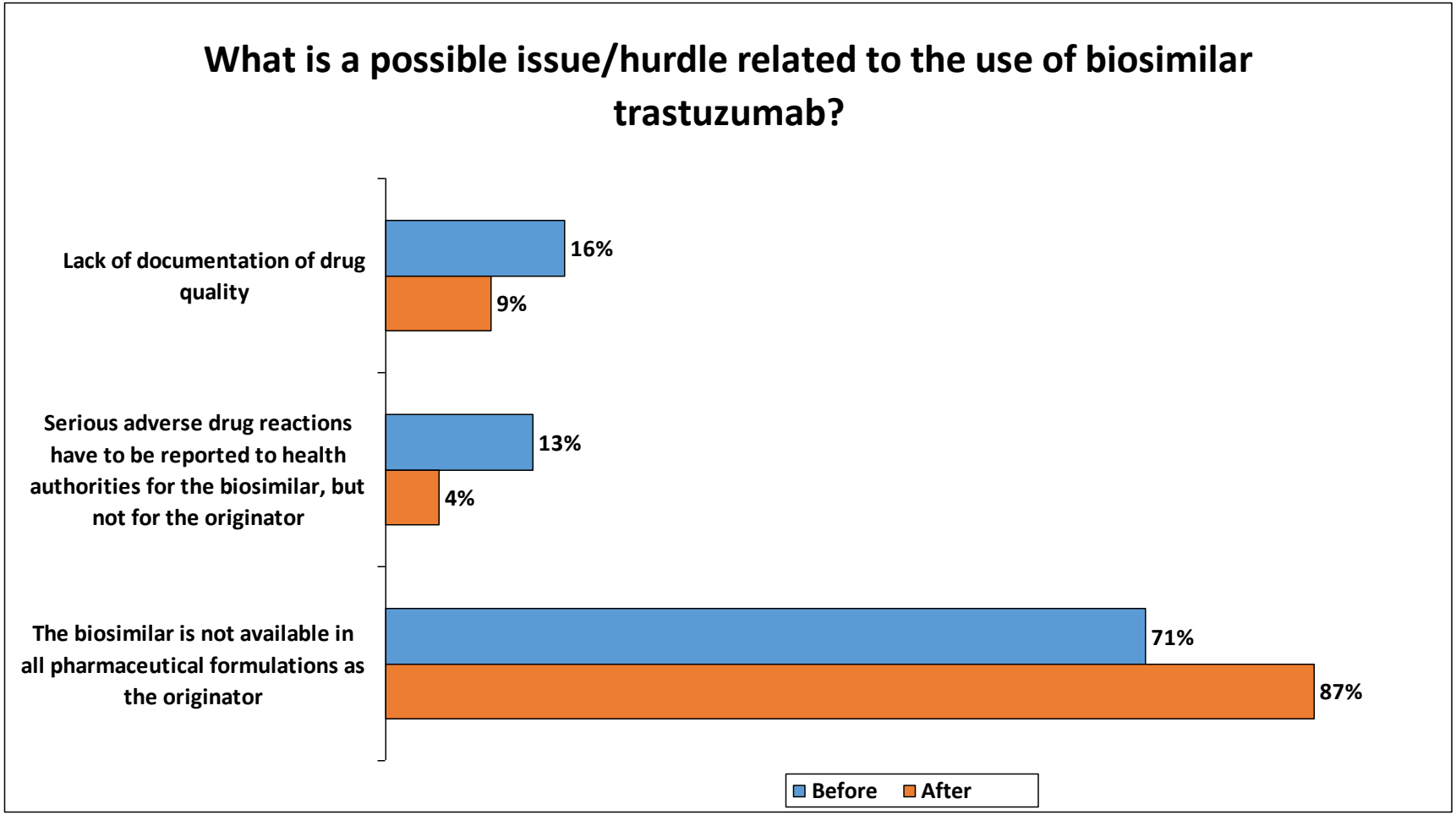


What is a possible issue/hurdle related to the use of biosimilar trastuzumab?

