Armando A. Genazzani
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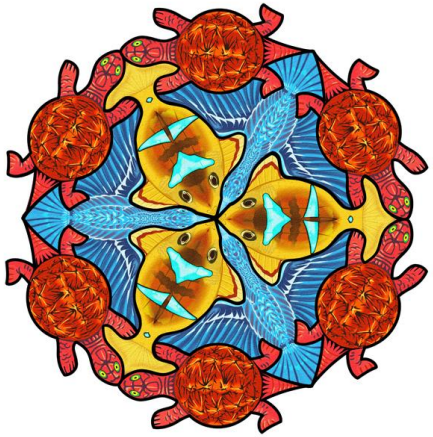
347.9829981



Centro
Ricerca
Interdipartimentale
Farmacogenetica
Farmacogenomica

Conflict of interest disclosure on biosimilars (two-years): Sandoz, Hospira, Roche, Boehringer-Ingheleim, Eli-Lilly, Mundipharma

1970s	Chemical sameness	“copies”	available data
1980s	+ pharmacokinetic comparability	“generics”	+ bioequivalence
2000s	+ therapeutic comparability	“biosimilars”	+ clinical studies

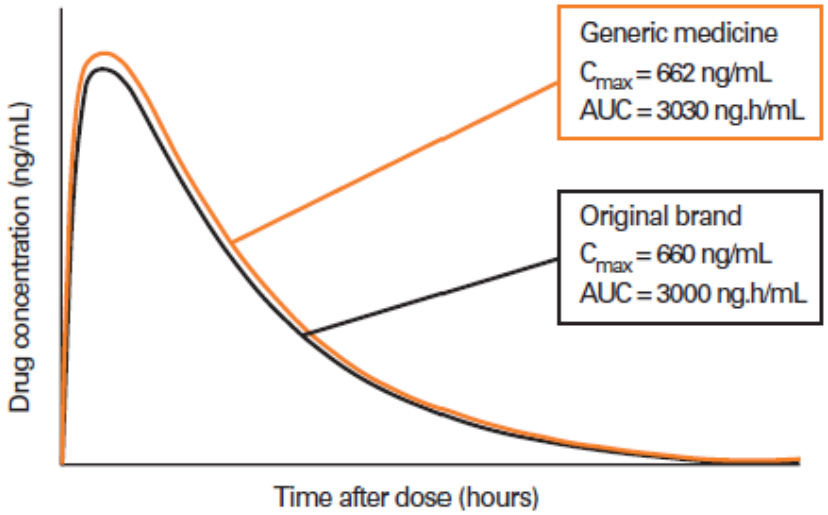
Bioequivalence is then determined by comparing the peak plasma concentration (Cmax), time to achieve a maximal concentration (Tmax) and the extent of absorption (area under the concentration-time curve, AUC) of the products.

The same bioequivalence principles apply to new drugs when different formulations of an active ingredient are compared.

Fig. 1

Bioequivalence analysis – a hypothetical bioequivalence study

Mean concentration–time curves for two brands of a drug after single oral doses



The original brand:generic medicine ratio for AUC is 0.99 (90% CI 0.91 to 1.04) and for C_{max} is 0.99 (90% CI 0.92 to 1.07).

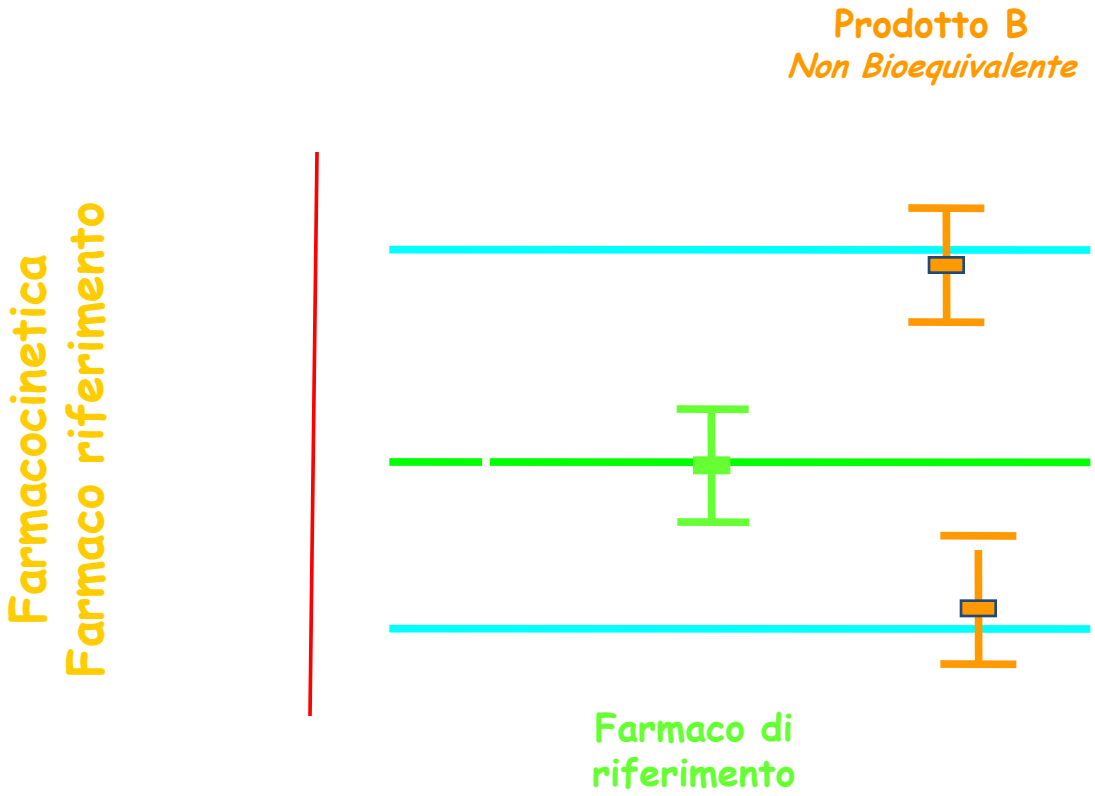
C_{max}	peak plasma concentration
AUC	area under the concentration–time curve
CI	confidence interval

Reprinted with permission from NPS News 2006;44:3.

Aust Prescr 2007;30:41-3

Requisiti per la bioequivalenza imposti dalla FDA

Il Prodotto A è bioequivalente al farmaco di riferimento; 90% CI della AUC cade tra 80% - 125% del farmaco di riferimento



Il Prodotto B non è bioequivalente al farmaco di riferimento; 90% CI della AUC cade fuori 80% -125% del farmaco di riferimento

THE ANNALS OF PHARMACOTHERAPY

Ann Pharmacother. 2009 Oct;43(10):1583-97. Epub 2009 Sep 23.

Comparing generic and innovator drugs: a review of 12 years of bioequivalence data from the United States Food and Drug Administration.

Davit BM, Nwakama PE, Buehler GJ, Conner DP, Haidar SH, Patel DT, Yang Y, Yu LX, Woodcock J.

Division of Bioequivalence II, Office of Generic Drugs, Office of Pharmaceutical Sciences, Center for Drug Evaluation and Research, United States Food and Drug Administration, Derwood, MD 20855, USA. barbara.davit@fda.hhs.gov

Abstract

BACKGROUND: In the US, manufacturers seeking approval to market a generic drug product must submit data demonstrating that the generic formulation provides the same rate and extent of absorption as (ie, is bioequivalent to) the innovator drug product. Thus, most orally administered generic drug products in the US are approved based on results of one or more clinical bioequivalence studies.

