Estrapolazione, intercambiabilità e switch: ho qualche dubbio?

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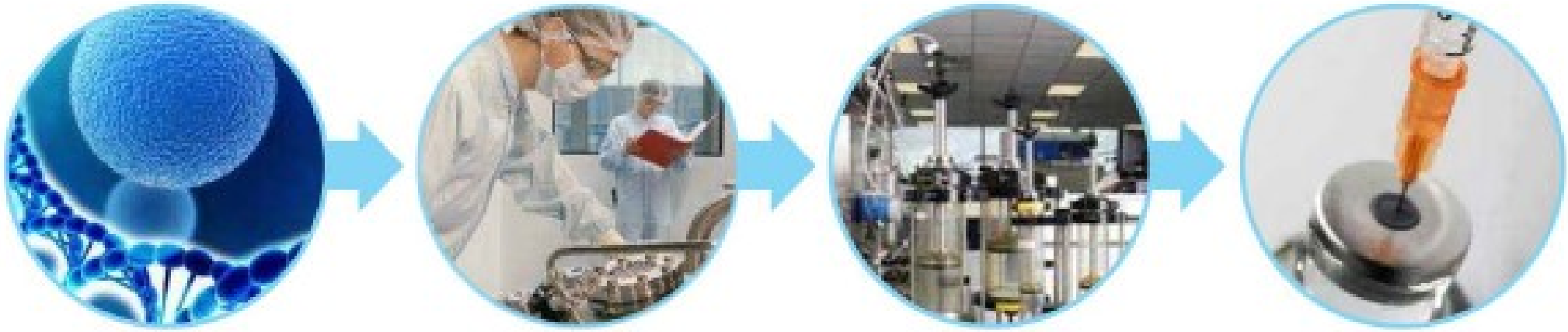
Extrapolation is not a new concept

- If a biosimilar is highly similar to a reference medicine and has comparable safety and efficacy in one therapeutic indication, safety and efficacy data may be extrapolated to other indications approved for the reference medicine.
- Fewer clinical trials or no trials at all need to be carried out with the biosimilar in certain indications.
- Extrapolation of data to other indications is always supported by scientific evidence generated in robust comparability studies (quality, non-clinical and clinical)
- Well established scientific principle routinely applied when biological medicines with several approved indications undergo major changes to their manufacturing process.

Biosimilars in the EU: Information guide for healthcare professionalsPrepared jointly by the European Medicines Agency and the European Commission

Biologic manufacture

- Biologics are produced from living organisms



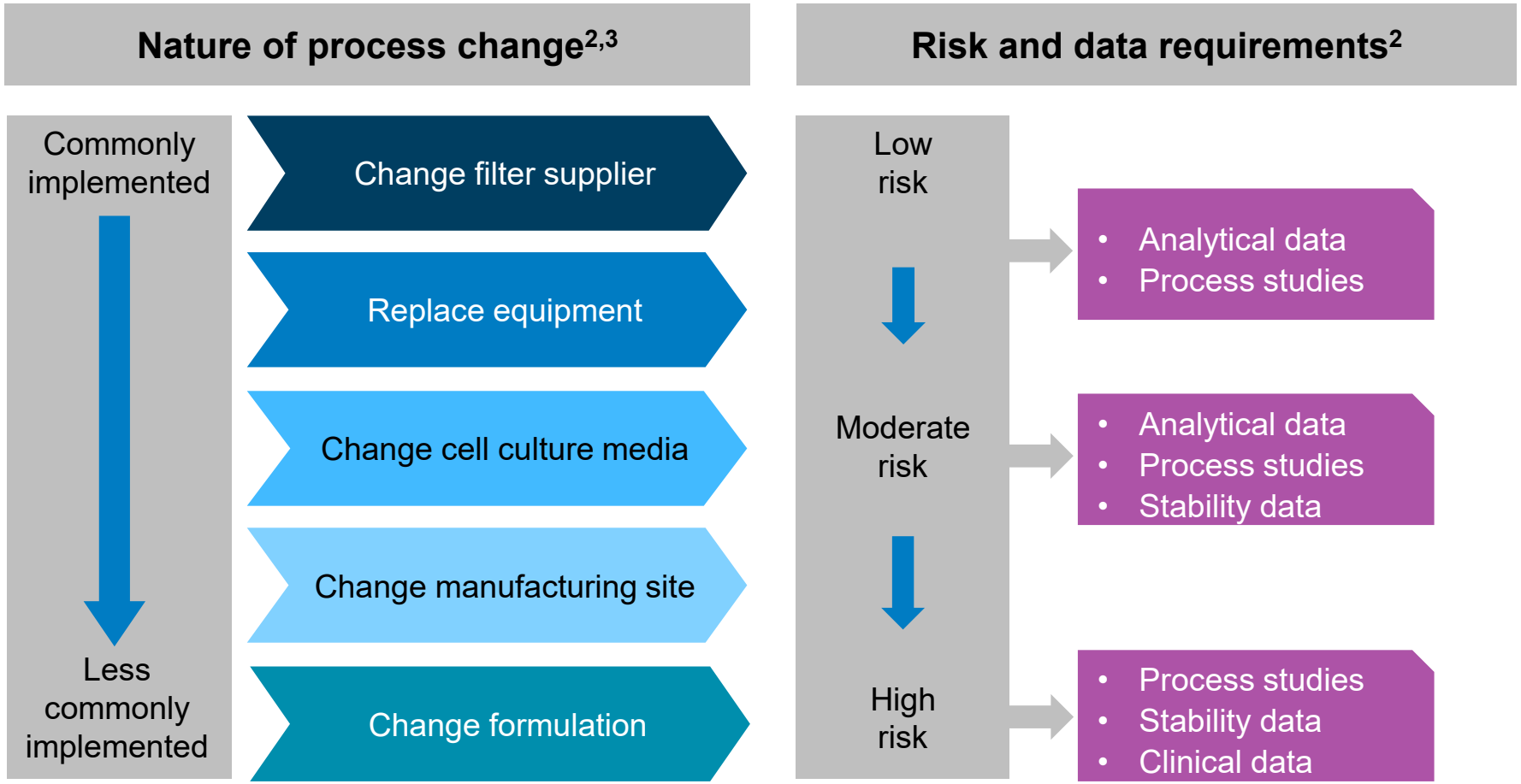
Modify host cells
(e.g. bacteria, yeast, mammalian)
to produce recombinant proteins