A. Lack of documentation of drug quality
B. Serious adverse drug reactions have to be reported to health authorities for the biosimilar, but not for the originator
✓ C. The biosimilar is not available in all pharmaceutical formulations as the originator

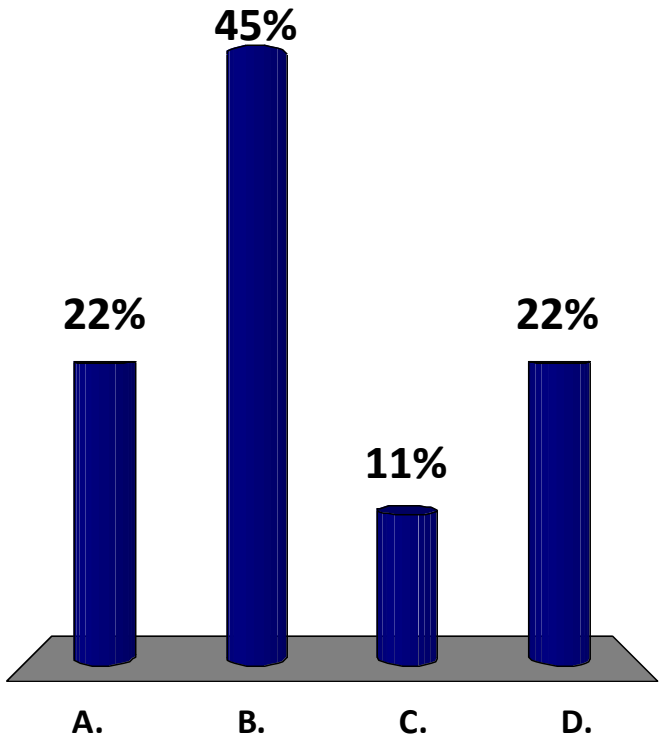


What is a possible issue/hurdle related to the use of biosimilar trastuzumab?