OBJECTIVE: To evaluate how well the bioequivalence measures of generic drugs approved in the US over a 12-year period compare with those of their corresponding innovator counterparts.

METHODS: This retrospective analysis compared the generic and innovator bioequivalence measures from 2070 single-dose clinical bioequivalence studies of orally administered generic drug products approved by the Food and Drug Administration (FDA) from 1996 to 2007 (12 y). Bioequivalence measures evaluated were drug peak plasma concentration (C(max)) and area under the plasma drug concentration versus time curve (AUC), representing drug rate and extent of absorption, respectively. The generic/innovator C(max) and AUC geometric mean ratios (GMRs) were determined from each of the bioequivalence studies, which used from 12 to 170 subjects. The GMRs from the 2070 studies were averaged. In addition, the distribution of differences between generic means and innovator means was determined for both C(max) and AUC.

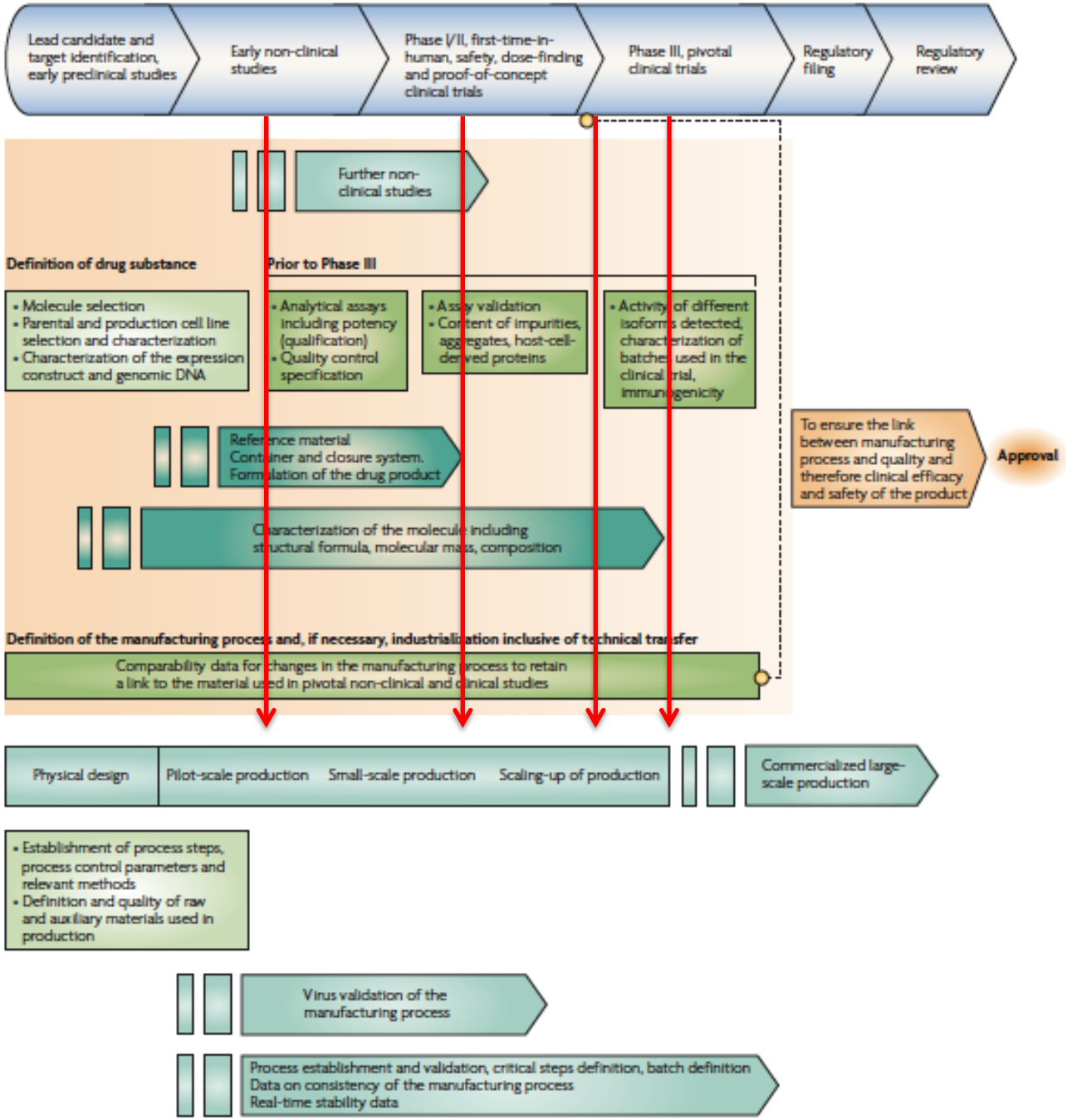
RESULTS: **The mean +/- SD of the GMRs from the 2070 studies was 1.00 +/- 0.06 for C(max) and 1.00 +/- 0.04 for AUC. The average difference in C(max) and AUC between generic and innovator products was 4.35% and 3.56%, respectively. In addition, in nearly 98% of the bioequivalence studies conducted during this period, the generic product AUC differed from that of the innovator product by less than 10%.**

CONCLUSIONS: The criteria used to evaluate generic drug bioequivalence studies support the FDA's objective of approving generic drug formulations that are therapeutically equivalent to their innovator counterpart.

Bioequivalenza nel pre-marketing

- Gli studi sperimentali sono eseguiti di solito con formulazioni del prodotto farmaceutico diverse da quelle successivamente introdotte sul mercato e spesso le aziende produttive modificano il procedimento industriale di produzione.

Anche in tutte queste circostanze si applicano le regole che sono richieste per valutare la bioequivalenza di un prodotto generico.


Lead candidate and target identification, early preclinical studies
Early non-clinical studies
Phase I/II, first-time-in-human, safety, dose-finding and proof-of-concept clinical trials
Phase III, pivotal clinical trials
Regulatory filing
Regulatory review
Further non-clinical studies
Definition of drug substance
Prior to Phase III
• Molecule selection
• Parental and production cell line selection and characterization
• Characterization of the expression construct and genomic DNA
• Analytical assays including potency (qualification)
• Quality control specification
• Assay validation
• Content of impurities, aggregates, host-cell-derived proteins
• Activity of different isoforms detected, characterization of batches used in the clinical trial, immunogenicity
Reference material
Container and closure system.
Formulation of the drug product
Characterization of the molecule including structural formula, molecular mass, composition
To ensure the link between manufacturing process and quality and therefore clinical efficacy and safety of the product
Approval
Definition of the manufacturing process and, if necessary, industrialization inclusive of technical transfer
Comparability data for changes in the manufacturing process to retain a link to the material used in pivotal non-clinical and clinical studies
Physical design
Pilot-scale production
Small-scale production
Scaling-up of production
Commercialized large-scale production
• Establishment of process steps, process control parameters and relevant methods
• Definition and quality of raw and auxiliary materials used in production
Virus validation of the manufacturing process
Process establishment and validation, critical steps definition, batch definition
Data on consistency of the manufacturing process
Real-time stability data

Bioequivalenza dei farmaci branded

- Modifiche nel procedimento industriale o nell' impianto di produzione dei farmaci condizionano la bioequivalenza di **tutti** i farmaci
- Inoltre i farmaci con stesso principio attivo prodotti in co-marketing contengono spesso eccipienti differenti

In tutti questi casi si applicano gli stessi concetti di bioequivalenza validi per i generici

INFORMATION FROM EUROPEAN UNION INSTITUTIONS AND BODIES

COMMISSION

Communication from the Commission – Guideline on the details of the various categories of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products

1. INTRODUCTION

Commission Regulation (EC) No 1234/2008 of 24 of November 2008, concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products[1], hereinafter 'the variations regulation', was published in the Official Journal on 12 December 2008. The variations regulation aims to establish a simple, clearer and more flexible legal framework for the handling of variations to marketing authorisation of medicinal products, while ensuring a high level of protection of public and animal health.

