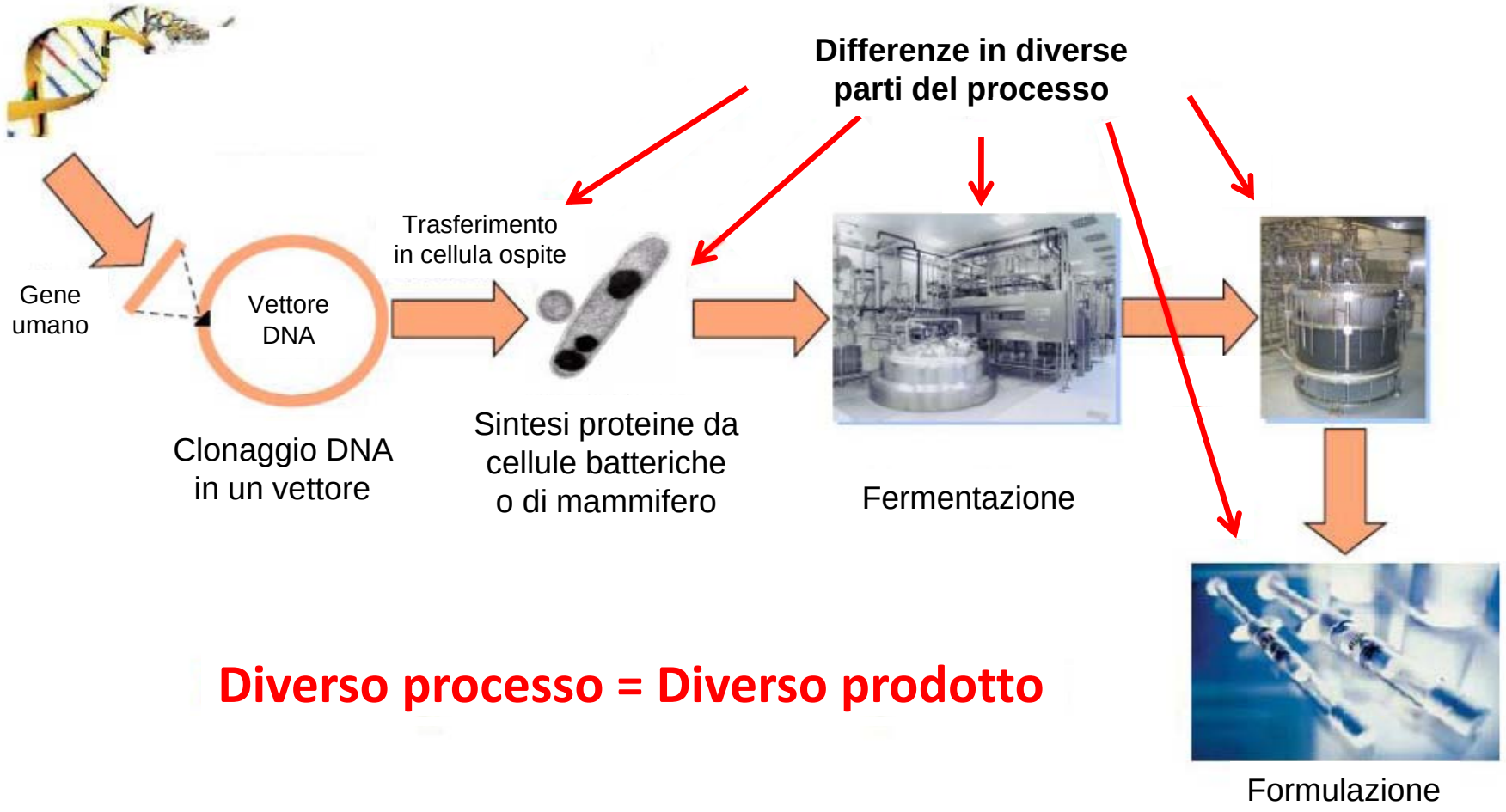
I BIOSIMILARI:
UN INQUADRAMENTO

Armando Genazzani

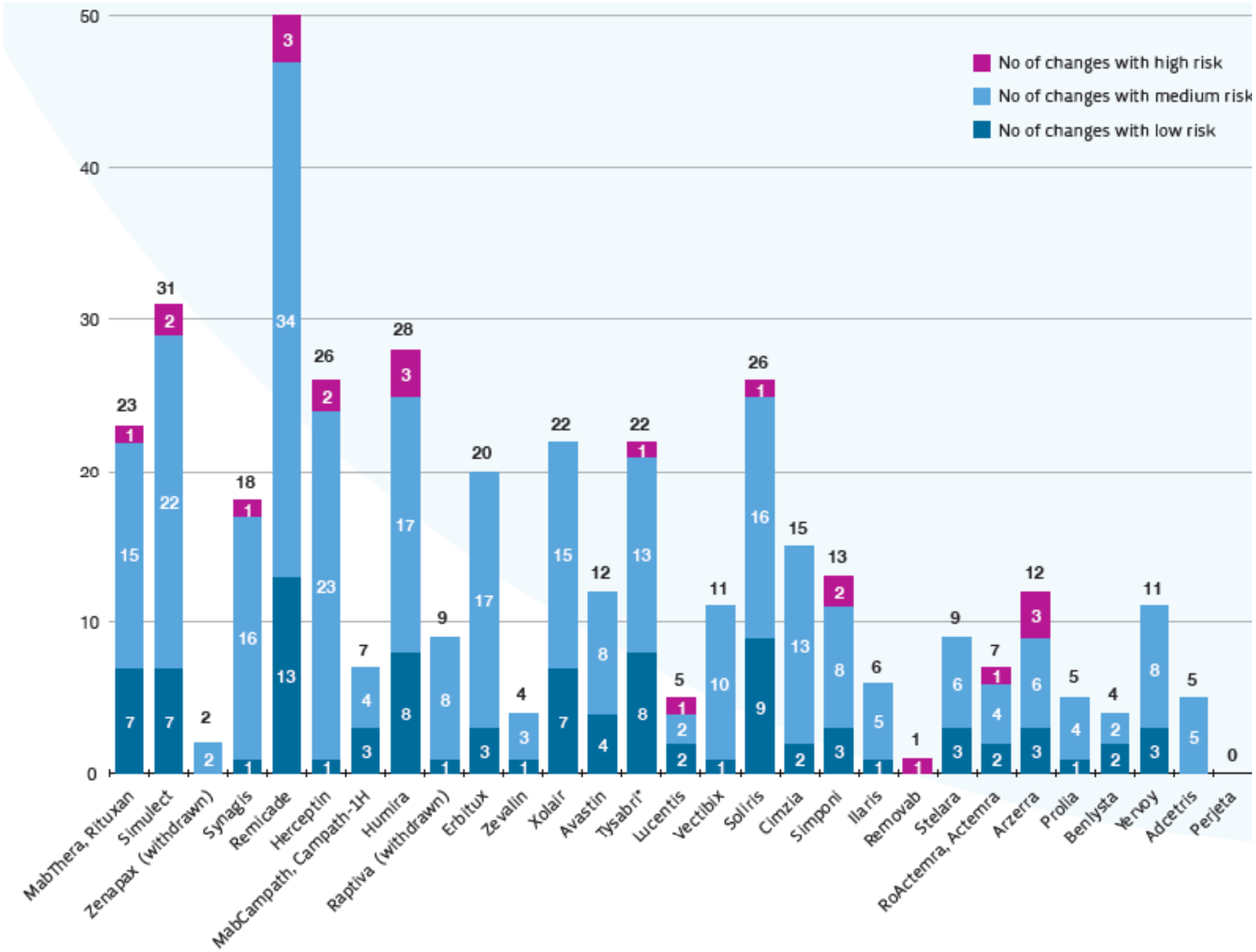
Il processo produttivo di un farmaco biologico è complesso