Grow cells
Under controlled conditions
(fermentation, upstream process)

Extract, refold, purify
To generate drug substance
(downstream process)

Formulate to stable
finished drug product
Vial, syringe, cartridge

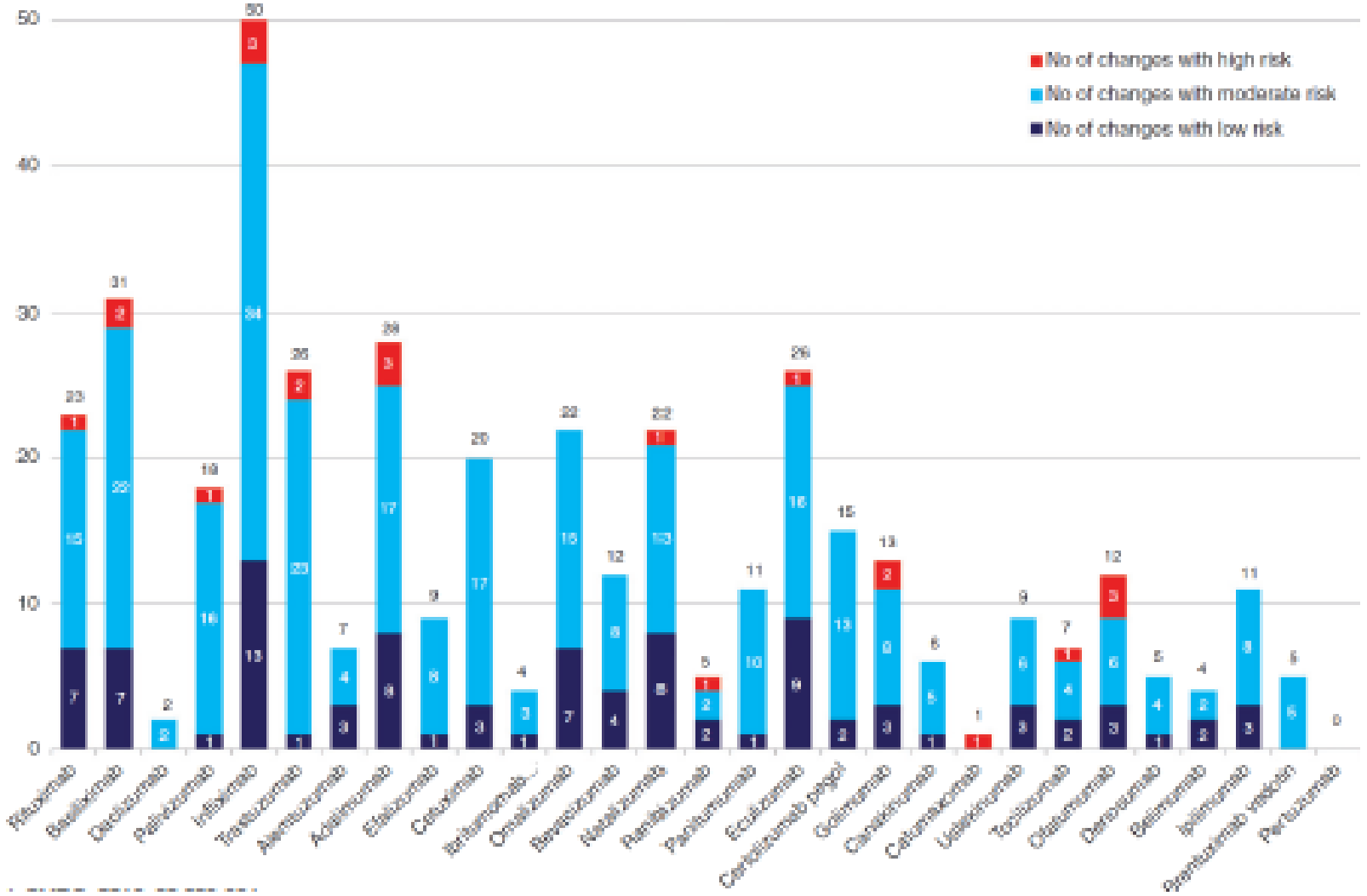
Comparability testing is required when manufacturers make process changes for approved biologics[1]