83 pagine

1970s	Chemical sameness	“copies”	available data
1980s	+ pharmacokinetic comparability	“generics”	+ bioequivalence
2000s	+ therapeutic comparability	“biosimilars”	+ clinical studies

Browse by letter for medicines that have a European Public Assessment Report:

A B C D E F G H I J K L M N O P Q R S T U V W X Y Z View all

Or for other types of content pick from the navigation on the left.

Include:

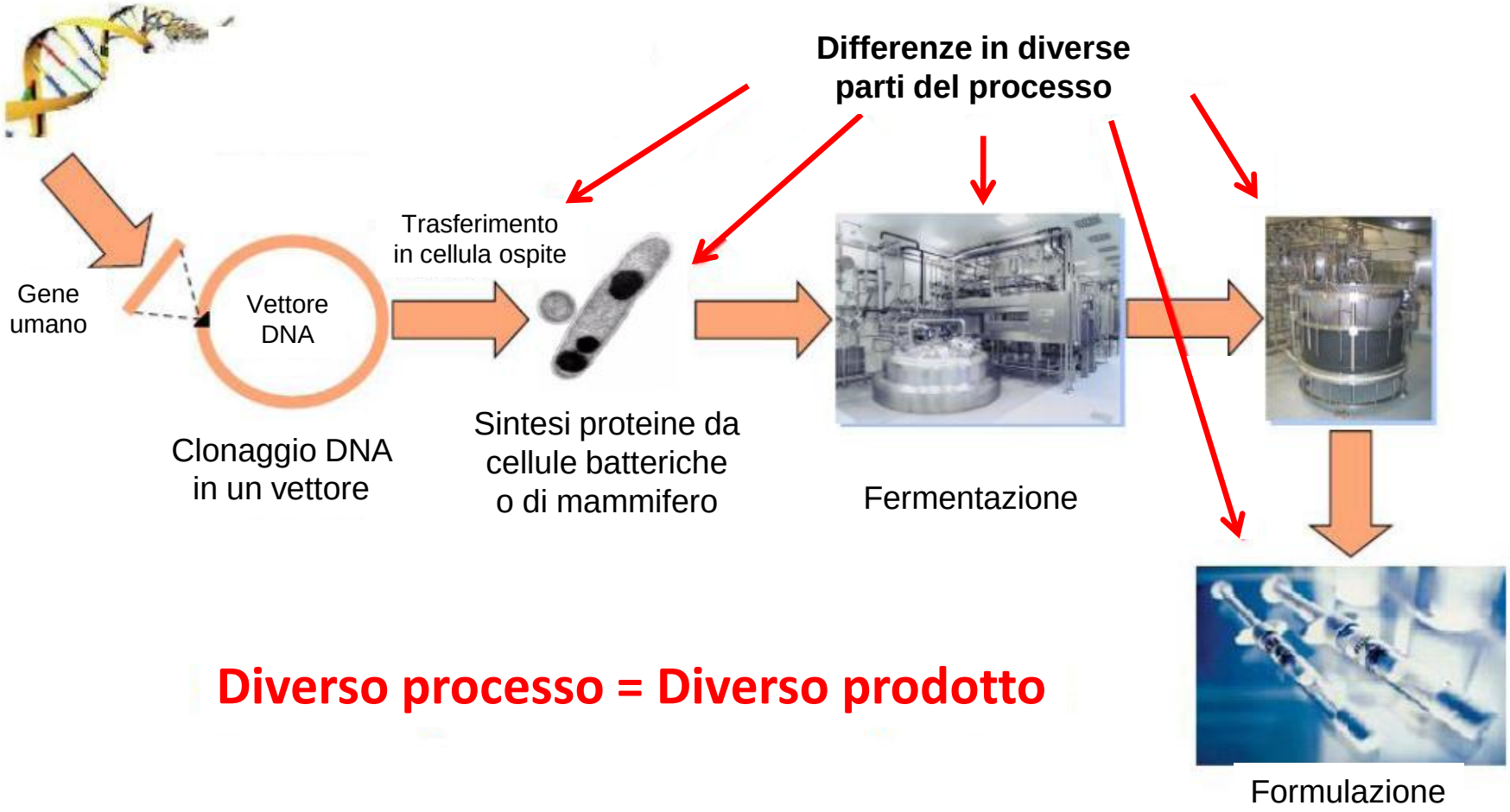
- [x] Authorised medicine
- [x] Withdrawn post-approval
- [x] Suspended
- [x] Refused

Download results to spreadsheet

Name	Active substance	Therapeutic area	Date of authorisation / refusal	▼	O	C	E	⚠	Status
Abasaglar (previously Abasria)	insulin glargine	Diabetes Mellitus	09/09/2014	▼					Authorised
Lantus	insulin glargine	Diabetes Mellitus	09/06/2000						Authorised
Toujeo (previously Optisulin)	insulin glargine	Diabetes Mellitus	27/06/2000						Authorised

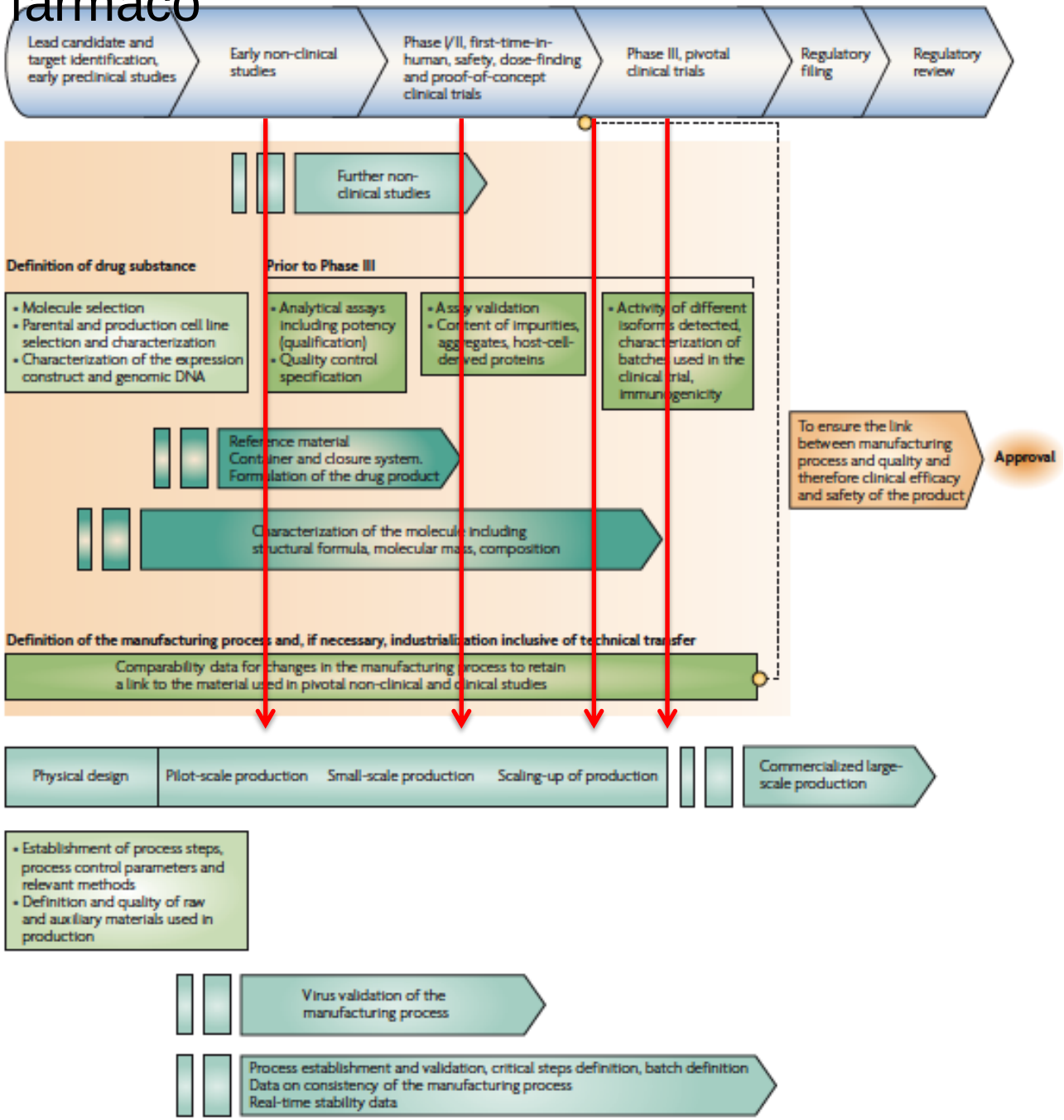
15 EMA 30 Churchill Place . Canary Wharf . London E14 5EU . United Kingdom . Tel. +44 (0)20 3660 6000 . Fax +44 (0)20 3660 5555