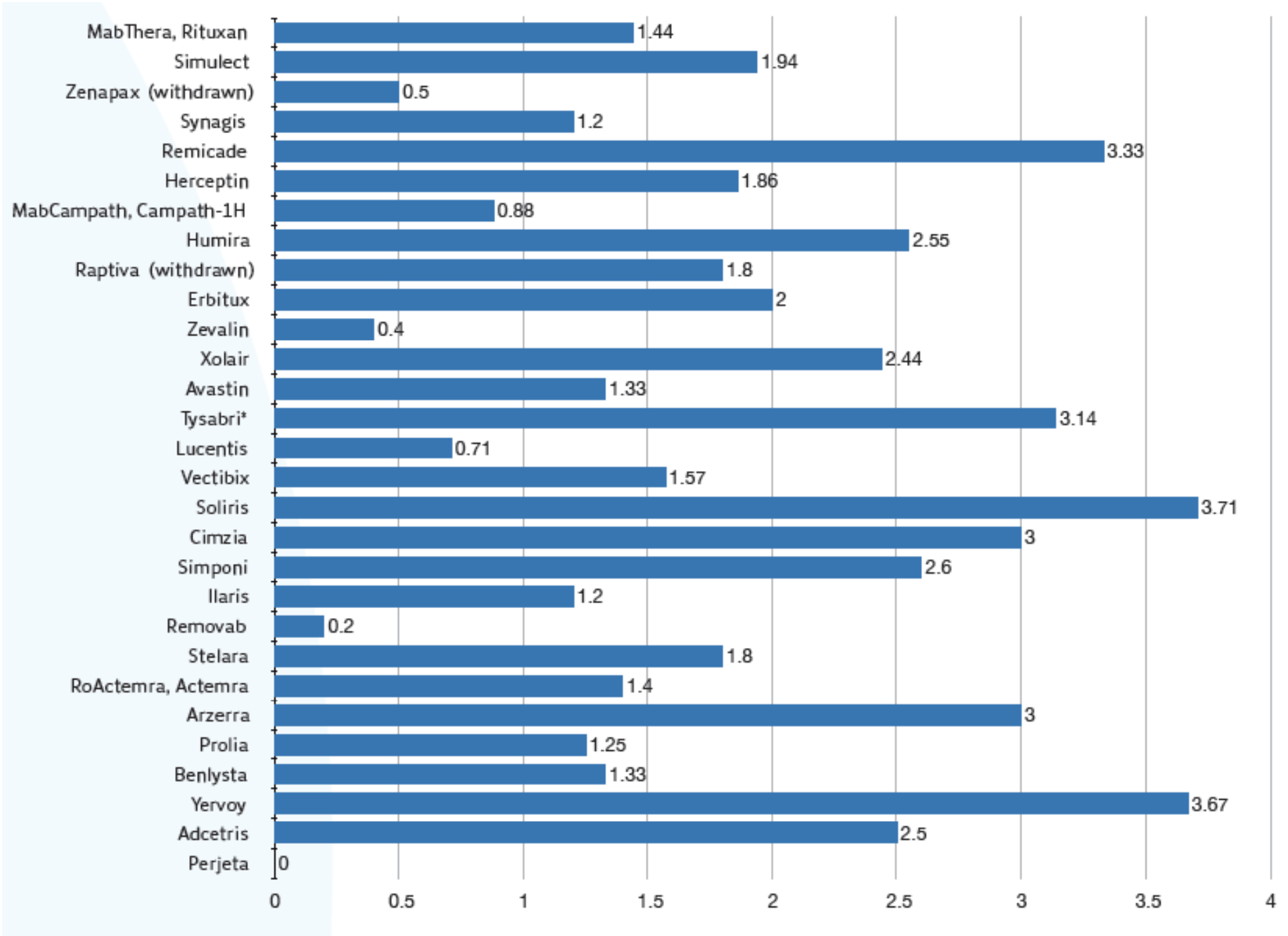


Diverso processo = Diverso prodotto

A

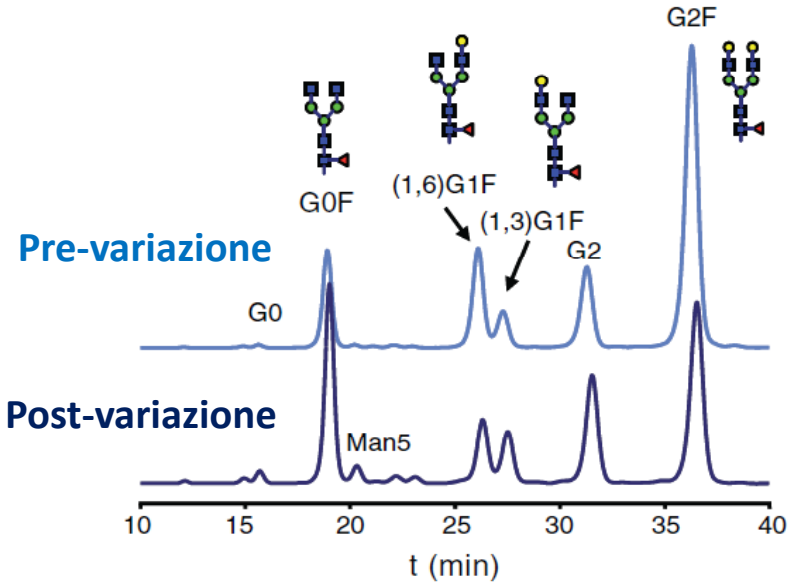

Changes in the manufacturing process after approval
0
5
10
15
20
25
30
35
40
MabThera®
Remicade®
Enbrel®
Humira®
Orencia®
RoActemra®
Simponi®
Cimzia®
Rilonacept Regeneron®
Ilaris®
Benlysta®

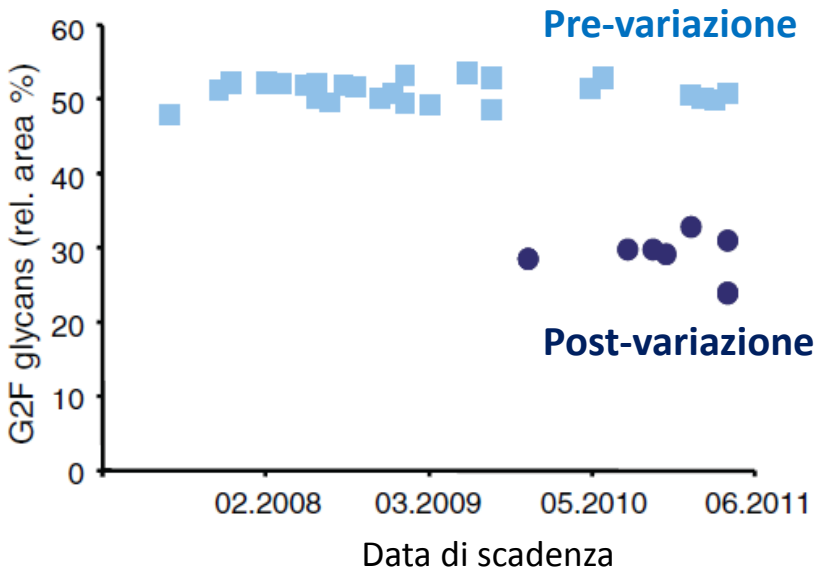

No of changes with high risk
No of changes with medium risk
No of changes with low risk
50
40
30
20
10
0
MabThera, Rituxan
Simulect
Zenapax (withdrawn)
Synagis
Remicade
Herceptin
MabCampath, Campath-1H
Humira
Raptiva (withdrawn)
ErbituX
Zevalin
Xolair
Avastin
Tysabri®
Lucentis
Vectibix
Soliris
Cimzia
Simponi
Ilaris
Removab
Stelara
RoActemra, Actemra
Arzerra
Prolia
Benlysta
Yervoy
Adcetris
Perjeta


MabThera, Rituxan
1.44
Simulect
1.94
Zenapax (withdrawn)
0.5
Synagis
1.2
Remicade
3.33
Herceptin
1.86
MabCampath, Campath-1H
0.88
Humira
2.55
Raptiva (withdrawn)
1.8
Erbitux
2
Zevalin
0.4
Xolair
2.44
Avastin
1.33
Tysabri*
3.14
Lucentis
0.71
Vectibix
1.57
Soliris
3.71
Cimzia
3
Simponi
2.6
Ilaris
1.2
Removab
0.2
Stelara
1.8
RoActemra, Actemra
1.4
Arzerra
3
Prolia
1.25
Benlysta
1.33
Yervoy
3.67
Adcetris
2.5
Perjeta
0
0
0.5
1
1.5
2
2.5
3
3.5
4