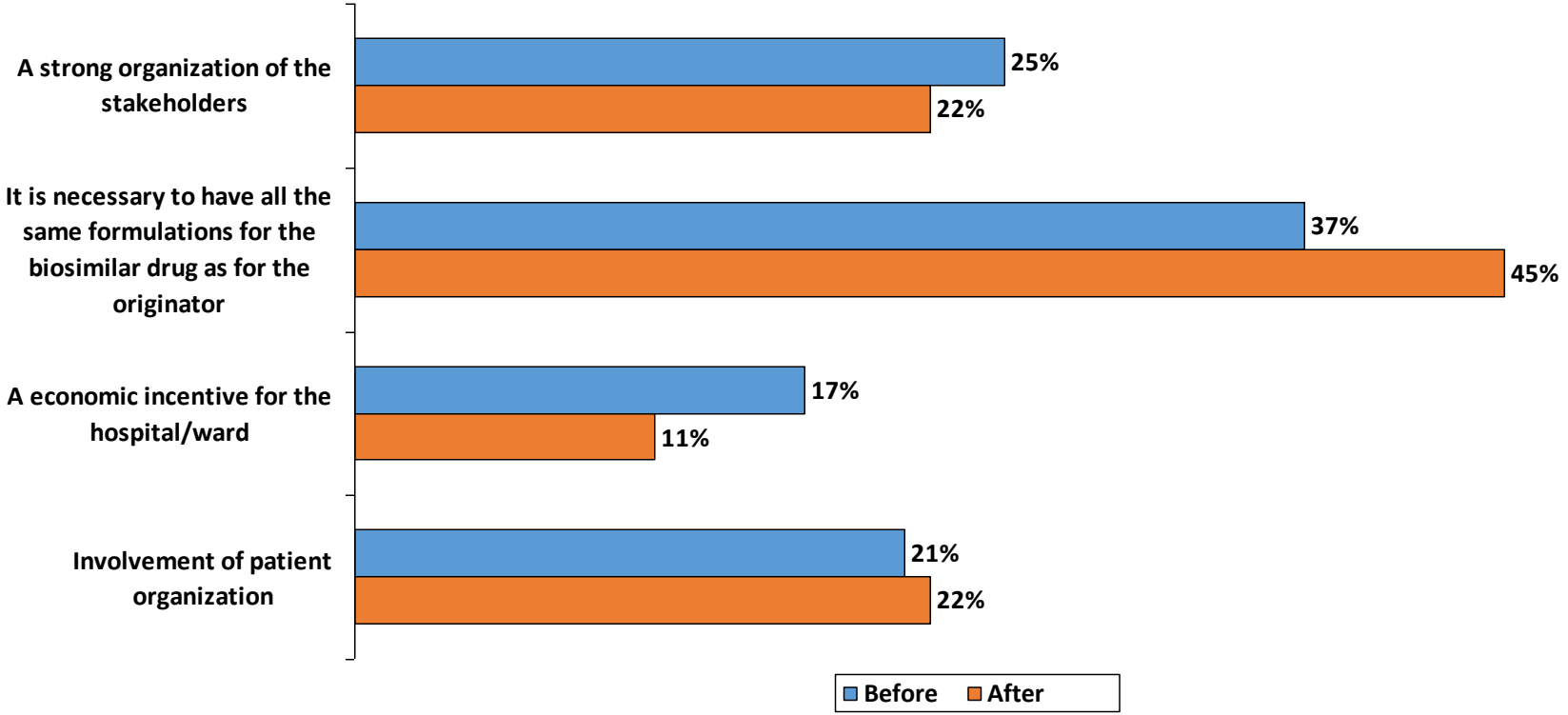


Which factor is <u>not</u> important to successfully implement the use of biosimilar trastuzumab (*instead of the originator product*)?

A. A strong organization of the stakeholders
B. ✓ It is necessary to have all the same formulations for the biosimilar drug as for the originator
C. A economic incentive for the hospital/ward
D. Involvement of patient organization



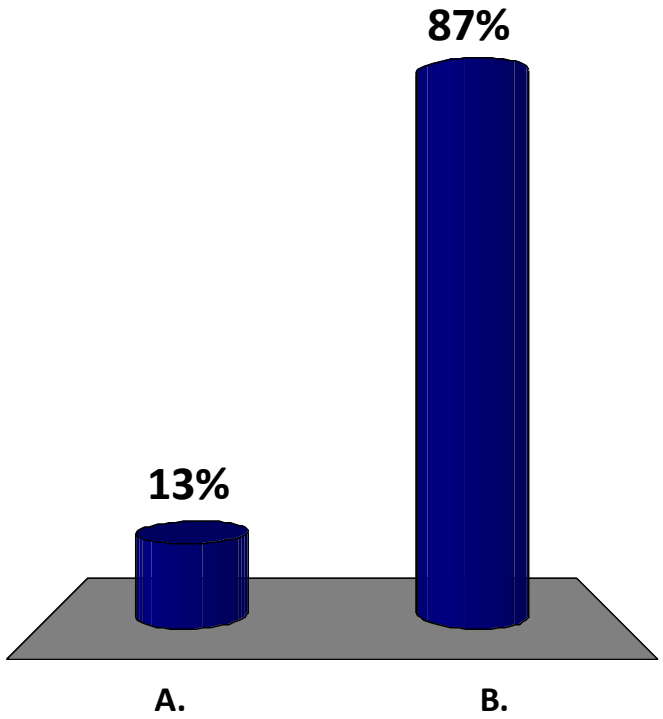
Which factor is not important to successfully implement the use of biosimilar trastuzumab (instead of the originator product)?