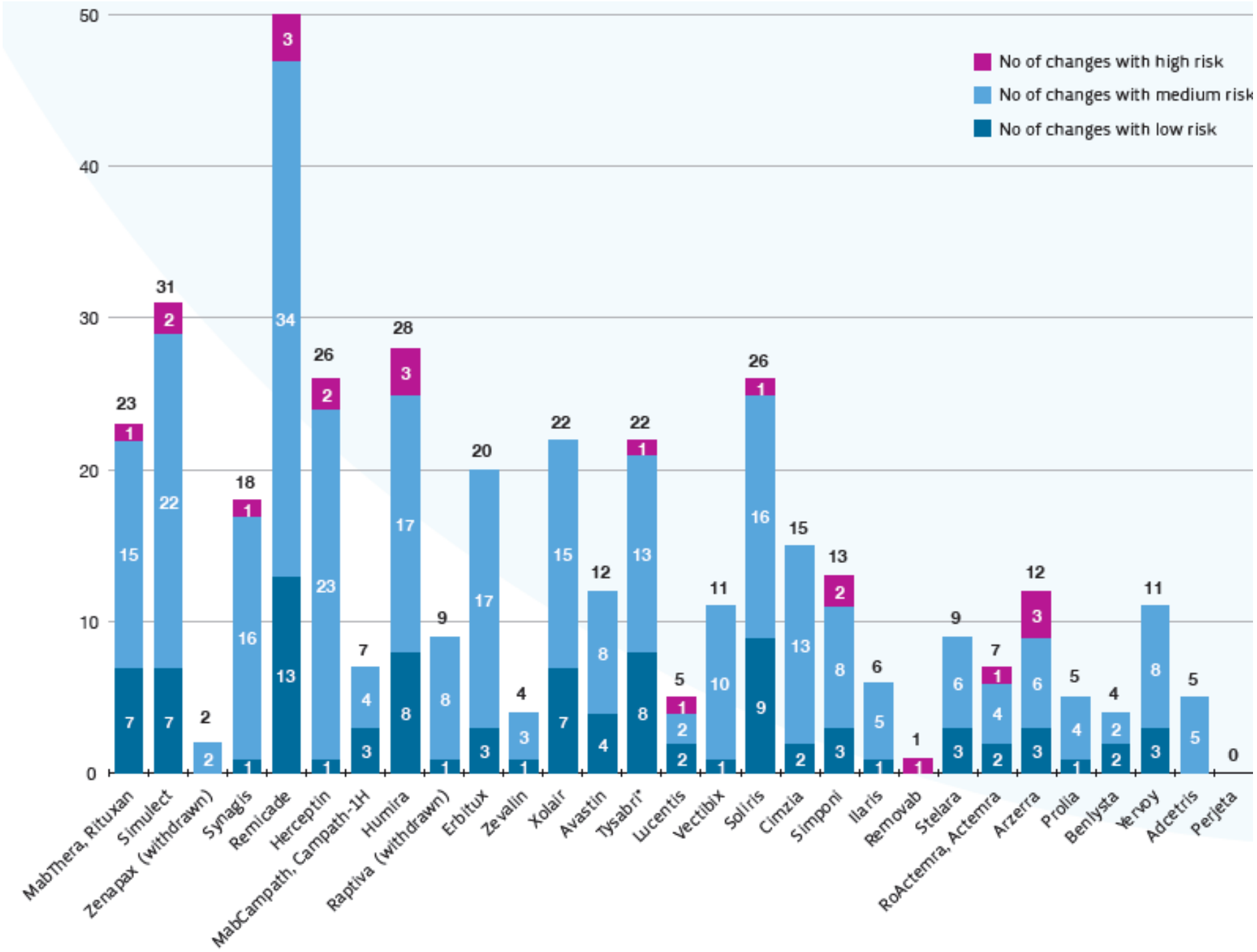
Il processo produttivo di un farmaco biologico è complesso



Diverso processo = Diverso prodotto

Lo sviluppo di un farmaco biotecnologico




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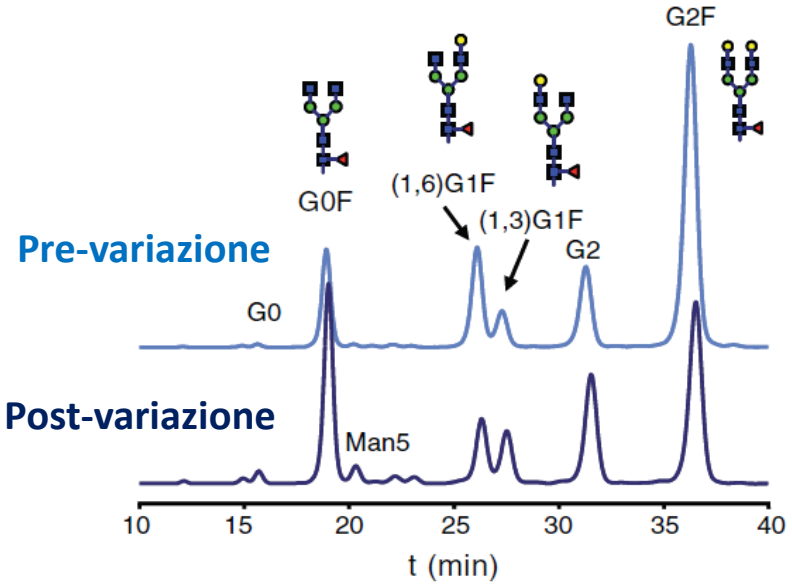
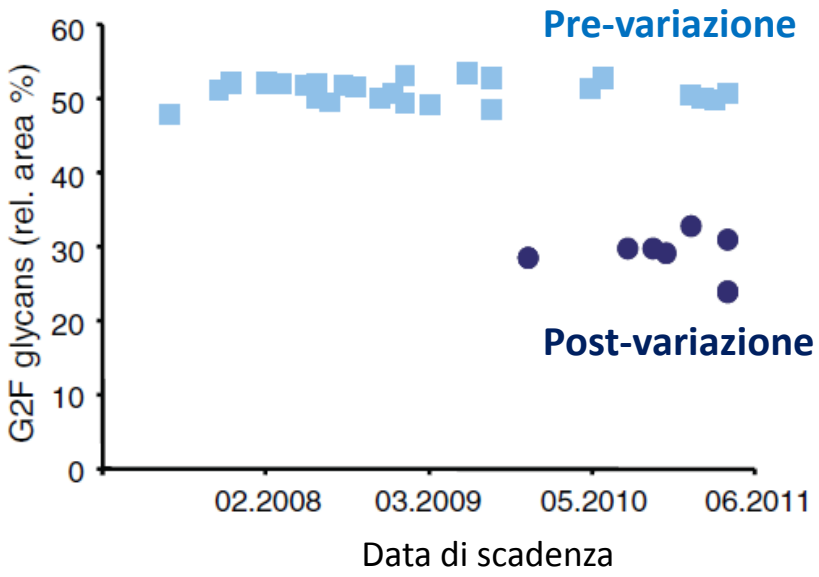
MabThera, Rituxan
Simulect
Zenapax (withdrawn)
Synagis
Remicade
Herceptin
MabCampath, Campath-1H
Humira
Raptiva (withdrawn)
Erbitux
Zevalin
Xolair
Avastin
Tysabri*
Lucentis
Vectibix
Soliris
Cimzia
Simponi
Ilaris
Removab
Stelara
RoActemra, Actemra
Arzerra
Prolia
Benlysta
Yervoy
Adcetris
Perjeta