Caratterizzazione di lotti commerciali: Enbrel® (etanercept)

Variazioni lotto-lotto - Profili glicosilazione





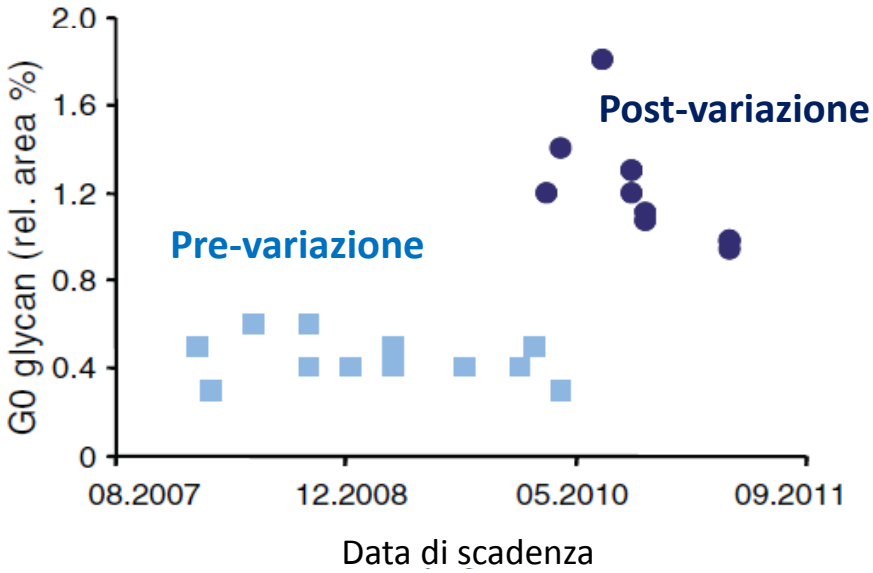
- **Differenze/shift nei pattern di glicosilazione**
- **Il nome di prodotto è rimasto invariato – indicando qualità comparabile**

Schiesti M et al. Acceptable changes in quality attributes of glycosylated biopharmaceuticals. Nat. Biotechnol, 2011;29:310-312

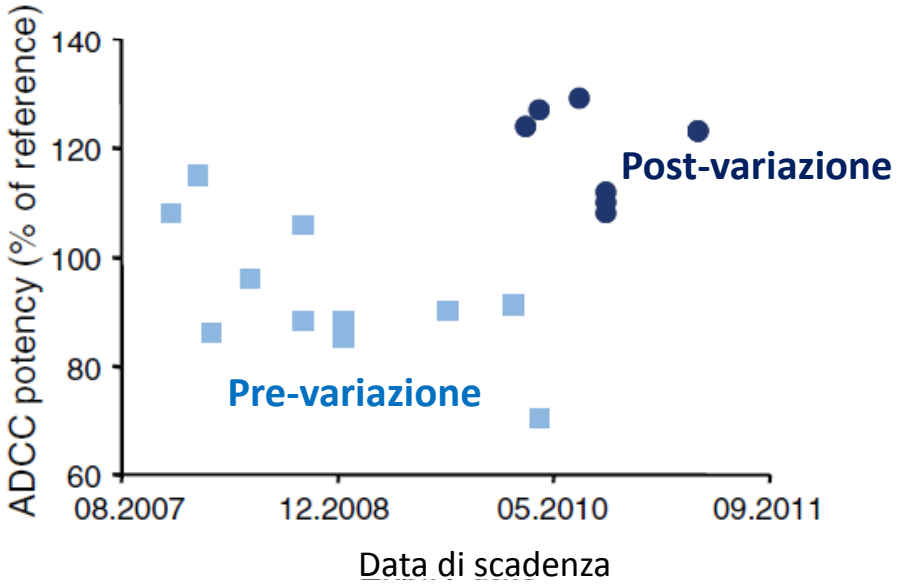
Caratterizzazione di lotti commerciali: Mabthera®/Rituxan® (rituximab)

Variazioni lotto-lotto- Glicosilazione e Potenza ADCC

Profilo glicosilazione (no fucosilato)