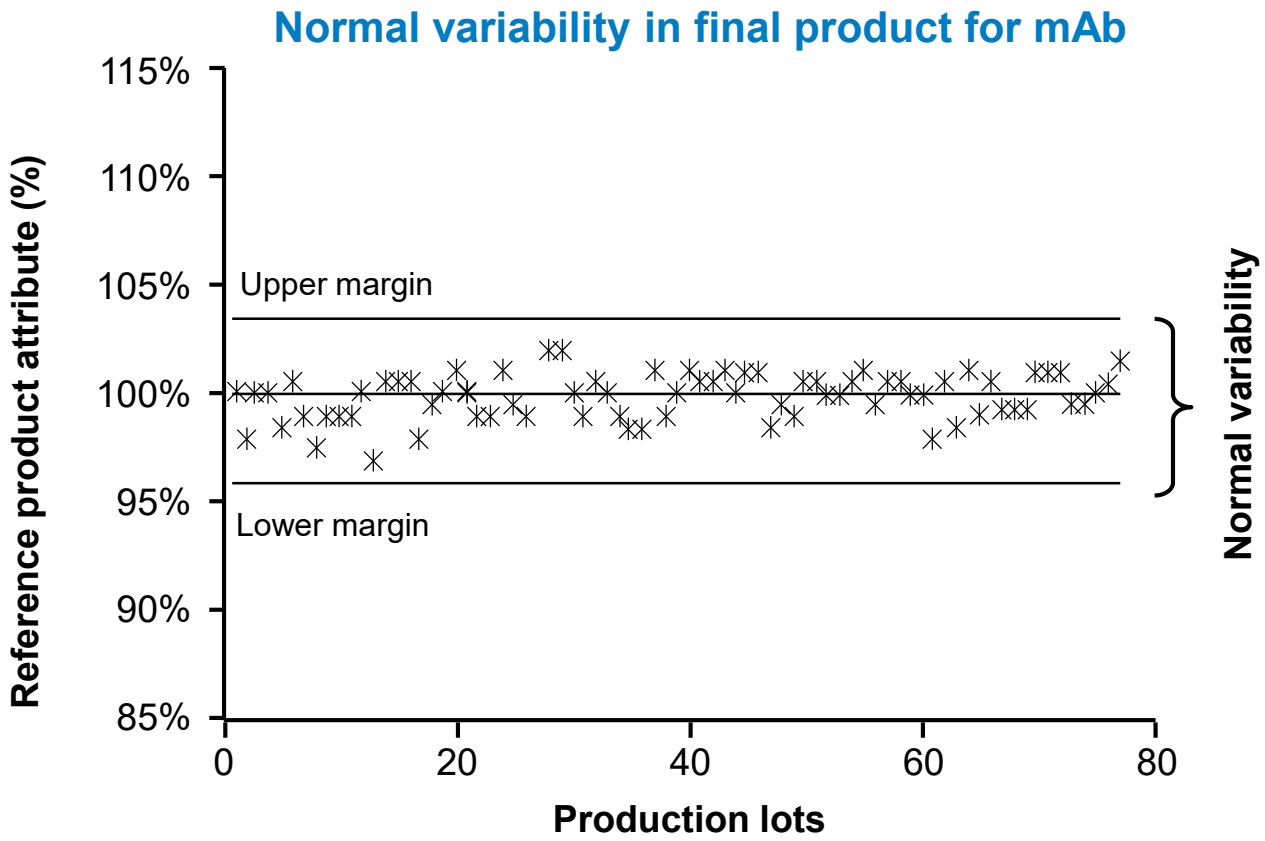
1. ICH Harmonised Tripartite Guideline, Comparability of biotechnological/biological products subject to changes in their manufacturing process Q5E, 2004;
2. Lee JF, et al. Curr Med Res Opin 2012;28:1053–58; 3. Ramanan S, et al. BioDrugs 2014;28:363–72

Variability is in the nature of biologics

- Manufacturing changes are tightly regulated



Manufacturers establish acceptable ranges of variation through extensive characterisation and monitor for adherence to these specifications



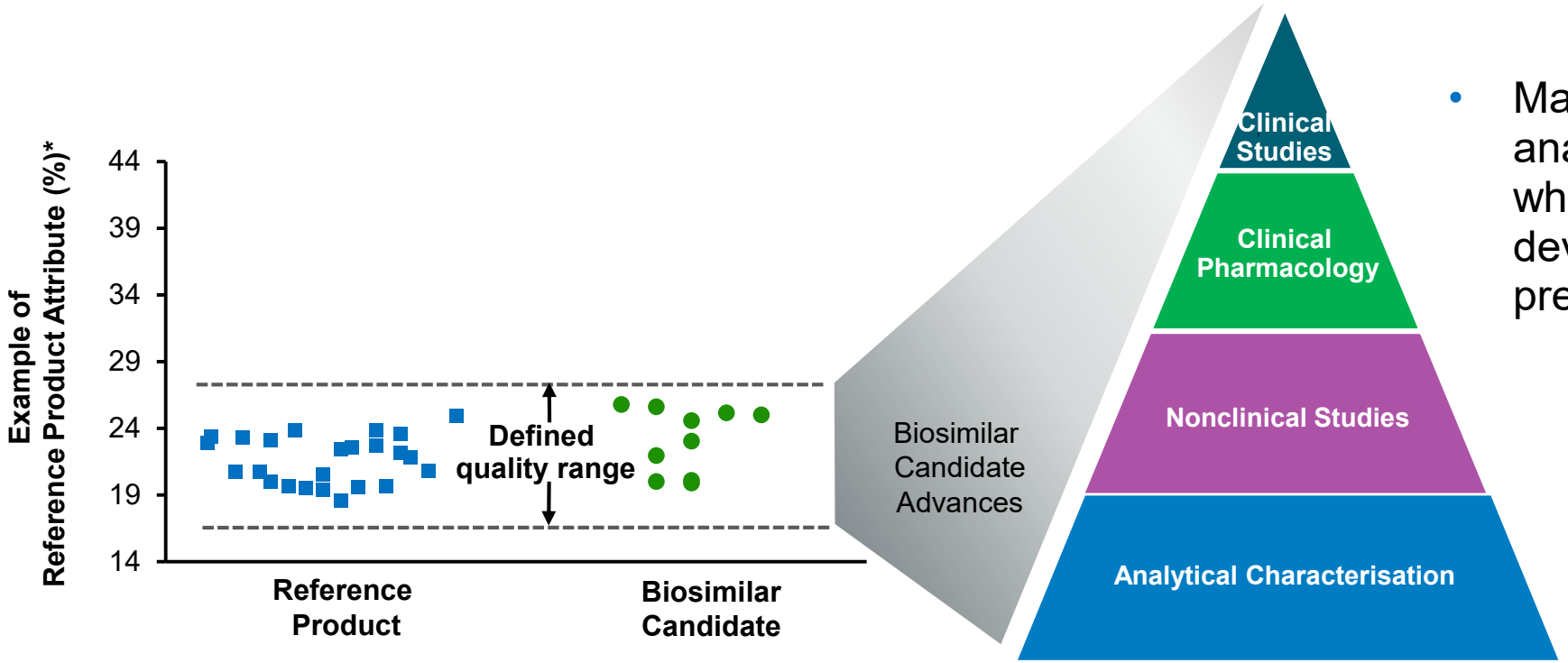
Acceptable range of variation is established by the manufacturer on the basis of data from historical batches