Caratterizzazione di lotti commerciali: Enbrel® (etanercept)

Variazioni lotto-lotto - Profili glicosilazione





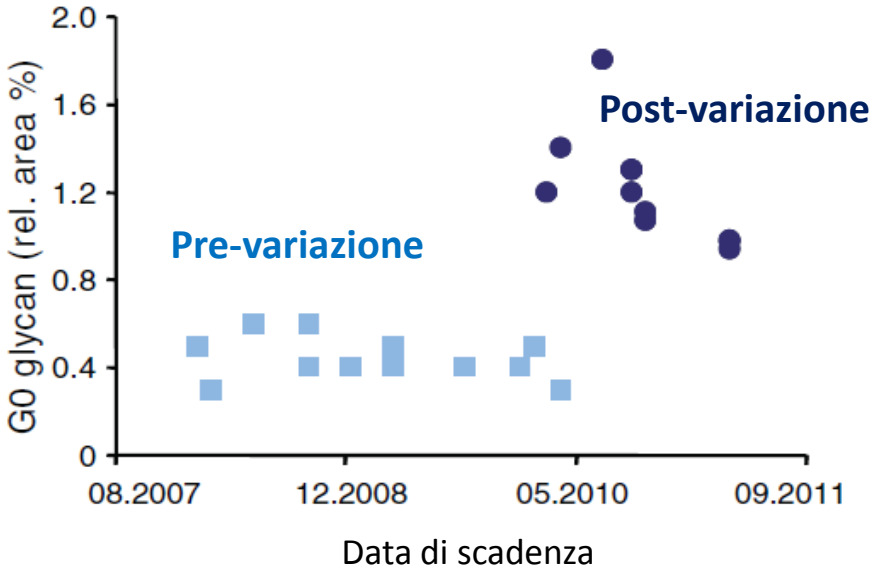
- **Differenze/shift nei pattern di glicosilazione**
- **Il nome di prodotto è rimasto invariato – indicando qualità comparabile**

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

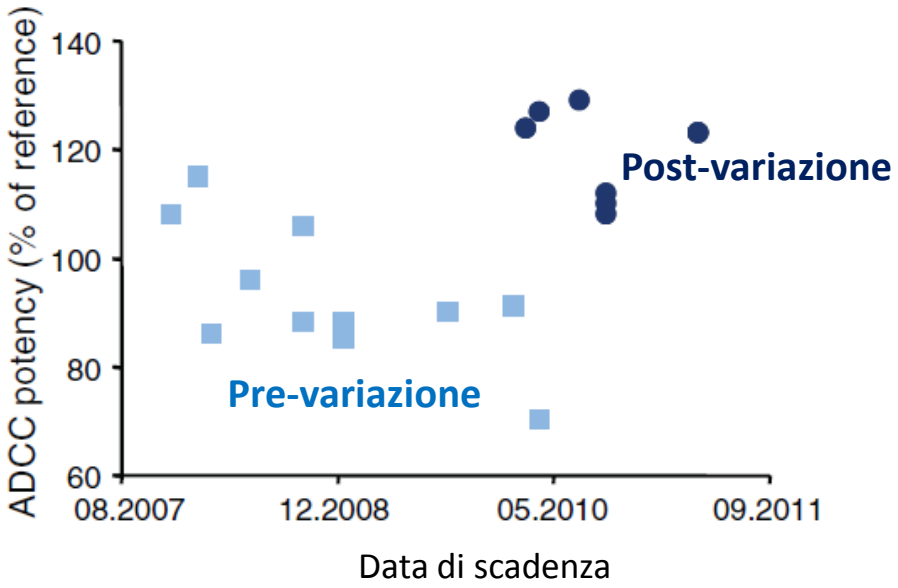
Caratterizzazione di lotti commerciali: Mabthera®/Rituxan® (rituximab)

Variazioni lotto-lotto- Glicosilazione e Potenza ADCC

Profilo glicosilazione (no fucosilato)