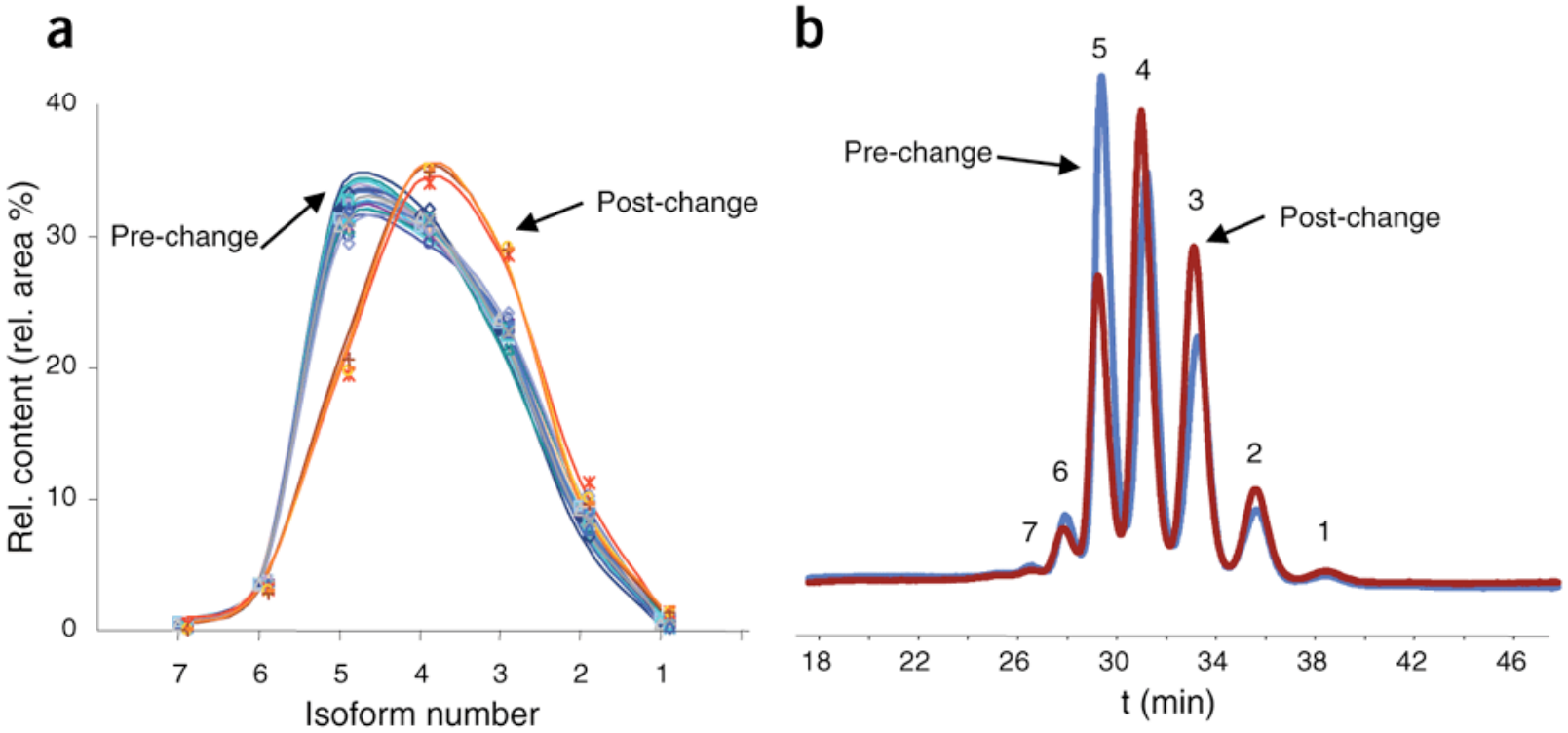
Potenza ADCC



- **Significative variazioni strutturali determinano anche variazioni funzionali**
- **Il nome di prodotto è rimasto invariato – indicando qualità comparabile**

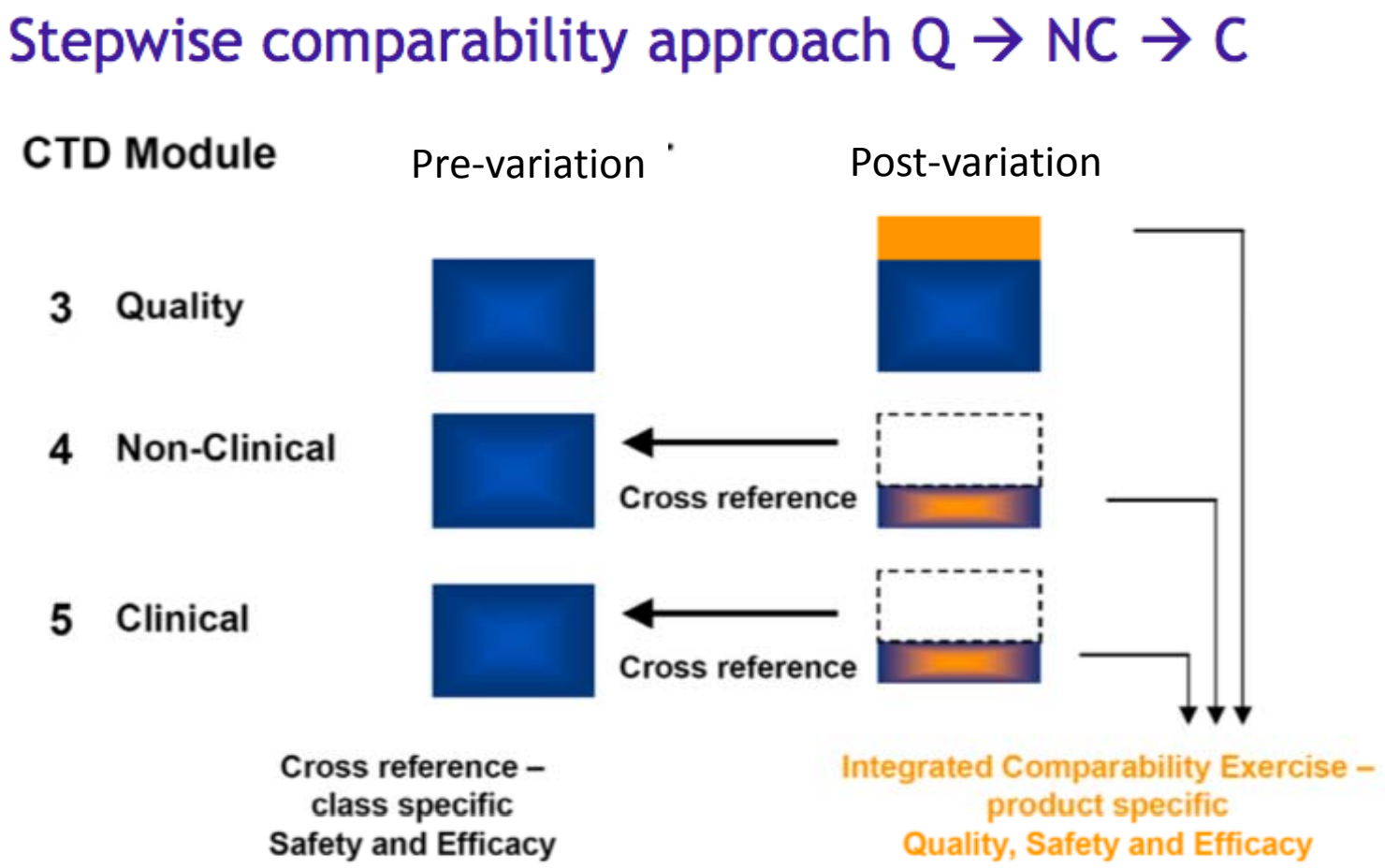
Schiesti M et al. Acceptable changes in quality attributes of glycosylated biopharmaceuticals. Nat. Biotechnol, 2011;29:310-312