During the development process, relationships between inputs and product attributes are studied to further inform normal range specifications

During routine manufacturing process, input parameters and product quality attributes are monitored for adherence to normal variability standards

Figure adapted from Ramanan S, et al. BioDrugs. 2014;28:363–372

Similarity in structure and function of the biosimilar candidate is established via an iterative process[1–3]

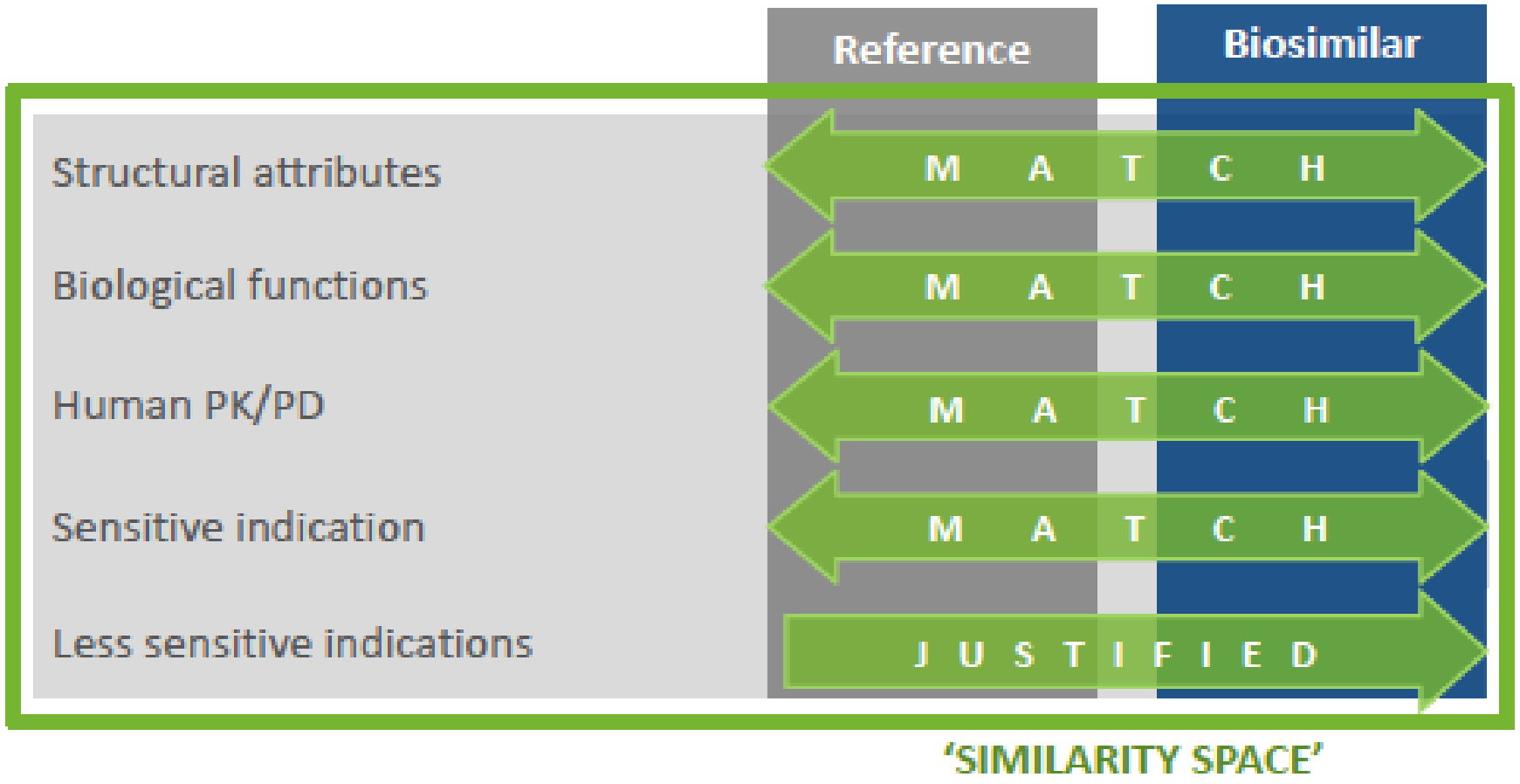


- Manufacturer evaluates analytical data and determines whether to proceed with development or conduct further preclinical optimisation[1,3]

1. FDA. Scientific considerations in demonstrating biosimilarity to a reference product. Guidance for industry, 2015;
2. FDA. Quality considerations in demonstrating biosimilarity of a therapeutic protein product to a reference product. Guidance for industry, 2015;
3. EMA. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1), 2014 *Each data point represents test results from a unique lot

Extrapolation of indication

- Extrapolation is based on the entire similarity exercise, including clinical experience with the reference product



Selection of sensitive endpoints for biosimilar trastuzumab clinical trials

Goal: demonstrate similar efficacy and safety *vs* the reference product, not patient benefit *per se* which has already been established for the reference product[1]

Many potential endpoints[2,3]

- Event-free survival (EFS)
- Disease-free survival (DFS)
- Relapse-free survival (RFS)
- Progression-free survival (PFS)
- Overall survival (OS)
- Overall response rate (ORR)
- Duration of response (DoR)
- Pathological complete response (pCR)
- Time to progression (TTP)
- Clinical benefit rate (CBR)

Regulatory opinion

"It is not necessary to use the same primary efficacy endpoints as those that were used in the marketing authorisation application of the reference product"[4]

"Such endpoints… may not be feasible or sensitive enough for establishing comparability of a biosimilar mAb to a reference mAb"[1]