Potenza ADCC

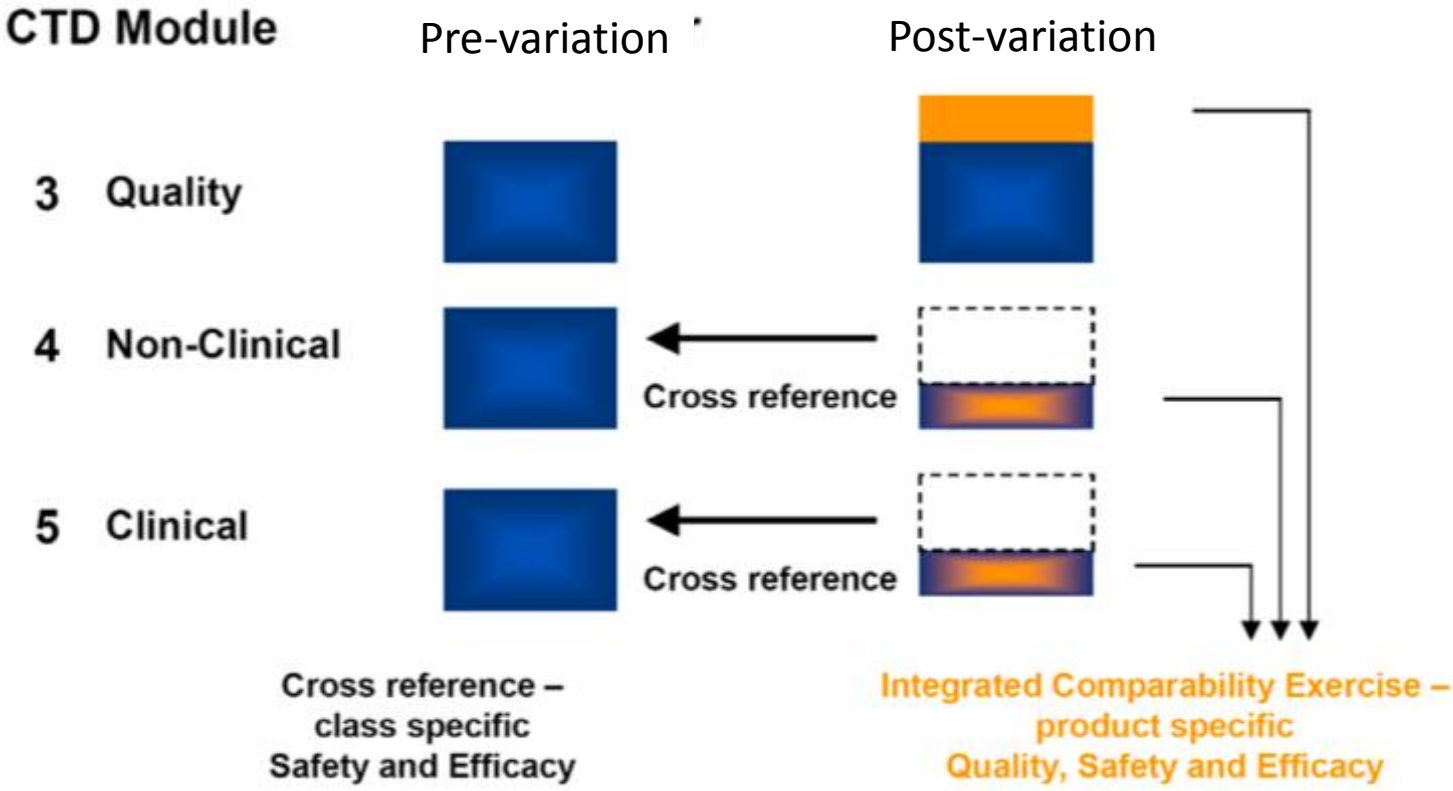


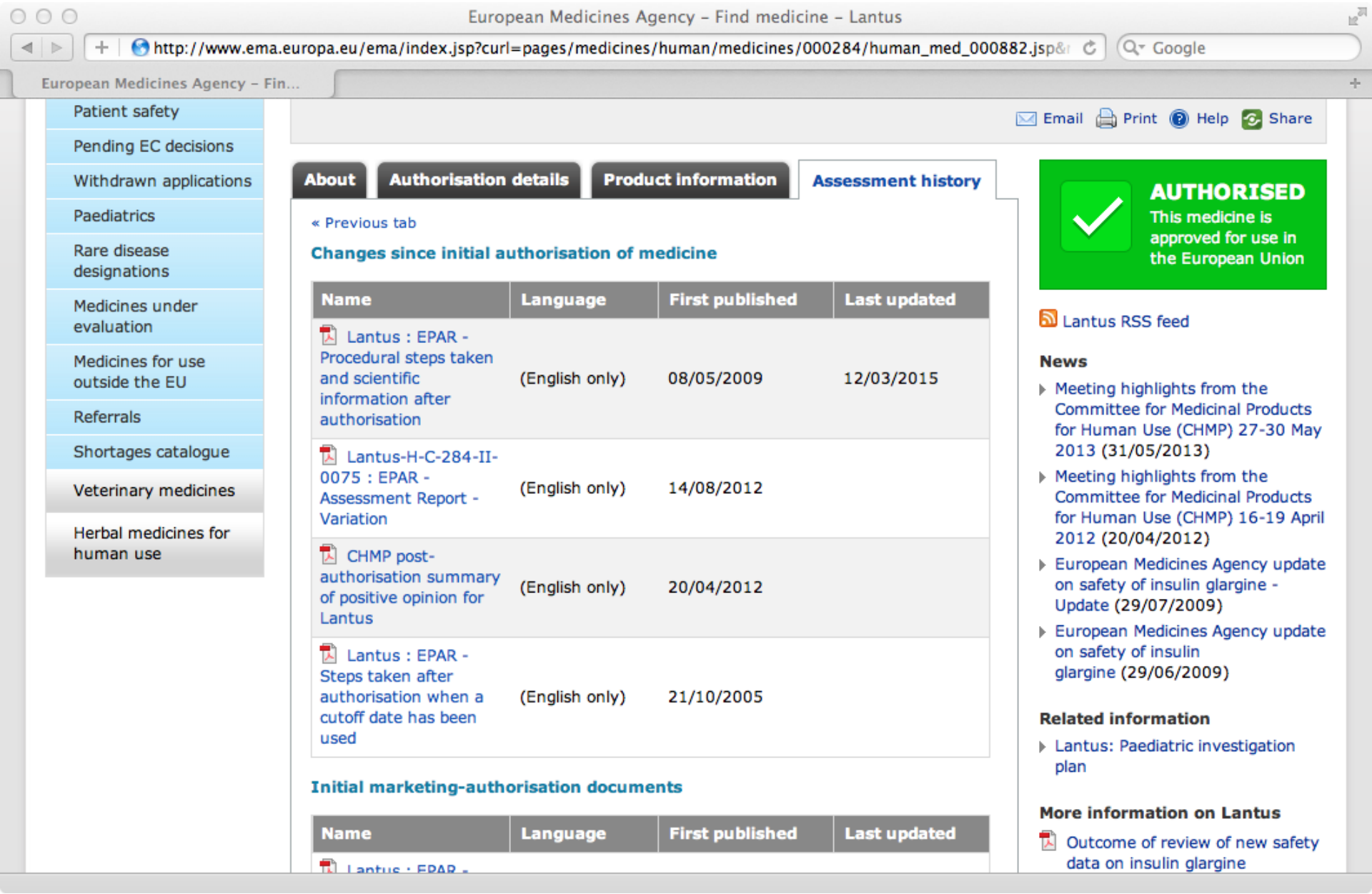
- **Significative variazioni strutturali determinano anche variazioni funzionali**
- **Il nome di prodotto è rimasto invariato – indicando qualità comparabile**

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

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.

Stepwise comparability approach Q → NC → C





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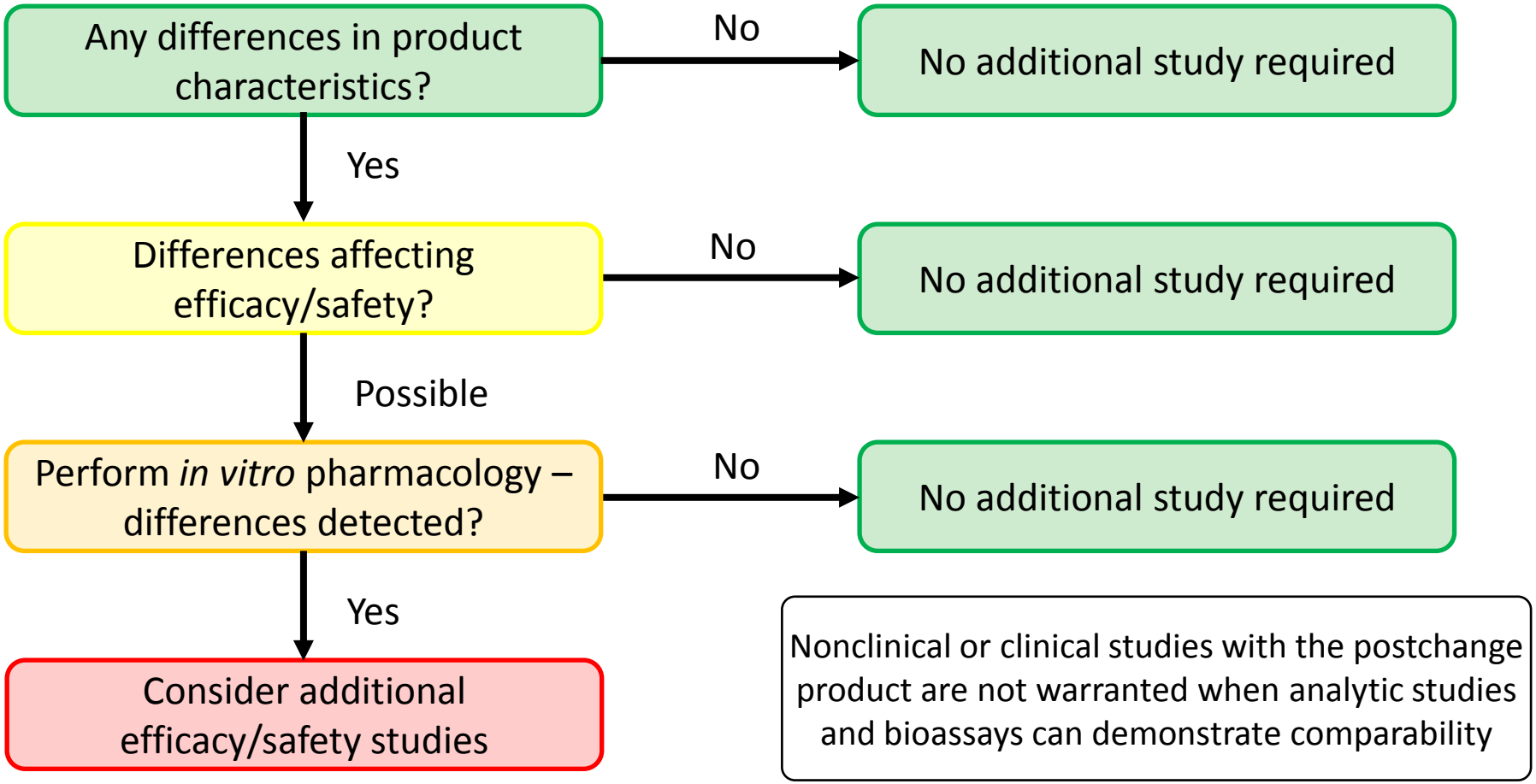
Requirement for Bridging Studies