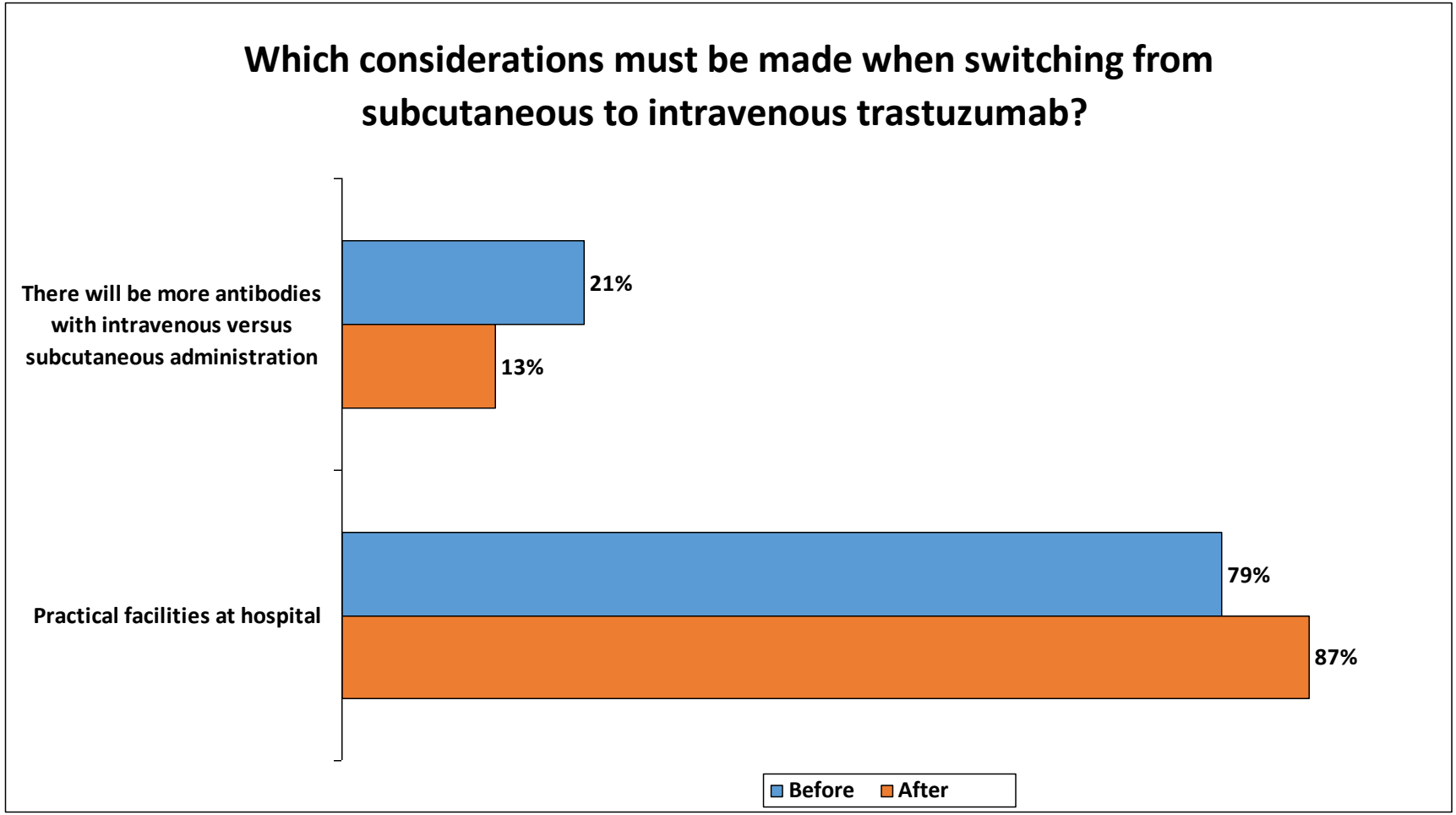


Which considerations must be made when switching from subcutaneous to intravenous trastuzumab?

A. There will be more antibodies with intravenous versus subcutaneous administration

✓ B. Practical facilities at hospital




Which considerations must be made when switching from subcutaneous to intravenous trastuzumab?
There will be more antibodies with intravenous versus subcutaneous administration
21%
13%
Practical facilities at hospital
79%
87%
Before
After