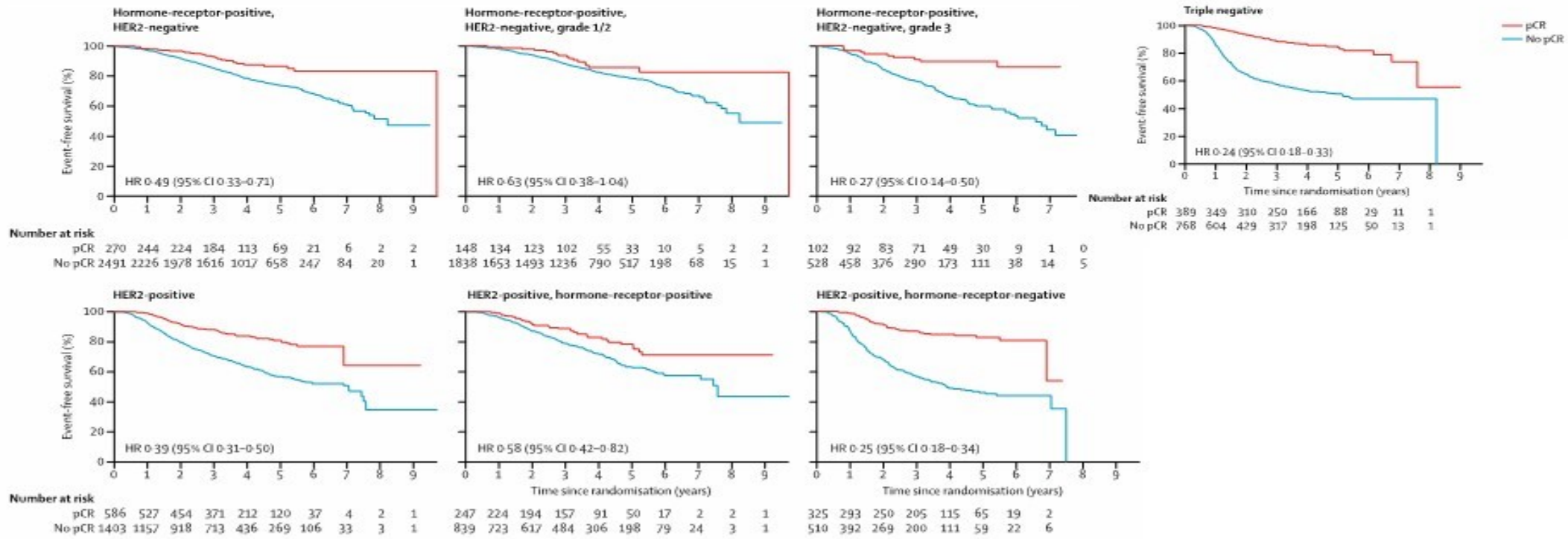
"A clinical endpoint that measures activity as primary endpoint may be considered"[1]

- Example for mAbs in oncology:
  ORR, pCR
- Less likely than survival endpoints to be influenced by factors such as previous lines of therapy and tumour burden

1. EMA. Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues. 2012;
2. Herceptin® (trastuzumab) Summary of Product Characteristics. Roche Registration Limited, 2016;
3. Perjeta® (pertuzumab) Summary of Product Characteristics. Roche Registration Limited, 2015;
4. EMA. Guideline on similar biological medicinal products containing biologicall-derived proteins as active substance: non-clinical and clinical issues, 2014

pCR and long-term survival in clinical trials of neoadjuvant treatment of early breast cancer

Relationship between pCR and EFS by breast cancer subtype CTNeoBC pooled analysis

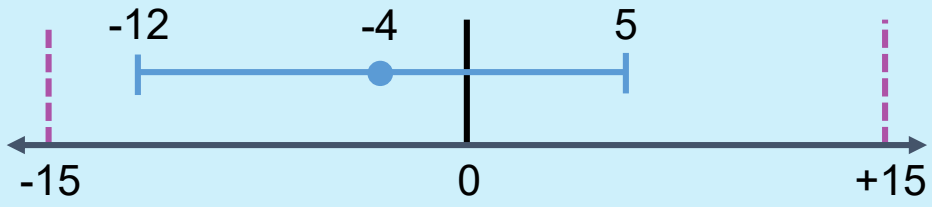


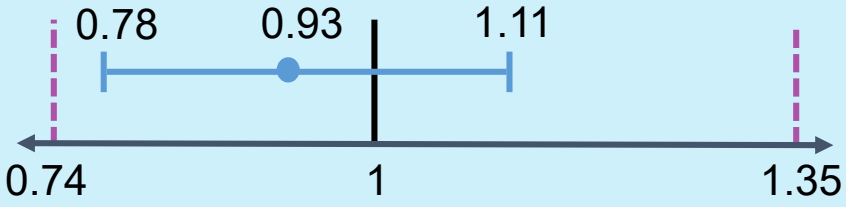
EFS, event-free survival; pCR, pathological complete response

Cortazar P, et al. Lancet 2014;384:164–72

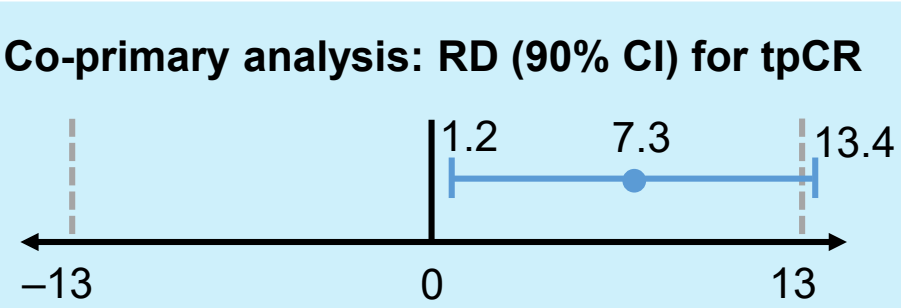
Summary: results of equivalence analyses of biosimilar vs trastuzumab in studies of HER2+ EBC