Schlegel and Bobinnec. 2013. BioProcess International 11(6): 30 – 41; European Medicines Agency. Note for guidance on biotechnological/biological products subject to changes in their manufacturing process. 2005

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)

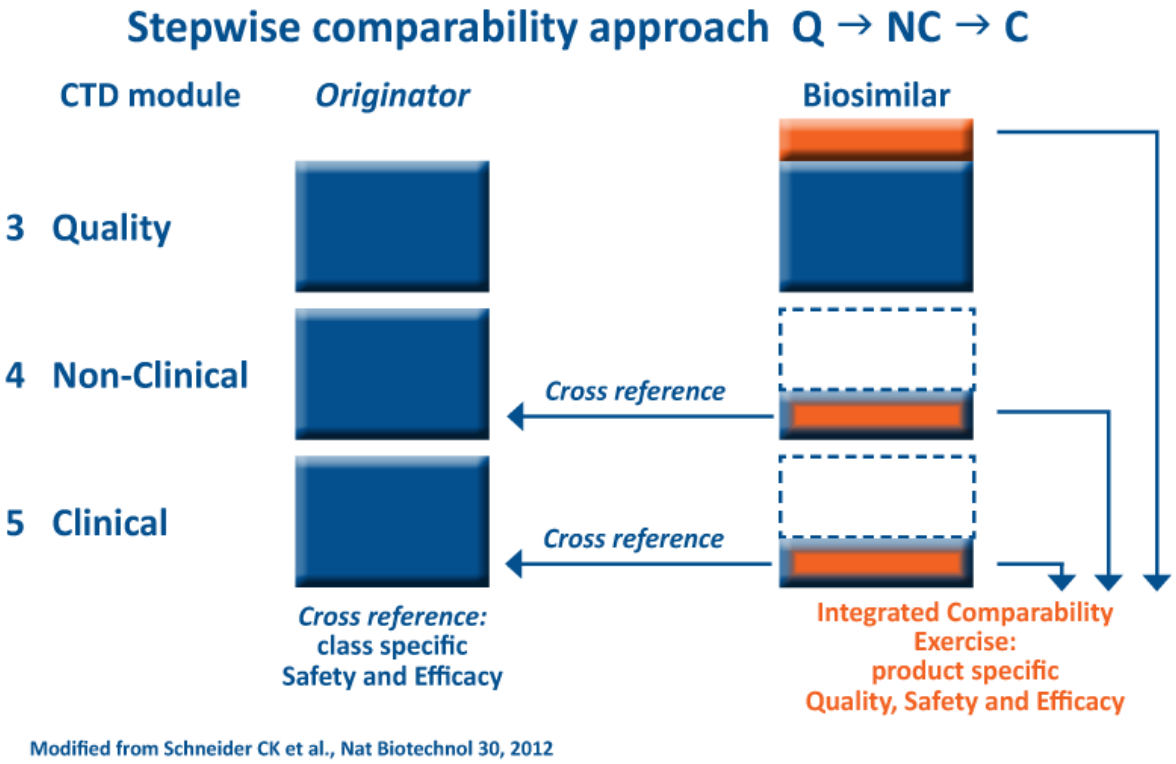
TRANSMISSION TO CHMP	November 2003
TRANSMISSION TO INTERESTED PARTIES	November 2003
DEADLINE FOR COMMENTS	May 2004
FINAL APPROVAL BY CHMP	December 2004
DATE FOR COMING INTO OPERATION	June 2005