Farmaci che hanno subito un cambiamento produttivo



darbepoetina

1) Farmaci biotecnologici prodotti con processi diversi saranno diversi tra loro (*the process is the product and the product is the process*)
2) Piccole differenze in un prodotto biotecnologico possono portare a grandi differenze cliniche e grandi differenze in un prodotto biotecnologico possono portare a nessuna differenza clinica.



European Medicines Agency

June 2005
CPMP/ICH/5721/03

ICH Topic Q 5 E
Comparability of Biotechnological/Biological Products

Step 5

NOTE FOR GUIDANCE ON BIOTECHNOLOGICAL/BIOLOGICAL PRODUCTS SUBJECT TO CHANGES IN THEIR MANUFACTURING PROCESS

(CPMP/ICH/5721/03)

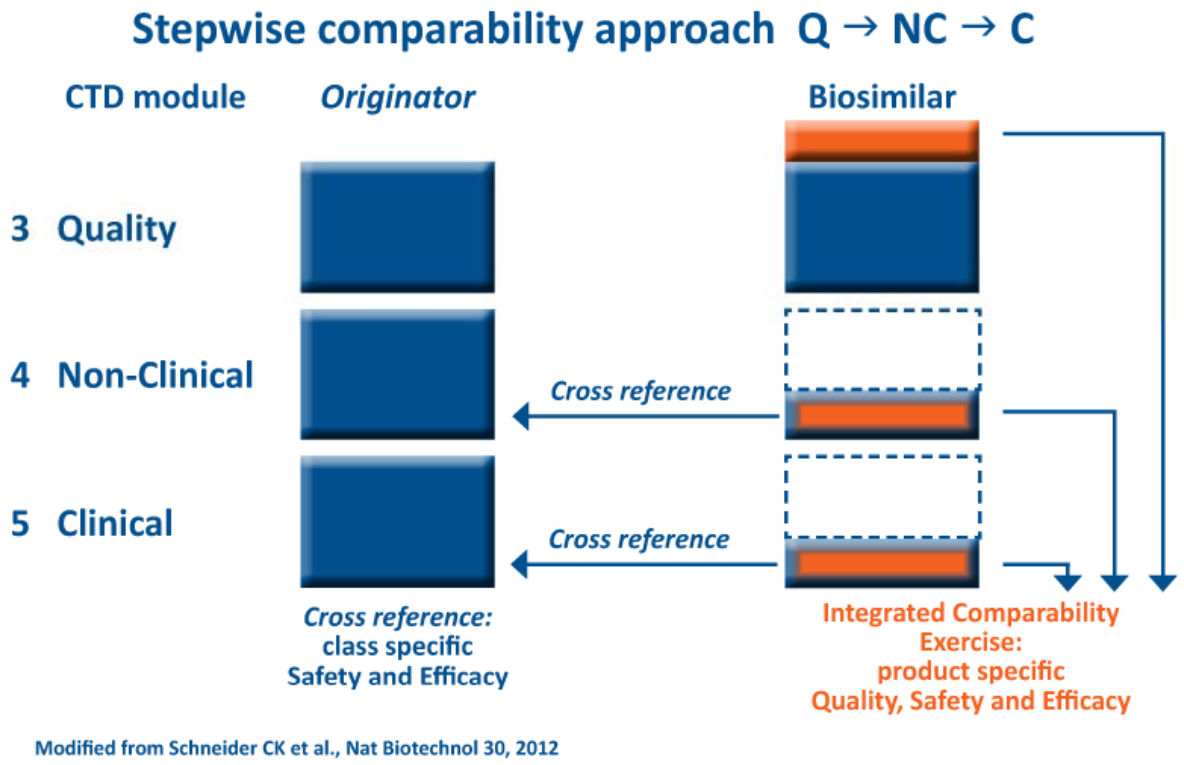
TRANSMISSION TO CHMP	November 2003
TRANSMISSION TO INTERESTED PARTIES	November 2003
DEADLINE FOR COMMENTS	May 2004
FINAL APPROVAL BY CHMP	December 2004
DATE FOR COMING INTO OPERATION	June 2005

The goal of the comparability exercise is to ensure the quality, safety and efficacy of drug product produced by a changed manufacturing process, through collection and evaluation of the relevant data to determine whether there might be any adverse impact on the drug product due to the manufacturing process changes.