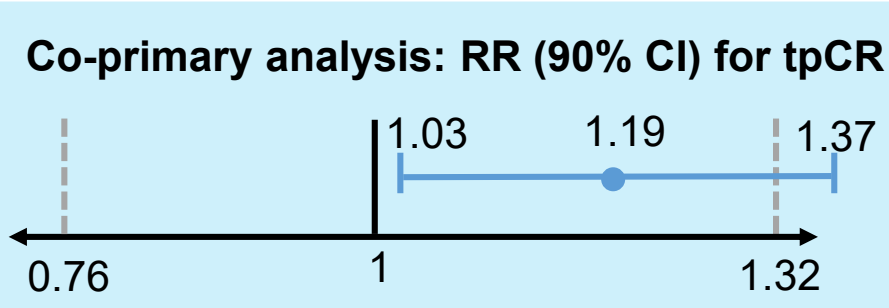
Celltrion (CT-P6)[1] (N=504)*



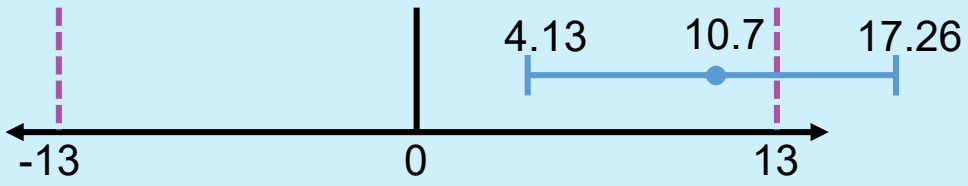


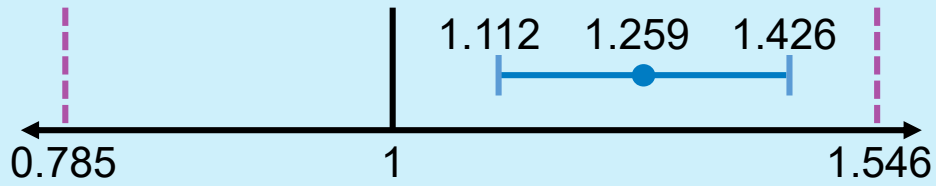
Amgen (ABP 980)[2] (N=696)†





Samsung Bioepis (SB3)[3] (N=800)*





1. Stebbing J, et al. Lancet Oncol 2017;18:917–928; 2. von Mickwitz G, et al. ESMO 2017; Poster 151PD; 3. Pivot XB, et al. ASCO 2017; Abstract 509 and poster

NOTE: results cannot be directly compared due to differences in study design.
*In per-protocol population. †In tpCR evaluable population. ABP 980 is an investigational product

Sensitivity of the neoadjuvant-adjuvant setting to detect differences in immunogenicity

Design

HannaH study

- Pivotal Phase III trial of:
  SC trastuzumab *vs*
  IV trastuzumab
- Neoadjuvant-adjuvant setting sensitive to detect differences between formulations should they exist

Results

Observed ADA rates*

- SC trastuzumab: 14.6% (43/295) *vs*
- IV trastuzumab: 7.1% (21/295)

Impact

- No correlation of ADA with efficacy/safety/PK detected

Jackisch C, et al. Ann Oncol 2015;26:320–325

*All patients who tested positive for ADAs at least once post-baseline

Extrapolation across indications

Topic	Conclusion
Mechanism of action	• Common MOA across indications (binds to HER2 and inhibits proliferation of tumor cells that overexpress HER2)[1–3] • Functional and pharmacological similarity of ABP 980 and trastuzumab RP have been demonstrated in relevant *in-vivo* and *in-vitro* assays, including a gastric cancer xenograft study[3-5]
Pharmacokinetics	• PK similarity of ABP 980 and trastuzumab RP demonstrated in healthy subjects following a single dose[6] and in subjects with HER2+ EBC following multiple dosing[7]
Toxicities	• Neoadjuvant and adjuvant phases of treatment in early breast cancer are representative and sensitive of the safety risks in mBC and mGC[2,8] • HER2+ EBC indication represents a sensitive and homogenous population[8,9] • Similar safety profiles of ABP 980 and trastuzumab RP demonstrated in healthy subjects[6] and in the HER2+ EBC population[10,11]
Immunogenicity	• Low incidence of ADA reported for trastuzumab RP across indications sought[12,13] • Comparable ADA incidence observed for ABP 980 and trastuzumab RP in the PK similarity and clinical similarity studies[6,10,11]

1. Hudis CA. N Engl J Med 2007;357:39–51; 2. Bang Y-J et al. Lancet 2010;376;687–97; 3. Hanes V, et al. EBCC 2016; Abstract 436 and poster;
4. Hanes V, et al. SABCS 2015; Abstract P6-13-12 and poster; 5. Hutterer K, et al. WCBP Symposium 2017; Abstract P-207-TH and poster;
6. Hanes V, et al. Cancer Chemother Pharmacol 2017;79:881–8; 7. Holberg H-C, et al. EBCC 2018; Abstract 365 and poster; 8. Cortes J, et al. Breast Cancer Res Treat 2014;144:233–9;
9. Jackisch C, et al. Future Oncol 2015;11:61–71; 10. von Minckwitz G, et al. ESMO 2017; Abstract 151PD and poster; 11. Kolberg H-C, et al. SABCS 2017; Abstract PD3-10 and poster;
12. Herceptin 150 mg Powder for concentrate for solution for infusion. Summary of Product Characteristics. Roche Products Limited. November 2017;
13. Herceptin (trastuzumab) for injection, for intravenous use. Prescribing Information. Genentech Inc. April 2017

Intercheangeability, switch and substitution

- Interchangeability refers to the possibility of exchanging one medicine for another medicine that is expected to have the same clinical effect. This could mean replacing a reference product with a biosimilar (or vice versa) or replacing one biosimilar with another. Replacement can be done by:
- Switching, which is when the prescriber decides to exchange one medicine for another medicine with the same therapeutic intent.
- Substitution (automatic), which is the practice of dispensing one medicine instead of another equivalent and interchangeable medicine at pharmacy level without consulting the prescriber.