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

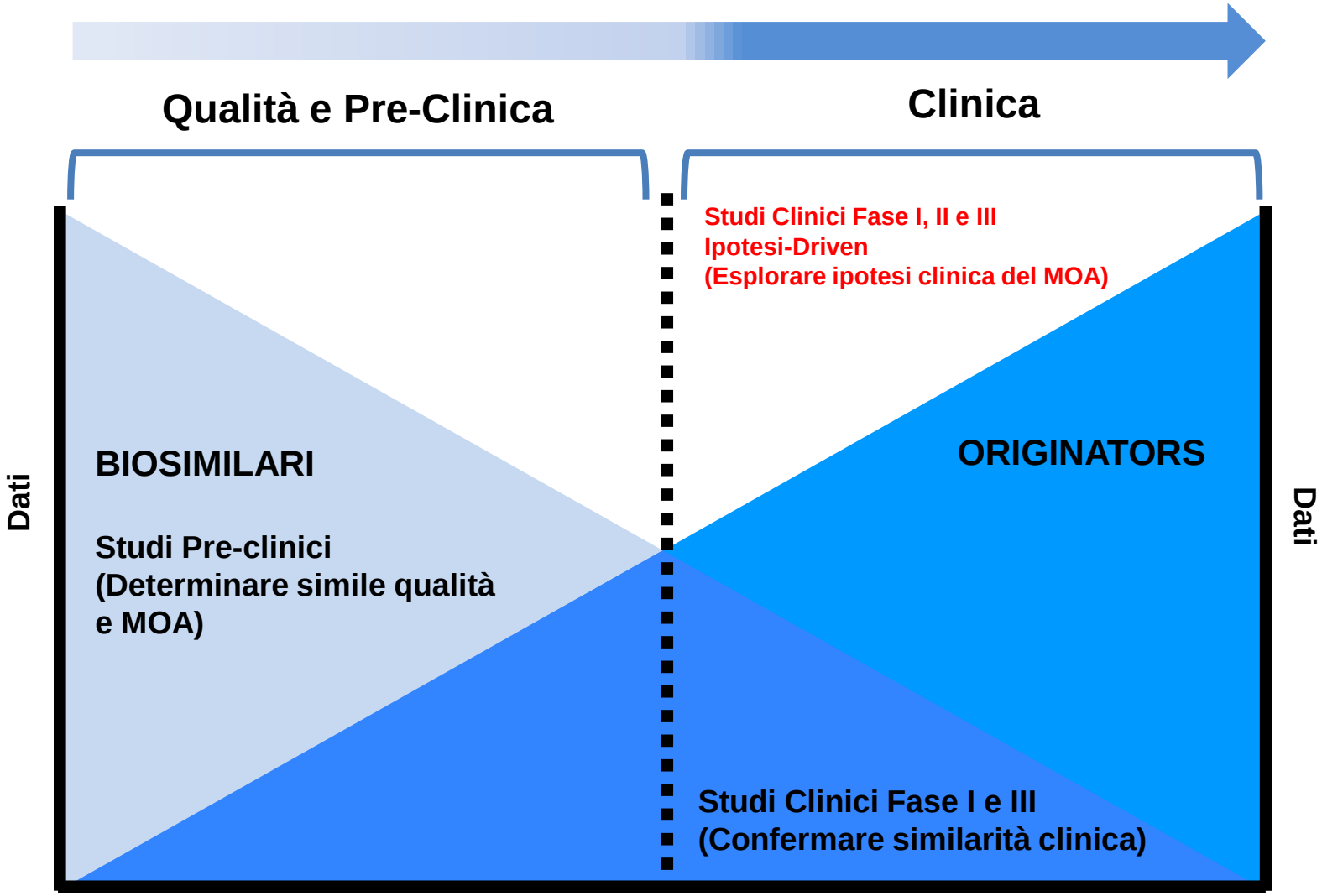
IL *COMPARABILITY EXERCISE*



Modified from Schneider CK et al., Nat Biotechnol 30, 2012

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

Cos’è un farmaco biosimilare?

Un farmaco di origine biotecnologica che ha effettuato un *comparability exercise* nei confronti del farmaco di riferimento, è stato approvato dall’EMA ed è commercializzato alla scadenza brevettuale del farmaco di riferimento.

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.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 June 2014
EMA/CHMP/340840/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Abasria

International non-proprietary name: insulin glargine

Procedure No. EMEA/H/C/002835/0000

Gli EPAR sono strumenti indispensabili di informazione indipendente

THE TIP OF THE ICEBERG

Study Alias	Objective	Study Population	Number of Subjects Randomised
Phase I Studies			
ABEA	Comparison of the PK and PD of LY2963016 and EU-approved Lantus	Healthy subjects	80
ABEE	Comparison of the PD of LY2963016 and EU-approved Lantus	Patients with T1DM	20
ABEI	Relative bioavailability of LY2963016 to EU-approved Lantus	Healthy subjects	16
ABEM	Relative bioavailability of LY2963016 to EU-approved Lantus	Healthy subjects	24
ABEN[a]	Comparison of the PK and PD of EU- and US-approved Lantus	Healthy subjects	40
Phase III Studies			
ABEB	Comparison of LY2963016 with Lantus (EU- and US-approved), as measured by change in HbA1c, when each is used in combination with pre-meal insulin lispro	Patients with T1DM (open-label)	536
ABEC	Comparison of LY2963016 with Lantus (EU- and US-approved), as measured by change in HbA1c, when each is used in combination with OAMs	Patients with T2DM (double-blind)	759

[a] *Study ABEN was a comparison of EU- and US-approved Lantus; no LY2963016 was administered.*

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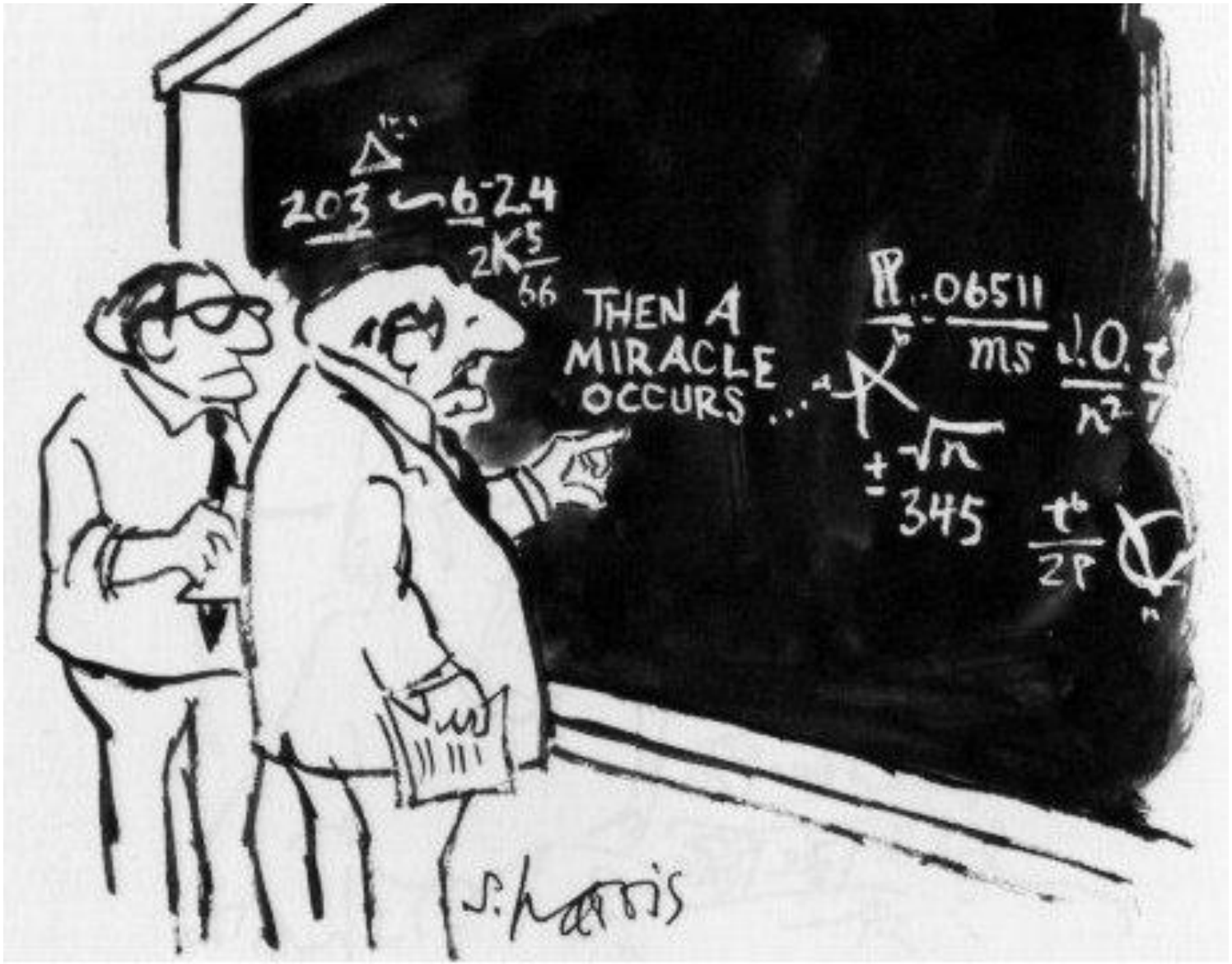
Posizioni ufficiali sui biosimilari da innumerevoli Società Scientifiche

Nel periodo iniziale dell'immissione in commercio quando ancora le nostre conoscenze sono limitate…

- automatic substitutability should be excluded
- substitution should be cautiously considered
- decisions should be taken by clinicians

Drug naïve patients can be treated with biosimilars if the clinician is willing



"I think you should be more explicit here in step two."

from *What's so Funny about Science?* by Sidney Harris (1977)

Competizione

1877: A dead heat at the Oxford Vs Cambridge University Boat Race in 1877