The demonstration of comparability does not necessarily mean that the quality attributes of the pre-change and post-change product are identical, but that they are highly similar and that the existing knowledge is sufficiently predictive to ensure that any differences in quality attributes have no adverse impact upon safety or efficacy of the drug product.

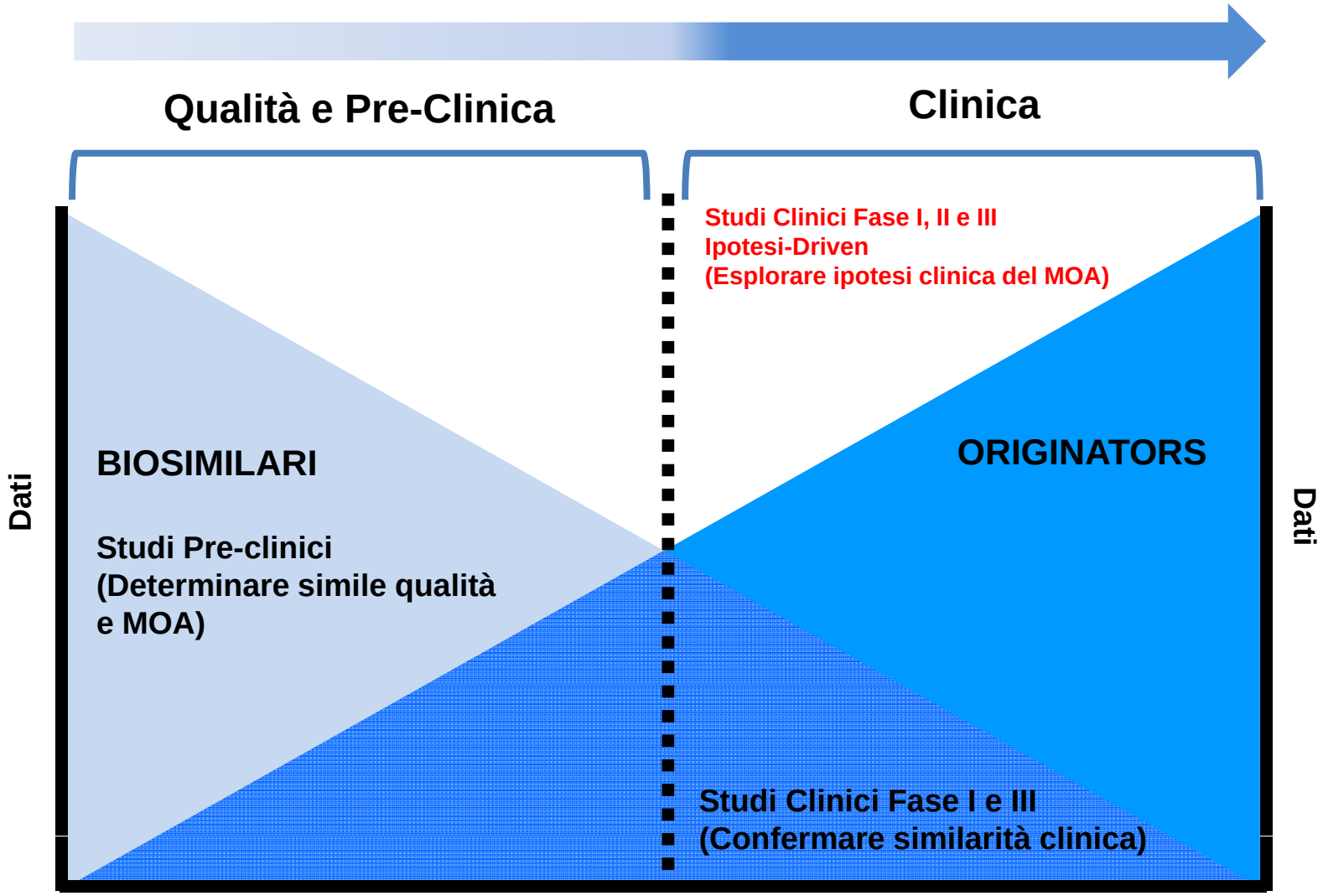
SOCIETÀ ITALIANA DI FARMACOLOGIA

IL *COMPARABILITY EXERCISE*



L'EMA delega alle singole Agenzie Nazionali il tema della sostituibilità e intercambiabilità

Biosimilari e Originator: basi scientifiche



Modificata da Schneider CK et al., Nat Biotechnol 30, 2012

Estrapolazione delle indicazioni in pratica

Remicade indicazioni	Remsima indicazioni
Sponsilite Anchilosante →	Fase I, randomizzato, in doppio cieco in 250 AS pts. Profili di farmacocinetica, sicurezza ed efficacia tutti paragonabili a INX-Ref.
Artrite Reumatoide →	Fase III, randomizzato, in doppio cieco in 606 pazienti. Efficacia, immunogenicità e sicurezza paragonabili a INX-Ref.
Artrite Psoriasica	↓ Ulteriori indicazioni estrapolate sulla base dei dati clinici in AS & RA, dettagliata dimostrazione di **similarità molecolare,** e risonoscimento della **patologia molecolare conservata** per tutte le attuali indicazioni di INX-Ref
Psoriasi	
Malattia di Crohn	
Colite Ulcerosa	

L'EMA approva quindi, in seguito al *comparability exercise*, il farmaco biosimilare come sovrapponibile al farmaco di riferimento (rischio/beneficio sovrapponibile tra i due farmaci).