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Interchangeability, switching and substitution: EMA and Member States' responsibilities

For questions on prescribing or interchangeability practices, information may be available at the national competent authority in the relevant Member State (the list can be found on EMA's website).

Any decision on switching should involve the prescriber in consultation with the patient, and take into account any policies that the country might have regarding the prescribing and use of biological medicines.

ESMO and EAHP have different opinions on switching biosimilars

ESMO[1]
European Society for Medical Oncology

"The decision to change or switch should be taken by the physician having grasped a deep understanding of the product (via the information on the SmPC and EPAR), and subsequently informing the patient (based on all the factual information) and closely monitoring the patient at all times, in collaboration with nursing teams."

"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."

EAHP[2]
European Association of Hospital Pharmacists

"On matters concerning interchangeability, switching and substitution of biosimilar medicines, EAHP

- *Supports that a reference product and its biosimilar(s) are interchangeable and therefore can be switched;*
- *Supports that a biosimilar product and other biosimilar(s) to the same reference product are interchangeable and therefore can be switched;*
- *Supports that decisions regarding switching and substitution should involve the relevant stakeholders (patients, prescribers, pharmacists and others);*
- *Acknowledges that such decisions may be made on the national level, involving the relevant stakeholders (patients, prescribers, pharmacists and others);*
- *Supports that under certain conditions substitution on hospital pharmacy level can occur."*

1. Tabernero J, et al. ESMO Open 2016;1:e000142. doi:10.1136/ esmoopen-2016-000142;
2. EAHP. EAHP Position Paper on Biosimilar Medicines. June 2017. Available at: http://www.eahp.eu/practice-and-policy/biosimilar

Secondo Position Paper AIFA sui Farmaci Biosimilari

In Italia la posizione dell'AIFA chiarisce che i medicinali biologici e biosimilari non possono essere considerati sic et simpliciter alla stregua dei prodotti generici, o equivalenti.

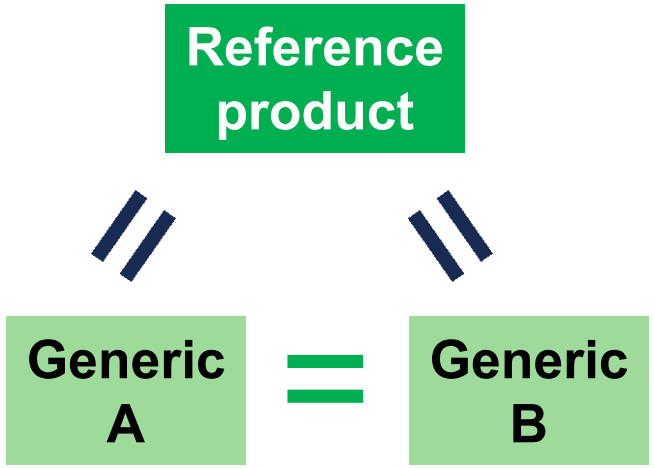
Pur considerando che la scelta di trattamento rimane una decisione clinica affidata al medico prescrittore, a quest'ultimo è anche affidato il compito di contribuire a un utilizzo appropriato delle risorse ai fini della sostenibilità del sistema sanitario e la corretta informazione del paziente sull'uso dei biosimilari.

Come dimostrato dal processo regolatorio di autorizzazione, il rapporto rischio-beneficio dei biosimilari è il medesimo di quello degli originatori di riferimento.

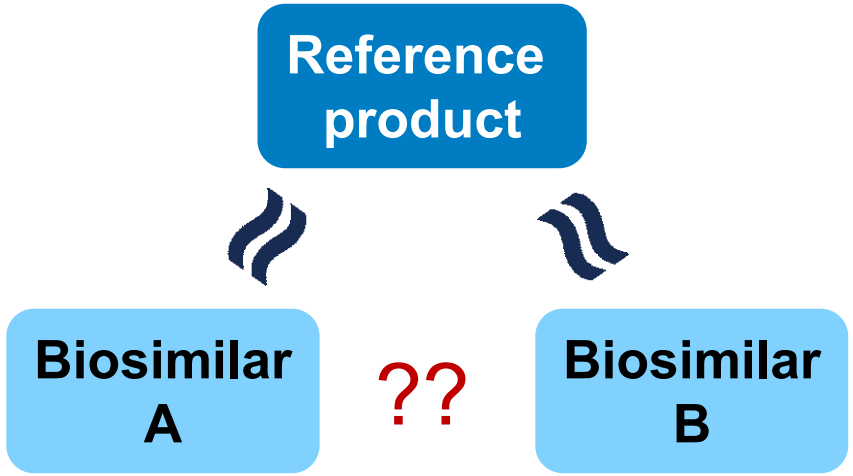
Per tale motivo, l'AIFA considera i biosimilari come prodotti intercambiabili con i corrispondenti originatori di riferimento. Tale considerazione vale tanto per i pazienti naïve quanto per i pazienti già in cura.

Biosimilarity does not automatically imply interchangeability

Chemical drugs
Generic A and B



Biological drugs
Biosimilar A and B



Declerck PJ. GaBI Journal 2012;1:13–16

Example safety findings: switching from RP to ABP 980

Continued trastuzumab RP vs switch to ABP 980 in the adjuvant phase: events of interest

	Switch (Trastuzumab RP/ABP 980) (n=171)		Continued RP (Trastuzumab RP/trastuzumab RP) (n=171)	
	Total, n (%)	Grade ≥3, n (%)	Total, n (%)	Grade ≥3, n (%)
Any AE of interest	45 (26.3)	5 (2.9)	39 (22.8)	5 (2.9)
Infections and infestations	21 (12.3)	2 (1.2)	14 (8.2)	2 (1.2)
Neutropenia	13 (7.6)	1 (0.6)	16 (9.4)	2 (1.2)
Infusion reactions	15 (8.8)	3 (1.7)	10 (5.8)	1 (0.6)
Hypersensitivity	7 (4.1)	0	3 (1.8)	0
Pulmonary toxicity	1 (0.6)	1 (0.6)	2 (1.2)	1 (0.6)
Cardiac failure	1 (0.6)	0	1 (0.6)	0

Switching did not increase the frequency or severity of AEs or the incidence of developing ADAs

von Minckwitz, G et al. SABCS 2017; Poster P5-20-13

ABP 980 is an investigational product

Example safety findings: anti-drug antibodies (ADAs)

ABP 980 vs trastuzumab RP: development of anti-drug antibodies – by phase

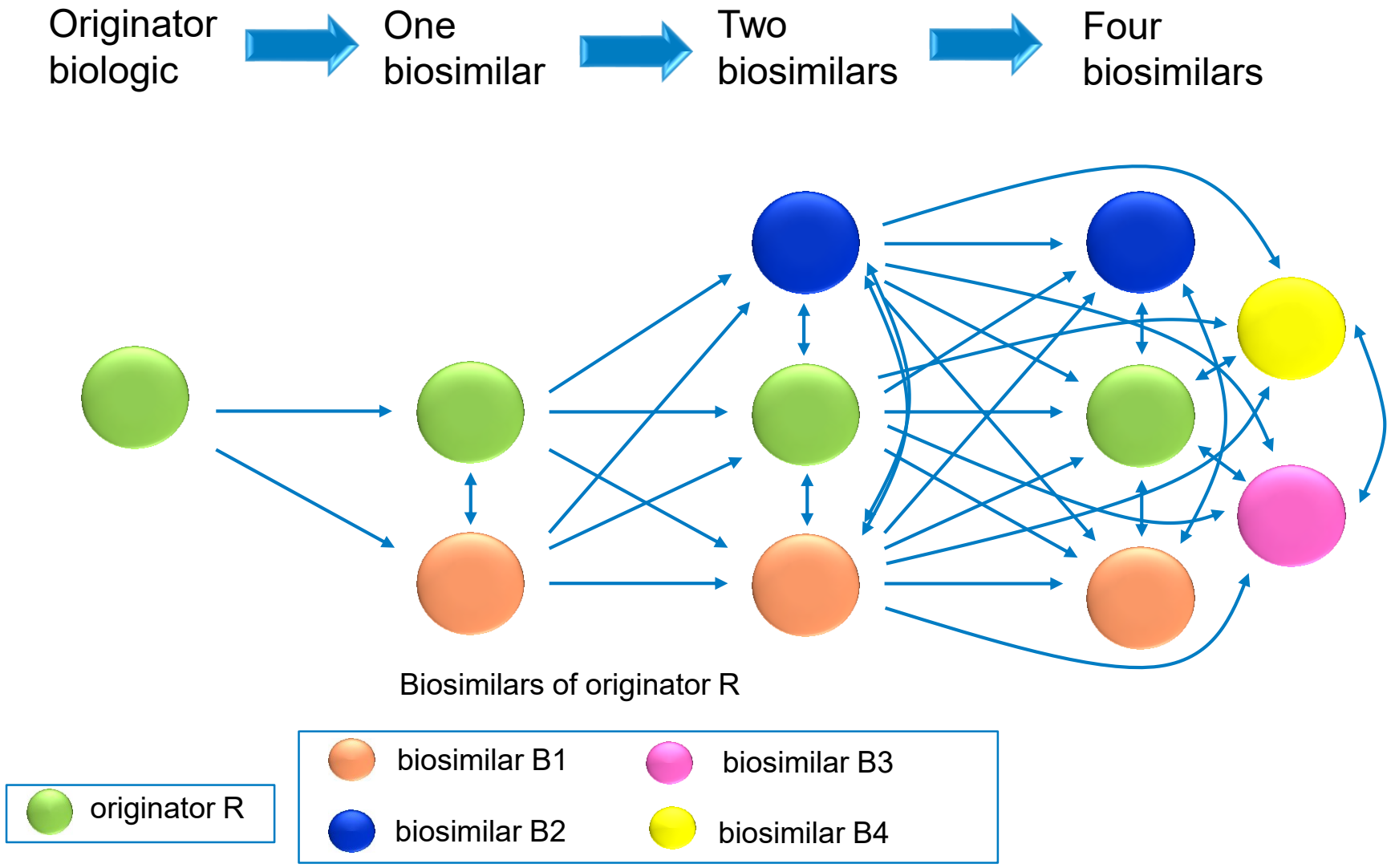
	Neoadjuvant phase[1] (+ paclitaxel)		Adjuvant phase[2]		
	ABP 980 (N=364) n (%)	Trastuzumab RP (N=361) n (%)	Continued ABP 980 (N=349) n (%)	Continued Trastuzumab RP (N=171) n (%)	Trastuzumab RP/ ABP 980 (N=171) n (%)
Development of binding ADAs during the study,* n (%)	2 (0.6)	2 (0.6)	0 (0.0)	0 (0.0)	1 (0.6)
Development of neutralizing ADAs, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

*Patients with a negative or no result at baseline.

1. von Minckwitz G, et al. ESMO 2017; Poster 151 PD; 2. Kolberg H-C, et al. SABCS 2017; Poster PD3-10

ABP 980 is an investigational product

Multiple switches between biosimilars and reference product could occur



In questo Position Paper AIOM, SIF,SIFO, CIPOMO e Fondazione AIOM sottolineano che la scelta di trattamento con un farmaco biologico di riferimento o con un biosimilare rimane una decisione clinica affidata al medico prescrittore. Tale considerazione vale anche per i pazienti già in cura, nei quali l'opportunità dello switch resta affidata al giudizio clinico.