Analoghe considerazioni valgono anche per i farmaci biologici, inclusi i biotecnologici ed i corrispondenti biosimilari. Per quanto concerne i farmaci biosimilari, infatti, l'identità del principio attivo e l'accertamento della biosimilarità rispetto al biologico di riferimento, compiuto dall'EMA in sede di rilascio dell'AIC, assicurano che tra il biologico di riferimento e il corrispondente biosimilare non vi siano differenze cliniche rilevanti, in termini di qualità, sicurezza ed efficacia, per le indicazioni terapeutiche autorizzate. Conseguentemente, l'art. 15, comma 11 *ter*, non trova applicazione, sia in quanto la norma fa testuale riferimento all'"*equivalenza terapeutica fra medicinali contenenti diversi principi attivi*", sia in quanto la valutazione della biosimilarità, che si fonda su uno specifico "*esercizio di comparabilità*" condotto a livello europeo dall'EMA seguendo i massimi standard scientifici, assorbe e rende superflua, ai fini della tutela della salute pubblica, ogni ulteriore valutazione in ordine alla sovrapponibilità di un biosimilare rispetto al biologico di riferimento.

ICH Q5E vs EMA guidelines

Sostituibilità
intercambiabilità

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

March 2015
EMA/940451/2011
Committee for Human Medicinal Products (CHMP)

EMA Procedural advice for users of the Centralised Procedure for Similar Biological Medicinal Products applications

44. Will my similar biological medicinal product be considered interchangeable with the reference medicinal product?

The decisions on interchangeability and/or substitution rely on national competent authorities and are outside the remit of EMA/CHMP. Member States have access to the scientific evaluation performed by the CHMP and all submitted data in order to substantiate their decisions.

Stati Uniti

L'FDA ha deciso di procedere ad una doppia procedura di approvazione:

The manufacturer must submit an application for a **biosimilar** or **interchangeable** biological product that includes, among other things, information demonstrating biosimilarity based upon data from analytical studies, animal studies, and clinical studies such as the assessment of immunogenicity and pharmacokinetics (PK) or pharmacodynamics (PD).

If the manufacturer wants its product to be reviewed as an interchangeable product, the application must also include data or information to show that the proposed interchangeable product is expected to produce the same clinical result as the reference product in any given patient. In addition, when a product will be administered more than once to an individual (as many biological products are), the manufacturer must also demonstrate that the risk in terms of safety or reduced effectiveness of alternating or switching between use of the proposed interchangeable product and the reference product is not greater than the risk of using the reference product without alternating or switching. This is in addition to the data described above to demonstrate biosimilarity.

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm241718.htm

10 SEP 2014 (prima dell'uscita del primo biosimilare)

Currently, **only eight states have enacted biosimilar substitution laws** (Delaware, Florida, Indiana, Massachusetts, North Dakota, Oregon, Utah and Virginia). All these laws are of the permissive type – even where the same state requires mandatory generic substitution for small-molecule drugs, as in Florida. Many newly enacted laws also include provisions that further restrict the substitution or place additional requirements on the pharmacist. For example, Indiana only allows a biosimilar substitution if the prescriber writes "may substitute" on the prescription. Utah, North Dakota and Oregon all require the pharmacist to notify the prescriber of the substitution within one to three days

An additional 13 states have considered or currently have legislation pending to govern biosimilar substitution, including Georgia, New Jersey, Pennsylvania, Washington and Vermont, which have newly introduced legislation or bills under active consideration.

fimea

22.05,2015

Interchangeability of Biosimilars – Position of Finnish Medicines Agency Fimea

In this document, interchangeability means the medical practice of changing one medicine for another that is expected to achieve the same clinical effect in a given clinical setting and in any patient on the initiative, or with the agreement of the prescriber. This document does not deal with substitution at the pharmacy level.

The following conclusions can be made on the basis of the above considerations:

- Switches between biological products are common and usually not problematic, e.g. in the context of hospital tendering processes.
- For time being, there is no evidence for adverse effects due to the switch from a reference product to a biosimilar
- The theoretical basis of such adverse effects is weak

Un problema irrilevante?

	Anno	Dati Osmed 2013	
		Convenzionata Tab. 7.2.21	Strutture pubbliche Tab. 7.2.22
Approvati EMA			
epoetina alfa	2009		2,60*
filgrastim	2011		
ormone della crescita	2006	0.2*	1,49*
infliximab	2015		1,5
insulina glargine	2015	0.5	1,43
follitropina	2015		0.68
Prodotti in valutazione Aprile 2015			
enoxaparina		2.6	1.32
etanercept			3.72
insulina umana			
infliximab			
Alcuni Biosimilari in sviluppo			
trastuzumab			4.02
adalimumab			3.83
rituximab			3.18
pegfilgrastim			0.79
bevacizumab			2.39
ranibizumab			1,41
darbepoetina alfa			1,87
cetuximab			0.94

Spesa farmaci già scaduti di brevetto: 8,4 euro pro capite*
Spesa farmaci in valutazione: 7,6 euro pro capite
Spesa farmaci in sviluppo: 18,43 euro pro capite